Paramètres biologiques et échocardiographiques et remodelage ventriculaire gauche après syndrome coronarien aigu avec sus-décalage du segment ST

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Résumé

Le remodelage ventriculaire gauche est une complication fréquente des patients ayant présenté un syndrome coronarien aigu, pouvant conduire à terme à une situation d'insuffisance cardiaque. Il est donc important de connaître les facteurs associés à la survenue d'un remodelage ventriculaire afin de dépister plus précocement les patients à plus haut risque d'insuffisance cardiaque et ainsi optimiser leur prise en charge. Ce travail comprend deux axes. Le premier porte sur la recherche de nouveaux paramètres d'imagerie associés à la survenue du remodelage. Nous avons dans un premier temps réalisé une revue de la littérature concernant la définition du remodelage ventriculaire gauche en imagerie par résonance magnétique. Puis, nous avons conduit deux études ayant pour but de rechercher une association entre (i) le strain atrial gauche et, (ii) le gradient de pression intraventriculaire gauche diastolique, évalués en échocardiographie 24-48 heures après le syndrome coronarien aigu et le remodelage ventriculaire gauche au cours du suivi. Le second axe porte sur les biomarqueurs associés au remodelage ventriculaire post-infarctus. Nous avons réalisé une revue de la littérature au sujet des biomarqueurs qui, dosés lors de l'hospitalisation initiale, sont associés à l'existence d'un remodelage lors du suivi. Nous avons ensuite étudié la valeur prédictrice de deux biomarqueurs (la néprilysine et le coenzyme Q10) pour la survenue d'un remodelage ventriculaire gauche.

Abstract

Left ventricular remodeling is a common complication in patients following acute myocardial infarction and may lead to heart failure. Some baseline parameters are associated with remodeling at follow-up, allowing to better discriminate patients with an increased risk of heart failure to optimize therapeutics. This work has two axes, focused on imaging and biological parameters associated with left ventricular remodeling, respectively. First, we reviewed past studies that defined remodeling using cardiac magnetic resonance imaging. Then, we studied the association between some echocardiographic parameters (left atrial strain and diastolic intraventricular pressure gradient) and left ventricular remodeling after ST-elevation myocardial infarction. In the other axis, we reviewed biomarkers that have been associated with left ventricular remodeling in prior studies. Then, we investigated the association between neprilysin and coenzyme Q10 levels and left ventricular remodeling in STEMI patients.

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AMPc adénosine monophosphate cyclique

ARA2 antagoniste du récepteur AT_1 de l'angiotensine-II

ARNI inhibiteur de la néprilysine (angiotensin receptor-neprilysin inhibitor)

CoQ10 coenzyme Q10

ERO espèces réactives en oxygène

FEVG fraction d'éjection ventriculaire gauche

GPIVD gradient de pression intraventriculaire diastolique

IC insuffisance cardiaque

IEC inhibiteur de l'enzyme de conversion de l'angiotensine

IRM imagerie par résonance magnétique

MMP matrix metalloproteinase

OG oreillette gauche

PRVG pressions de remplissage ventriculaire gauche

RVG remodelage ventriculaire gauche

SCA syndrome coronarien aigu

SNA système nerveux autonome

SRAA système rénine angiotensine aldostérone

STEMI syndrome coronarien aigu avec sus-décalage du segment ST (ST-elevation myocardial infarction)

TGF-β transforming growth factor-β

TEP Tomographie par Émission de Positons

TM temps mouvement

VG ventricule gauche

VTD volume télédiastolique

VTS volume télésystolique

Introduction

Le syndrome coronarien aigu (SCA) est défini par la survenue d'une nécrose myocardique dans un contexte d'ischémie myocardique [1]. Il est courant de distinguer le syndrome coronarien aigu avec sus-décalage du segment ST (ST-elevation myocardial infarction) (STEMI) et le SCA sans sus-décalage du segment ST. En effet, les mécanismes physiopathologiques et la prise en charge des patients diffèrent significativement entre ces deux entités. La majorité des STEMI sont classés comme infarctus myocardique de type 1, c'est-à-dire en rapport avec un thrombus intracoronaire responsable d'une occlusion coronaire [2]. Il existe de rares situations de STEMI sans occlusion coronaire aiguë. Dans ce travail, nous utiliserons le terme STEMI pour désigner un SCA avec sus-décalage du segment ST en rapport avec une occlusion coronaire aiguë.

La stratégie de revascularisation dans le STEMI repose sur la reperfusion coronaire en urgence, par l'utilisation de moyens mécaniques (angioplastie primaire) et pharmacologiques (traitement fibrinolytique, antiagrégant plaquettaire ou anticoagulant). L'amélioration progressive de la prise en charge des patients ayant présenté un STEMI – et notamment la réduction des délais de prise en charge – a conduit à une diminution significative de la morbi-mortalité. La mortalité intrahospitalière est désormais estimée entre 4 et 12% en Europe [3] et la mortalité à 1 an, à 10% [4, 5]. L'amélioration du pronostic de ces patients à la phase aiguë a pour conséquence l'observation fréquente de complications à moyen ou long terme comme la survenue de troubles du rythme ventriculaire ou l'évolution vers l'insuffisance cardiaque (IC)). Une partie des patients vont ainsi présenter un remodelage ventriculaire gauche (RVG) au décours de leur STEMI, sous l'effet de mécanismes complexes associant

notamment perturbations hémodynamiques, inflammation et activation neurohormonale. Ces mécanismes d'action et les éventuelles cibles thérapeutiques qui en découlent sont un axe de recherche majeur pour améliorer encore le pronostic des patients en post-infarctus.

Le remodelage ventriculaire gauche après SCA

La survenue d'un RVG au décours d'un STEMI est un facteur pronostique majeur, indépendamment de la fraction d'éjection ventriculaire gauche (FEVG) [6–8]. Il est donc important de disposer d'une définition consensuelle du RVG afin de pouvoir classer les patients selon l'existence ou non d'un RVG après l'infarctus. Il est également nécessaire de comprendre les mécanismes impliqués dans la survenue de ce RVG afin de pouvoir disposer de marqueurs prédictifs précoces dans le but d'adapter la prise en charge de ces patients.

Physiopathologie et mécanismes du RVG

Le RVG est un processus visant initialement à compenser le dysfonctionnement du système cardiovasculaire en permettant de maintenir un débit cardiaque adapté aux besoins de l'organisme. Initialement bénéfique, le RVG va progressivement aboutir à une augmentation des volumes ventriculaires gauches, une augmentation des besoins myocardiques en oxygène (potentiellement pourvoyeur de nouvelles zones d'ischémie myocardique) [9], et éventuellement une fuite mitrale [10] et une altération de la FEVG.

Le SCA va entraîner une réponse inflammatoire et une activation neuro-hormonale. Ces systèmes vont conduire d'une part au remplacement des tissus nécrosés par une cicatrice fibrotique et d'autre part, à une hypertrophie des cardiomyocytes et à la survenue d'une fibrose interstitielle dans les tissus non directement concernés par l'infarctus [11]. Ce processus

dynamique concerne donc l'ensemble du myocarde, aussi bien en zone infarcie que dans les zones "remote" non directement touchées par l'infarctus.

L'ensemble du processus de RVG est habituellement divisé en 3 phases. La première est la phase inflammatoire et débute immédiatement après l'occlusion coronaire [12]. Un élément fondamental dans la régulation des phénomènes inflammatoires initiaux est l'expression de gènes codant pour des cytokines pro-inflammatoires, sous le contrôle du facteur nucléaire NF-κB [13]. Cette réponse inflammatoire intense active les cellules sentinelles résidentes, augmente la perméabilité des capillaires et conduit au recrutement de leucocytes [14, 15] dans le but de nettoyer les cellules nécrosées et les débris de la matrice extracellulaire, par l'intermédiaire de l'activité protéolytique de métalloprotéases matricielles (MMP pour matrix metalloproteinase) [16, 17]. La durée et l'amplitude de l'inflammation et de sa résolution sont des points fondamentaux de la qualité de la cicatrisation. Ainsi, une prolongation de la phase inflammatoire peut entraîner des lésions tissulaires propres, pouvant aboutir à une diminution de la fonction contractile, l'expansion de l'infarctus et contribuer au RVG [18, 19]. La seconde phase est la phase de réparation et de prolifération, sous le contrôle de TGF-β (transforming growth factor-β), caractérisée par la résolution de l'inflammation, une augmentation du nombre de fibroblastes cardiaques et leur transformation en myofibroblastes, cellules capables de synthétiser des protéines matricielles. On assiste également à des phénomènes de néovascularisation [20–23]. La dernière phase est la phase de maturation où survient l'apoptose des cellules réparatrices encore présentes et l'organisation des fibres de collagène en systèmes réticulés.

De très nombreux travaux ont étudié les voies de signalisation mises en jeu dans le processus de cicatrisation tissulaire en post-infarctus [24, 25]. La plupart de ces voies de signalisation peuvent être régulées par l'activation neuro-hormonale mise en évidence

après un SCA. Le système rénine angiotensine aldostérone (SRAA) aboutit à la synthèse d'angiotensine-II dont les effets sont vasoconstricteurs, pro-inflammatoires, apoptotiques et fibrosants [26, 27]. Elle est aussi responsable d'une hypertrophie des cardiomyocytes et d'une réactivation de gènes fœtaux [27]. Il a été montré que le taux d'aldostérone est un facteur pronostic chez les patients ayant présenté un STEMI [28]. Le blocage du SRAA permet d'ailleurs de limiter le RVG post-infarctus et améliore le pronostic [29, 30]. Après un SCA, il existe également une augmentation de l'activité du système nerveux autonome (SNA), à l'échelle de l'organisme mais également au niveau du tissu cardiaque [31]. En réponse à une diminution du débit cardiaque, le SNA va induire une stimulation de la production d'adénosine monophosphate cyclique (AMPc) [32], activant ainsi la protéine kinase A. Il en résulte une augmentation de la concentration intracellulaire en calcium et la phosphorylation – et donc la régulation – de canaux ioniques [33, 34] et de plusieurs protéines intervenant dans le couplage excitation-contraction [35–39]. Ainsi, le SNA a des actions chronotrope $\oplus$, inotrope $\oplus$ et lusitrope $\oplus$. L'activation prolongée du SNA va induire une modification de la densité et de la signalisation des récepteurs β [40, 41], et avoir une action pro-inflammatoire [42, 43], fibrosante [44, 45], apoptotique [46] et favorisant le stress oxydatif [45]. Une partie des lésions tissulaires au décours immédiat du SCA sont en rapport avec l'existence de lésions d'ischémie-reperfusion, dont les causes sont multiples : production d'espèces réactives en oxygène (ERO), altération de la régulation du calcium intracellulaire, dysfonction endothéliale [47], peroxidation des lipides, perturbations de l'énergétique cellulaire ou encore déficit en vitamines anti-oxydantes et en coenzyme Q10 [48–50]. Les mécanismes responsables du RVG post-SCA sont donc complexes et font donc notamment intervenir les systèmes neuro-hormonaux et les fonctions endothéliales et mitochondriales.

L'imagerie du RVG : définition et facteurs prédictifs de survenue

Les bases mécanistiques du remodelage cardiaque et la caractérisation des liens entre le RVG et la progression de l'IC ont été les thèmes de l'*International Forum on Cardiac Remodeling* qui s'est tenu en 1998 [51]. Le RVG y a été défini comme les modifications de l'expression génomique ayant pour conséquences des changements à l'étage moléculaire, cellulaire ou interstitiel et aboutissant à des modifications de la taille, de la forme ou de la fonction du cœur et des vaisseaux. En pratique clinique quotidienne, il est proposé que la quantification du RVG se fasse sur des mesures des volumes télédiastolique et télésystolique du ventricule gauche (et donc aussi de la FEVG) mais aussi sur la masse du ventricule gauche (VG). Les premiers travaux cliniques sur le RVG datent de plus de 20 ans et utilisaient majoritairement l'échocardiographie [52, 53]. Le RVG a souvent été défini dans les études comme une augmentation d'au moins 20% du volume télédiastolique en échocardiographie entre un examen réalisé à la phase initiale du SCA et un second au cours du suivi [52]. L'imagerie par résonance magnétique (IRM) cardiaque possède une meilleure reproductibilité des mesures de volumes et de fonction du VG, et permet de visualiser la fibrose [54]. Pourtant, il n'existe aucune recommandation sur la façon de quantifier le RVG et notamment concernant la modalité d'imagerie, le délai de réalisation des examens d'imagerie ou encore la valeur seuil d'augmentation des volumes ventriculaires gauches à utiliser. Malgré cela, de très nombreuses publications ont proposé des paramètres prédictifs de survenue du RVG après SCA, que ce soit en échocardiographie [55–57] ou en IRM [58–60]. Certains de ces paramètres sont désormais communément admis, comme l'obstruction micro-vasculaire en IRM [61, 62], la taille de la zone infarcie [58–60] ou encore le strain longitudinal global en échocardiographie [55, 56].

Questions posées et objectifs du travail de thèse

Ce travail a pour objectif d'apporter de nouvelles données sur les mécanismes d'action conduisant à la survenue d'un RVG au décours d'un STEMI et de rechercher de nouveaux paramètres prédictifs de sa survenue. Le but est de pouvoir dépister le plus tôt possible les patients qui ont le plus de risques d'évoluer vers un RVG au cours du suivi afin de pouvoir sélectionner ceux qui pourraient bénéficier d'une intensification du traitement.

Ce travail a été organisé en deux axes :

- Premier axe (imagerie) : étudier les définitions du RVG utilisées dans la littérature, en proposer une définition plus précise et rechercher de nouveaux outils d'imagerie permettant d'identifier précocement les patients qui évolueront ultérieurement vers un RVG après STEMI.
- Second axe (biologie) : rechercher de nouveaux marqueurs biologiques d'intérêt chez le patient ayant un STEMI afin de mieux prédire la survenue d'un RVG.

S'agissant d'un travail de recherche clinique portant sur la thématique du RVG au décours d'un STEMI, ce travail de thèse a débuté par la constitution d'une cohorte de patients, pris en charge pour un STEMI, la cohorte RESIST (pour REgistre des Soins et Interventions pour les syndromes coronariens aigus avec sus-décalage du segment ST, cf. page suivante). Les cohortes de patients étudiées dans les sous-parties de ce travail de thèse sont toutes issues de ce registre.

Le registre RESIST

Le REgistre des Soins et Interventions pour les syndromes coronariens aigus avec sus-décalage du segment ST (RESIST) a débuté en juin 2015 et visait à recueillir des données démographiques, cliniques, biologiques et d'imagerie chez les patients admis pour un STEMI dans l'ancienne région Basse-Normandie. Les structures participantes à ce registre étaient les deux centres de cardiologie interventionnelle de la région (C.H.U. de Caen et Centre Hospitalier Privé St Martin, à Caen) ainsi que l'ensemble des centres hospitaliers généraux et des SAMU-SMUR de la région. Un des objectifs était de mieux connaître le parcours des patients pris en charge pour un STEMI dans notre bassin de population, notamment les délais de prise en charge.

Données recueillies

Les données suivantes étaient saisies dans une base de données informatisée après recueil au format papier de la feuille de transmission des équipes SAMU-SMUR (spécialement éditée pour le registre), des données de la procédure de coronarographie en urgence, consultation de la base de données de l'établissement, et appel du patient à 3 mois de l'évènement initial $\pm$ données échocardiographiques de suivi si le patient était d'accord pour avoir un suivi sur le centre (feuille d'information et recueil du consentement):

- données démographiques : âge, sexe, coordonnées
- antécédents, facteurs de risque cardio-vasculaires
- prise en charge à la phase aiguë, en pré-hospitalier : premier contact médical, lieu de prise en charge, appelant, parcours de prise en charge, stratégie de reperfusion, évènements cardio-vasculaires et traitements reçus

- coronarographie : lésion coupable, formule coronaire, lésions associées, gestes d'angioplastie réalisés
- ± biologie de routine et biobanque
- ± données échocardiographiques 2D/3D, initiale et au cours du suivi (6 mois) :

  valve aortique

  - gradient moyen trans-valvulaire, quantification d'une éventuelle fuite valvulaire aortique ou d'une sténose
  - acquisition temps-mouvement avec doppler couleur
  - mesure de l'intégrale temps-vitesse dans la chambre de chasse ventriculaire gauche en doppler pulsé, calcul du débit cardiaque

  valve mitrale

  - recherche et quantification d'une fuite mitrale (calcul de la surface de l'orifice régurgitant), étude du mécanisme de la fuite le cas échéant
  - acquisition temps mouvement (TM) avec doppler couleur
  - flux doppler pulsé transmitral

  ventricule gauche

  - diamètres télédiastolique et télésystolique
  - volumes télédiastolique et télésystolique et calcul de la FEVG, en 2D (Simpson) et en 3D
  - étude de la cinétique segmentaire du ventricule gauche
  - épaisseur septale et de la paroi postérieure
  - acquisition en doppler tissulaire : paroi latérale, paroi septale
  - strain longitudinal global

  oreillette gauche

- volume de l'oreillette gauche en 2D
- mesure du strain de l'oreillette gauche

valve tricuspide et ventricule droit

- fraction de raccourcissement du ventricule droit
- doppler tissulaire à l'anneau tricuspide (onde S)
- vitesse maximale du flux d'insuffisance tricuspide
- mesure de l'excursion systolique du plan de l'anneau tricuspide en TM

– évènements intrahospitaliers et suivi à 3 mois (évènements cardiovasculaires majeurs)

Dates clefs

– juin 2015 : obtention de l'accord de mise en place du registre (CPP Nord-Ouest III)

– juin 2015 : premières inclusions dans le registre

– octobre 2015 : début de la biobanque (tubes citratés)

– novembre 2015 : début des acquisitions échocardiographiques complètes 2D/3D

– janvier 2017 : utilisation de tubes secs et de tubes EDTA

– mai 2019 : gel de la base

Données disponibles dans le registre RESIST

Entre le 1^e juin 2015 et le 31 mai 2019, un total de 1865 patients ont été inclus dans le registre RESIST. Dans notre cohorte, 176 patients sont décédés durant l'hospitalisation initiale ou dans les 3 mois suivant la sortie d'hospitalisation. Le détail des données biologiques et échocardiographiques disponibles chez les 1689 patients restants sont résumées dans la

Table 1 : Données biologiques et échocardiographiques disponibles chez les 1689 patients du registre RESIST vivants à 3 mois de la sortie d'hospitalisation. Des données échocardiographiques complètes (à la phase aiguë et dans le suivi sont disponibles pour 168 patients (en bleu). Parmi ces patients, nous disposons de tubes secs et EDTA pour 63 d'entre eux (en vert), nous permettant de réaliser des dosages de biomarqueurs d'intérêt.

Prélèvements sanguins	ETT initiale			ETT de suivi	Total
disponibles	non faite	mauvaise qualité	disponible	disponible	
Aucun	1018	6	15	17	1056
Tubes citratés	112	14	49	88	239
Tubes secs et EDTA	287	8	42	63	400
Total	1417	28	76	168	1689

Table 1. S'agissant d'un registre bicentrique, les données biologiques et d'imagerie ne sont pas disponibles pour tous les patients. Les caractéristiques de la population générale, du sous-groupe des patients ayant eu l'échocardiographie initiale et celle de suivi ainsi que le sous-groupe de patients ayant eu ces deux échocardiographies et un prélèvement sanguin sur tubes EDTA et tubes sec sont présentés dans la Table 2. Dans le sous-groupe de patients ayant eu la seconde échocardiographie dans notre centre, le délai médian de suivi était de 219 jours (espace interquartile : 182 – 228 jours).

Les travaux originaux détaillés dans la suite de ce document proviennent donc de l'exploitation des données prospectivement acquises dans le cadre du registre RESIST.

Table 2 : Caractéristiques de la population incluse dans le registre RESIST.

	Population générale	Patients vivants à 3 mois	Sous-groupe avec ETT complètes	valeur de p*	Sous-groupe avec biologie disponible	valeur de p†
	n=1865	n=1689	n=168		n=63	
Age, années	63,6 [53,5 – 73,7]	63,7 [53,6 – 73,8]	64,6 [54,5 – 72,4]	0,73	65,8 [54,5 – 72,0]	1
Sexe masculin	1389 (74,4%)	1268 (75,1%)	137 (81,5%)	0,051	52 (82,5%)	0,22
Hypertension artérielle	795 (42,6%)	691 (40,9%)	62 (36,9%)	0,31	23 (36,5%)	0,56
Tabagisme	943 (50,5%)	879 (52,0%)	98 (58,3%)	0,11	37 (58,7%)	0,34
Diabète de type 2	220 (11,8%)	186 (11,0%)	22 (13,1%)	0,44	10 (15,9%)	0,30
ATCD fam. cardio-vasc.	405 (21,7%)	388 (23,0%)	34 (20,2%)	0.43	15 (23,8%)	1
Hypercholestérolémie	675 (36,2%)	607 (35,9%)	65 (38,7%)	0,49	29 (46,0%)	0,12
IMC, kg/m^2	26,3 [24,2 – 29,1]	26,3 [24,2 – 29,1]	26,1 [23,8 – 29,1]	0,44	26,5 [23,8 – 29,4]	0,55
Infarctus antérieur	679 (36,4%)	596 (35,3%)	69 (41,1%)	0,12	23 (36,5%)	0,95
Délai ECG qualifiant, h	1,8 [1,0 – 3,7]	1,8 [1,0 – 3,6]	1,8 [1,0 – 3,2]	0,68	1,9 [1,1 – 4,6]	0,32
A l'admission						
FC, bpm (n=1666)	74 [62 – 87]	74 [62 – 86]	73 [63 – 88]	0,81	76 [66 –89]	0,20
PAS, mmHg (n=1644)	140 [120 – 160]	140 [122 – 160]	140 [120 – 155]	0,19	145 [123 – 158]	0,89
PAD, mmHg (n=1638)	81 [70 – 94]	82 [72 – 95]	80 [70 – 94]	0,36	86 [70 – 96]	0,85
Stratégie de reperfusion						
Fibrinolyse réalisée (n=1799)	240 (13,3%)	213 (12,2%)	19 (11,4%)	0,55	2 (3,2%)	0,02
Succès	116 (48,3%)	104 (48,8%)	14 (77,8%)	0,03	2 (100,0%)	0,24
Artère coupable (n=1785)				0,59		0,29
Tronc commun	17 (0,9%)	17 (1,1%)	0		0	
IVA	757 (42,4%)	691 (42,9%)	74 (44,6%)		32 (50,8%)	
Circonflexe	275 (15,4%)	250 (15,5%)	21 (12,7%)		6 (9,5%)	
Coronaire droite	722 (40,4%)	646 (40,1%)	70 (42,2%)		24 (38,1%)	
Pontage aorto-coronaire	4 (0,2%)	3 (0,2%)	0		0	
Pas de lésion coronaire	10 (0,6%)	5 (0,3%)	1 (0,6%)		1 (1,6%)	
Non précisé	80	77	2		0	
Angioplastie (n=1758)	1586 (90,2%)	1437 (90,7%)	145 (90,1%)	0,78	58 (93,5%)	0,66
Obtention flux TIMI3 (n=1604)	1503 (93,7%)	1401 (95,2%)	148 (96,7%)	0,66	56 (96,6%)	1
Délai → TIMI3, h‡ (n=995)	4,3 [2,9 – 6,8]	4,2 [2,8 – 6,7]	4,4 [3,0 – 6,7]	0,36	4,1 [2,7 – 6,3]	0,48

L'exhaustivité des données étant très variable d'un patient à l'autre, nous présentons ici les caractéristiques de la population générale, du sous-groupe de patients ayant eu les deux échocardiographies (initiale et de suivi) complètes (en bleu). Les caractéristiques de ces patients qui ont eu également un prélèvement sanguin sur tube EDTA et sur tube sec sont aussi présentées (en vert). Les données sont présentées sous forme de médiane et d'espace interquartile ou nombre (pourcentage). FC, fréquence cardiaque ; PAD, pression artérielle diastolique ; PAS, pression artérielle systolique. *Comparaison par rapport au reste de la population des patients vivants à 3 mois (n=1521 patients). †Comparaison par rapport au reste de la population des patients vivants à 3 mois (n=1626 patients). ‡Délai entre le début de la douleur et l'obtention d'un flux TIMI3 en coronarographie. La coronarographie étant différée en cas de succès de fibrinolyse, ces patients ne sont pas comptabilisés ici.

Axe imagerie du remodelage ventriculaire gauche en post-infarctus

Définition du remodelage ventriculaire gauche en IRM : revue de la littérature

Le RVG est fréquemment décrit dans la littérature comme un facteur de mauvais pronostic après un STEMI [6–8]. Pourtant, il n'existe pas de recommandation sur la modalité d'imagerie, le délai de réalisation de l'imagerie ou encore les valeurs seuils d'augmentation des volumes ventriculaires gauches à utiliser. L'échocardiographie et l'IRM sont les deux principales modalités d'imagerie utilisées pour quantifier l'évolution des volumes au décours d'un STEMI et donc pour affirmer l'existence d'un RVG. L'IRM possède une meilleure reproductibilité de la mesure des volumes ventriculaires [54] et nous nous sommes donc limités dans ce travail aux études ayant utilisé l'IRM pour la quantification des volumes VG. Nous avons donc recherché de façon exhaustive les études publiées dans les 10 dernières années ayant évalué la prévalence d'un RVG, au moyen de l'IRM, au décours d'un STEMI.

Entre janvier 2010 et août 2019, nous avons retrouvé 77 publications étudiant le RVG en IRM au décours d'un STEMI. Certaines cohortes ayant fait l'objet de plusieurs publications, nous avons retenu pour chaque cohorte la publication qui présente l'effectif le plus grand. Parmi les 37 publications retenues, 30 utilisent une valeur seuil pour définir le RVG (les autres le définissent comme une variable continue). La prévalence du RVG varie de 11,3 à

48,4% dans les études ayant utilisé une valeur seuil de définition du RVG (prévalence groupée de 22,8% [19,4% – 26,7%] dans la méta-analyse, I^2=84%). Les valeurs seuil de 20% et 15% d'augmentation des volumes VG sont les plus fréquemment retrouvées (respectivement dans 13 (35%) et 9 (24%) des études). Les définitions les plus fréquemment utilisées sont (i) une augmentation $\geq$20% du volume télédiastolique VG (indexé ou non), évalué 3 à 5 mois après le SCA (5 études, 638 patients, prévalence groupée du RVG: 18,8% [16,0% – 22,1%], I^2=0%), (ii) une augmentation $\geq$15% du volume télésystolique VG (indexé ou non), évalué 3 à 5 mois après le SCA (3 études, 224 patients, prévalence groupée du RVG: 23,7% [18,2% – 30,2%], I^2=9%) et, (iii) une augmentation $\geq$20% du volume télédiastolique VG (indexé ou non), évalué 6 mois après le SCA (4 études, 676 patients, prévalence groupée du RVG: 17,0% [12,1% – 23,5%], I^2=70%).

Cette revue a montré la grande hétérogénéité concernant la définition du RVG dans les études ayant utilisé l'IRM comme modalité d'imagerie, au décours d'un STEMI. De plus, les patients inclus dans ces études sont fréquemment sélectionnés et ne reflètent pas l'ensemble des patients qui présentent un STEMI. L'utilisation d'une unique mesure de volume (télédiastolique ou télésystolique) ne permet pas d'appréhender la fonction cardiaque. Une définition combinant les variations du volume télédiastolique et du volume télésystolique permet de faire la différence entre une situation où seul le volume télédiastolique est augmenté (et donc où la FEVG s'améliore) et une augmentation conjointe des volumes télédiastolique et télésystolique, pouvant s'accompagner d'une dégradation de la FEVG dans le suivi. Prenant en compte la reproductibilité des mesures en IRM, il serait pertinent d'étudier la valeur pronostique d'un RVG qui serait défini par une augmentation du volume télédiastolique de 12 à 20% associé à une augmentation du volume télésystolique de 12 à 15% dans une population

non sélectionnée de patients présentant un STEMI. Le délai de réalisation de 3 mois permet de dépister précocement les patients qui présentent un RVG, permettant ainsi d'optimiser au plus tôt leur prise en charge.

Legallois D, Hodzic A, Alexandre J, Dolladille C, Saloux É, Manrique A, Roule V, Labombarda F, Milliez P, Beygui F.

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Les données supplémentaires de cet article sont disponibles dans les annexes, page 165. Le poster accepté à l'ESC 2020 est reproduit, page 186. Enfin, l'éditeur a donné son accord à la reproduction du pdf de cet article dans ce travail de thèse, cf. ci-dessous.

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Definition of left ventricular remodelling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade

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Abstract
An increase in left ventricular volumes between baseline and follow-up imaging is the main criteria for the quantification of left ventricular remodelling (LVR) after ST-elevation myocardial infarction (STEMI), but without consensual definition. We aimed to review the criteria used for the definition of LVR based on cardiac magnetic resonance imaging (CMR) in STEMI patients. A systematic literature search was conducted using MEDLINE and the Cochrane Library from January 2010 to August 2019. Thirty-seven studies involving 4209 patients were included. Among these studies, 30 (81%) used a cut-off value for defining LVR, with a pooled LVR prevalence estimate of 22.8%, 95% CI [19.4–26.7%] and a major between-study heterogeneity (I^2 = 82%). The seven remaining studies (19%) defined LVR as a continuous variable. The definition of LVR using CMR following STEMI is highly variable, among studies including highly selected patients. A 20% increase or a 15% increase in left ventricular volumes between a baseline and a follow-up CMR imaging were the two most common criterion (13 [35%] and 9 [24%] studies, respectively). The most frequent LVR criterion was a 20% increase in end-diastolic volumes or a 15% increase in end-systolic volumes. A composite cut-off value of a 12 to 15% increase in end-systolic volume and a 12 to 20% increase in end-diastolic volume using a follow-up CMR imaging 3 months after STEMI might be proposed as a consensual cut-off for defining adverse LVR for future large-sized, prospective studies with serial CMR imaging and long-term follow-up in unselected patients.

Keywords ST-elevation myocardial infarction · Left ventricular remodelling · Cardiac magnetic resonance

Introduction

Cardiac remodelling may be defined as changes in genome expression resulting in molecular, cellular and interstitial changes, leading to changes in the size, shape and function of the heart and vasculature [1]. After acute myocardial infarction, inflammatory responses and neuroendocrine activation lead to the replacement of dead cardiomyocytes by a fibrotic scar. Left ventricular (LV) dilation and remodelling occur later due to myocyte hypertrophy, interstitial fibrosis and enhanced haemodynamic burden [2].

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Left ventricular remodelling (LVR) is associated with poor outcome in patients with acute myocardial infarction [3]. Hence, the assessment of LVR is of major importance since reversing, stopping or at least delaying remodelling is the goal of therapy in heart failure. However, there is no consensual definition of LVR after ST-elevation myocardial infarction (STEMI). An increase in LV volumes (end-diastolic volume (EDV) or end-systolic volume (ESV)) between baseline and follow-up imaging is the main criteria for the quantification of LVR, but the wide range of cut-offs used and the variable timing of imaging may contribute to the heterogeneity of results between studies and highlights the need for a uniform definition.

Cardiac magnetic resonance (CMR) imaging provides an accurate and reproducible assessment of global and regional LV function and allows for quantification of fibrosis [4]. A 20% increase in LV volumes has been used for the definition of LVR, but this cut-off was initially proposed in echocardiographic studies prior to the era of primary percutaneous coronary intervention (PPCI) [5]. However, even when using CMR, the criteria for cardiac remodelling remain controversial.

In the present work, we aimed to review the criteria used for the definition of LVR based on CMR imaging in studies including patients with STEMI.

Methods

Data sources and searches

We performed a systematic search in online literature databases (PubMed/MEDLINE and Cochrane Library, see Online Resource) for articles published between January 2010 and August 2019 that reported on LV remodelling and/or LV volumes using CMR imaging in STEMI patients. Studies before 2010 were not included, as recent developments in the management of STEMI (e.g. use of more potent P2Y12 inhibitors, wider use of PPCI) have led to significant changes in outcomes and adding older studies may lead to a cumbersome analysis. In addition, we searched the references of the articles identified to find other suitable studies. Only peer-reviewed and published studies were included. Authors were not contacted for additional information not included in the published papers.

Study selection

Eligible studies had to fulfil the following criteria: (i) patients were admitted with STEMI, (ii) a definition of LVR was given, (iii) the baseline CMR assessment was performed within 10 days following STEMI, (iv) the number of included patients was ≥ 30, (v) the time interval between the baseline and follow-up was ≥ 1 month and (vi) the article was written in English. Special attention was taken to exclude duplicate patient populations. The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Online Resource). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42018114977.

Data extraction and quality assessment

All data were independently extracted from the full reports by two investigators (DL and AH). Discrepancies were solved by consensus. The assessment of the quality of included randomized controlled trials was realized using the Cochrane Collaboration's tool for assessing the risk of bias [6]. Based on the evaluation, studies were classified into low, unclear, or high risk of bias. For the assessment of the quality of included non-interventional studies, we used the modified version of the Newcastle-Ottawa Scale [7] in order to account for concepts relevant to LVR that may bias study results or comparability. Non-interventional studies were judged to be at low (≥ 3 points) or high risk of bias (< 3 points).

Data synthesis and analysis

Studies were classified according to (i) LVR criteria and (ii) the time between the two CMR imaging sessions (3 to 5 months, 6 months or 7 to 12 months). In these subgroups, LVR prevalence among patients with STEMI was calculated by pooling the estimated prevalence of each study using a random effects meta-analysis that accounted for between-study heterogeneity. Binomial prevalence and 95% confidence intervals (95% CI) for individual studies were calculated using the Clopper-Pearson method. We assessed between-study heterogeneity using standard χ^2 tests (significant if $p < 0.10$) and the I^2 statistic (> 50% was considered as significant heterogeneity) in subgroup analysis. Sensitivity analysis of the pooled prevalence estimate was performed by excluding each study sequentially from the calculation. Bias secondary to the study's size effects was investigated by funnel plot and Egger test. Figures and analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were two-sided and used a significance threshold of $p < 0.05$.

Results

Literature search

The initial literature search yielded 4520 potentially relevant references, of which 3087 articles were excluded based on the title and 1009 after reading the abstract (Fig. 1). Citation tracking identified an additional 298 articles. A full-text review was

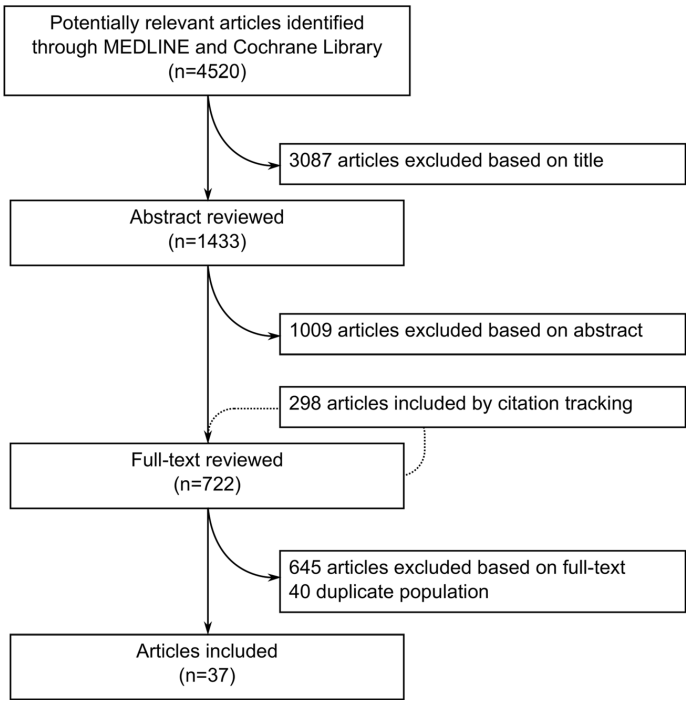


Fig. 1 Flowchart of studies reviewed and included

completed on the 722 remaining articles and 37 studies met our inclusion criteria.

Study and population characteristics

Thirty-seven studies involving 4209 patients were included [8–44]. The characteristics of the included studies are depicted in Table 1 and Online Resource. The median number of patients per study was 72 (range 31–383). Twelve (32%, 1256 patients) were part of a randomized clinical trial; 22 studies were prospectively recruited longitudinal studies, and the remaining 3 studies were retrospective or from registries. The median follow-up duration was 6 months (range, 3–12), and the second CMR session was performed at 6 months in 14 studies (38%). The median patient age was 59 years [interquartile range, 57.5–60.5], and 82% were male. Fifty percent of the patients had anterior STEMI and/or the left anterior descending artery as the culprit vessel. PPCI was an inclusion criterion in 24 studies, and 93% of the overall population underwent PPCI. Almost all the remaining patients had fibrinolysis with either success or rescue PCI.

Cardiac magnetic resonance imaging data

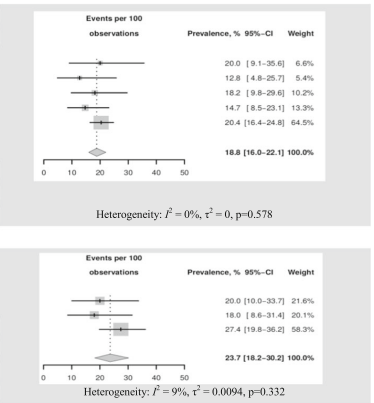
Paired EDV and ESV (indexed on body surface area or not) and LV ejection fraction (LVEF) were available in 29, 26 and 31 studies, respectively (Fig. 2 and Online Resource). Mean or median EDV at baseline ranged from 117 to 183 mL (median, 146 mL), indexed EDV ranged from 64.5 to 93.0 mL/m^2 (median, 79.7 mL/m^2), ESV ranged from 57 to 94 mL (median, 68 mL) and indexed ESV ranged from 33.6 to 53.5 mL/m^2 (median, 42 mL/m^2). Mean or median LVEF at baseline ranged from 40 to 58% (median, 48.6%). Mean or median EDV or EDVI increased in 26/29 studies and mean or median ESV or ESI decreased in 17/26 studies between the two CMR imaging sessions. As a consequence, mean or median LVEF improved in 30/31 studies between baseline and follow-up CMR imaging.

Definition of LVR

Thirty studies (81%) used a cut-off value for LVR (Table 1 and Online Resource), and 7 (19%) defined LVR as a continuous variable. When LVR was defined as dichotomous criteria, the prevalence of LVR ranged from 11.3 to 48.4%. Meta-analysis showed a pooled LVR prevalence of 22.8%, 95% CI [19.4–26.7%], (Fig. 3, 28 studies [8–35]) with significant between-study heterogeneity (I^2 = 82%). No individual study affected the overall prevalence estimate by more than 1% (Online Resource). The cut-off values of 20% and 15% increases in LV volumes were the two most common criteria (13 [35%] and 9 [24%] studies, respectively). Twenty-nine

Table 1 Main characteristics of the studies included in this systematic review. Subgroup meta-analysis of the prevalence of LVR among patients presenting with STEMI using CMR imaging. Further data are available in Online Resource. *CMR*, cardiac magnetic resonance; *EDV*, end-diastolic volume; *EDVI*, end-diastolic volume index; *ESV*, end-systolic volume; *ESVI*, end-systolic volume index; *LVR*, left ventricular remodelling; *RCT*, randomized clinical trial

First author, year	Sample size	Design	Timing of the follow-up CMR	Definition of LVR	Patients with LVR	Meta-analytic pooling of LVR prevalence, Proportion, 95%-CI, Weight *(only if there is ≥ 3 studies with similar characteristics)*
Follow-up CMR imaging session: 3 to 5 months						
EDV-based criteria						
Biesbrock, 2017	42	Prospective study	3 months	ΔEDV ≥ 15%	8 (19%)	
Bulluck, 2016	40	Prospective	5 months	ΔEDV ≥ 20%	8 (20%)	
Reinstadler, 2013	47	Prospective	4 months	ΔEDV ≥ 20%	6 (12.8%)	
Pokorney, 2012	66	Prospective	4 months	ΔEDVI > 20%	12 (18.2%)	
Reindl, 2018	102	Prospective	4 months	ΔEDV ≥ 20%	15 (14.7%)	
Symons, 2016	383	Prospective	4 months	ΔEDV > 20%	78 (20.4%)	
Shetelig, 2018	240	Post-hoc analysis of a RCT	4 months	increase EDVI ≥ 10mL/m2	not available	
Wong, 2013	64	Prospective	3 months	ΔEDV	NA	
ESV-based criteria						
Garg, 2017	50	Prospective	3 months	ΔESV > 15%	10 (20%)	
Van Melle, 2010	50	Prospective	4 months	ΔESV ≥ 15%	9 (18%)	
Gerbaud, 2014	124	Prospective	3 months	ΔESV ≥ 15%	34 (27.4%)	
Composite criteria						
Shetye, 2017	65	Prospective	4 months	ΔESVI ≥ 15% or ΔEDVI ≥ 20%	11 (16.9%)	
Hallen, 2010	132	Post-hoc analysis of a RCT	4 months	ΔESVI and ΔEDVI	NA	
Janssens, 2018	197	RCT	4 months	ΔESV and ΔEDV and sphericity index	NA	
Najjar, 2011	124	RCT	3 months	EDVI, ESVI and LV mass index	NA	



studies (78%) used EDV or EDVI to define LVR and 15 studies (41%) used ESV or ESVI. Seven studies used both end-diastolic and end-systolic LV volumes. Other criteria, including LV mass index [40] or sphericity index [39], were described. Three remodelling criteria were used in ≥ 3 studies: (i) a ≥ 20% increase in EDV or EDVI at 3 to 5 months (5 studies, 638 patients; prevalence of LVR, 18.8%; 95% CI [16.0–22.1%]; I^2 = 0%), (ii) a ≥ 15% increase in ESV or ESVI at 3 to 5 months (3 studies, 224 patients; prevalence of LVR, 23.7%; 95% CI [18.2–30.2%]; I^2 = 9%) and (iii) a ≥ 20% increase in EDV or EDVI at 6 months (4 studies, 676 patients; prevalence of LVR, 17.0%; 95% CI [12.1–23.5%]; with significant heterogeneity, I^2 = 70%).

Risk of bias assessment

Among the 25 non-interventional studies included in this review, 8 (32%) were at high risk of bias (see: Online Resource). Main biases were a small sample size and the lack of represenativeness of the average STEMI patients (e.g. exclusion of patients with low LVEF or clinical signs of heart failure). The risk of bias assessment in each randomized controlled trial is reported in the Online Resource. Most of the trials had a low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment and selective reporting. Seven trials had a high risk of bias for blinding of participants and personnel, and 4 a high risk of bias in outcome data completion. Funnel plot and Egger tests revealed no asymmetry (p = 0.17, Fig. 4).

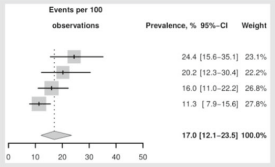
Discussion

This systematic review highlighted that (i) the definition of LVR using CMR in STEMI patients is highly variable; (ii) an increase of 20% of end-diastolic volumes or an increase of 15% of end-systolic volumes between a baseline and a follow-up CMR imaging ≤ 6 months after STEMI is commonly used as a definition of LVR; and (iii) the LVR prevalence estimate is 22.8%, 95% CI [19.4–26.7%], with significant between-study heterogeneity in this highly selected population.

The *International Forum on Cardiac remodelling* held in 1998 led to a consensus paper on the key concepts and definition of LVR [1]. Our review shows that 20 years later, the only consensual point is to describe LVR as a change in LV volumes. The lack of a standard definition has led to major heterogeneity and low-quality publications with subsequent imprecision in drawing conclusions about the definition, the incidence, the correlates and the prognostic value of LVR in the setting of STEMI.

Table 1 (continued)

First author, year	Sample size	Design	Timing of the follow-up CMR	Definition of LVR	Patients with LVR	Meta-analytic pooling of LVR prevalence, Proportion, 95%-CI, Weight *(only if there is ≥ 3 studies with similar characteristics)*
Follow-up CMR imaging session: 6 months						
EDV-based criteria						
Sugano, 2017	68	Prospective	6 months	ΔEDV > 5%	22 (32%)	
Fabregat-Andrés, 2015	31	Prospective	6 months	ΔEDV > 10%	15 (48%)	
Mele, 2017	41	Retrospective	6 months	ΔEDV ≥ 15%	10 (24%)	
Rodriguez-Palomares, 2019	374	Variable	6 months	ΔEDV > 15%	105 (28.1%)	
Cha, 2019	82	Retrospective	6.5 months	ΔEDV ≥ 20%	20 (24.4%)	
Yoon, 2013	84	RCT	6 months	ΔEDV > 20%	17 (20.2%)	
Caldentey, 2017	227	Prospective	6 months	ΔEDV ≥ 20%	29 (16.0%)	
Carberry, 2017	283	Prospective	6 months	ΔEDV ≥ 20%	32 (11.3%)	
Huttin, 2017	121	Prospective	6 months	ΔEDV > 17,3mL	36 (29.8)	
Grabmaier, 2017	44	Post-hoc analysis of a RCT	6 months	ΔEDV	NA	
ESV-based criteria						
Eitel, 2011	112	RCT	6 months	ΔESVI > 0%	51 (45.5%)	
Watabe, 2016	92	Prospective	6 months	ΔESV > 0%	29 (32%)	
Husser, 2013	234	Prospective	6 months	dilated ESVI (reference values)	94 (40%)	
Composite criteria						
Traverse, 2010	40	RCT	6 months	ΔESV and ΔEDV	NA	
Achilli, 2014	35	RCT	6 months	ΔEDV > 20mL or ΔLVEF > 5%	not available	
Follow-up CMR imaging session: 7 to 12 months						
EDV-based criteria						
Tanimoto, 2010	104	Prospective	8 months	ΔEDV > 15%	21 (20%)	
O'Regan, 2012	46	Prospective	12 months	ΔEDV ≥ 20%	16 (35%)	
Gohbara, 2015	69	Prospective	7 months	ΔEDVI ≥ 20%	18 (26%)	
ESV-based criteria						
Garcia, 2019	192	Prospective	12 months	ΔESV ≥ 10%	32 (16.7%)	
Sörensson, 2013	68	Post-hoc analysis of a RCT	12 months	ΔESV ≥ 15%	9 (13%)	
Composite criteria						
Mangion, 2016	72	Post-hoc analysis of a RCT	7 months	ΔESVI ≥ 20% and ΔEDVI ≥ 20%	11 (13%)	
Sürder, 2016	150	Post-hoc analysis of a RCT	12 months	ΔEDV, ΔESV	NA	



Patient's characteristics in CMR studies

The selected patients included in the CMR studies were relatively young (mean or median age, 59 years), had a preserved LVEF (median, 48.6%) and mostly underwent PPCI (93%). The reported rate of PPCI increased over time [45]. However, in the FAST-MI 2015 registry, the non-selected patients were older (63 ± 14 years), and only 71% underwent primary PCI [46]. In addition, 28% of the patients we included in the present review were included as part of a randomized clinical trial and very few studies enrolled consecutive STEMI patients. As a consequence, patients with heart failure or low kidney function were mostly excluded. Additionally, there was a low incidence of major adverse cardiovascular events (MACE) during follow-up, in line with the baseline LVEF. Hence, the patients included in CMR studies after STEMI were highly selected, questioning the extrapolation of their conclusions to non-selected STEMI patients.

Definition of the optimal cut-off value for LV volume increase

When defined, the cut-off value of a 15% increase in ESV or a 20% increase in EDV remains the most frequent criterion for LVR in CMR studies. An ideal threshold value for the volume variation has to be (i) wide enough to be beyond the test-retest repeatability of the assessment method, (ii) predictive of outcomes, hence leading to significant changes in the management of patients and (iii) reproducible among studies.

Most of the studies assessing the prognostic value of LVR following STEMI used echocardiography and were conducted > 15 years ago, prior to the era of PPCI [5]. A 20% increase in LV volumes, based on the upper limit of the 95% CI of the intra-observer variability for ΔEDV, has been widely used to define LVR [5]. The assessment of global and regional LV function using CMR is more accurate than TTE because of its 3D analysis, higher spatial resolution and superior intra-observer variability [4,

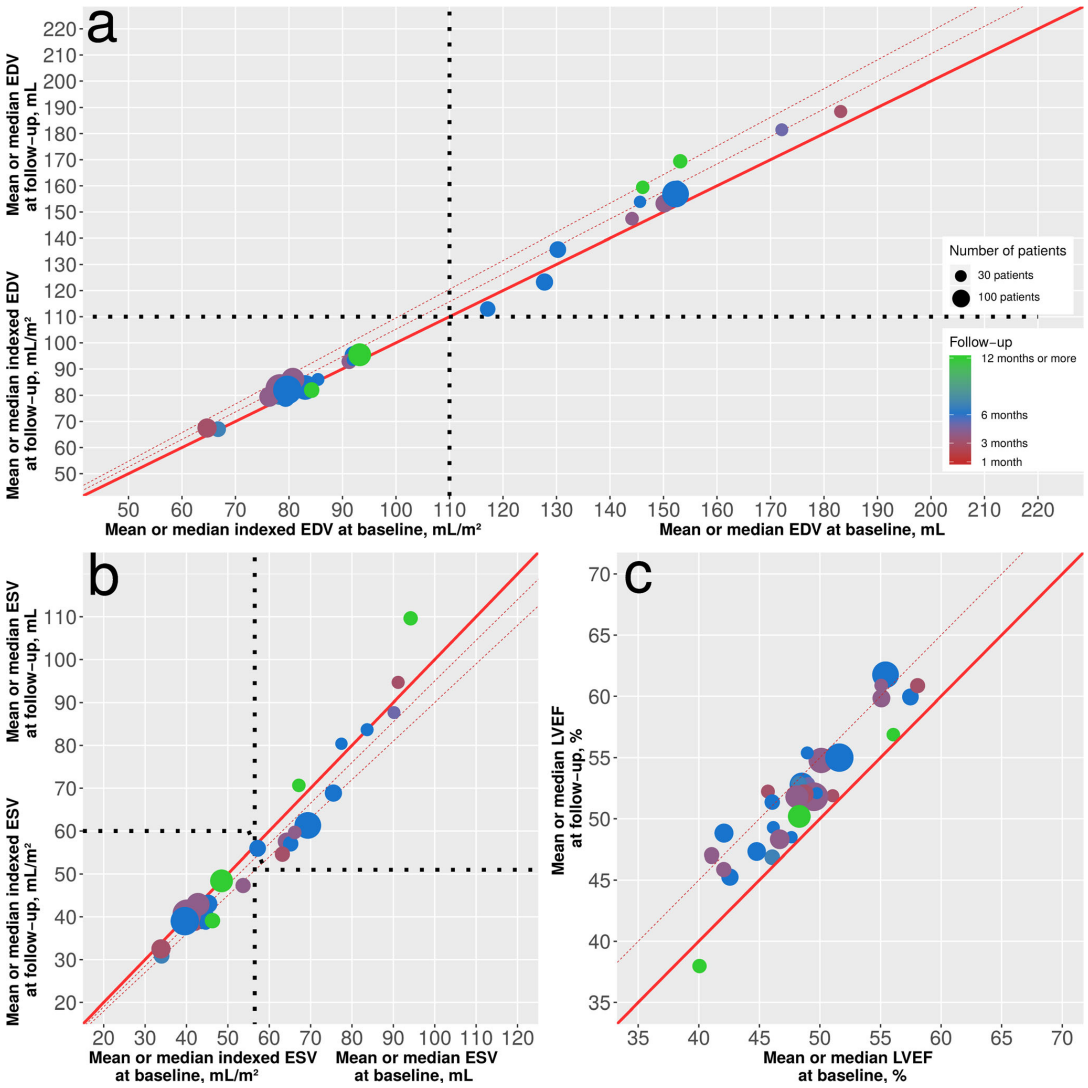


Fig. 2 End-diastolic volumes (**a**), end-systolic volumes (**b**) and LVEF (**c**) at baseline and during follow-up in studies with CMR paired data. Indexed LV volumes are depicted in the left lower corner of the plots, whereas non-indexed volumes are depicted in the upper right corner. Each study is represented once per plot. The area of each circle is related to the sample size of the study. The bold red line represents the identity line where volumes or LVEF is identical between baseline and follow-up. The two dotted lines show a 5% and a 10% increase in mean EDV or indexed EDV during the course of follow-up (panel **a**). The two dotted lines show a 5% and a 10% decrease in mean ESV or indexed ESV during follow-up (panel **b**). The dotted line in panel **c** shows an absolute improvement of 5% on LVEF between baseline and follow-up

47]. It remains unclear whether investigators should use EDV or ESV to define LVR. EDV reflects structural remodelling and preload, whereas ESV is influenced by both loading conditions and fibre shortening [1]. The recent studies that defined LVR using a prognostic-based approach may help to answer this question.

Only a few studies assessed the long-term outcomes associated with LVR, as the follow-up period mostly ended with the second CMR. When available, the event rates were too low to draw any conclusions (Online Resource). Recently, some studies suggested to define LVR using a prognostic-based approach. Reindl et al. [48] reported that

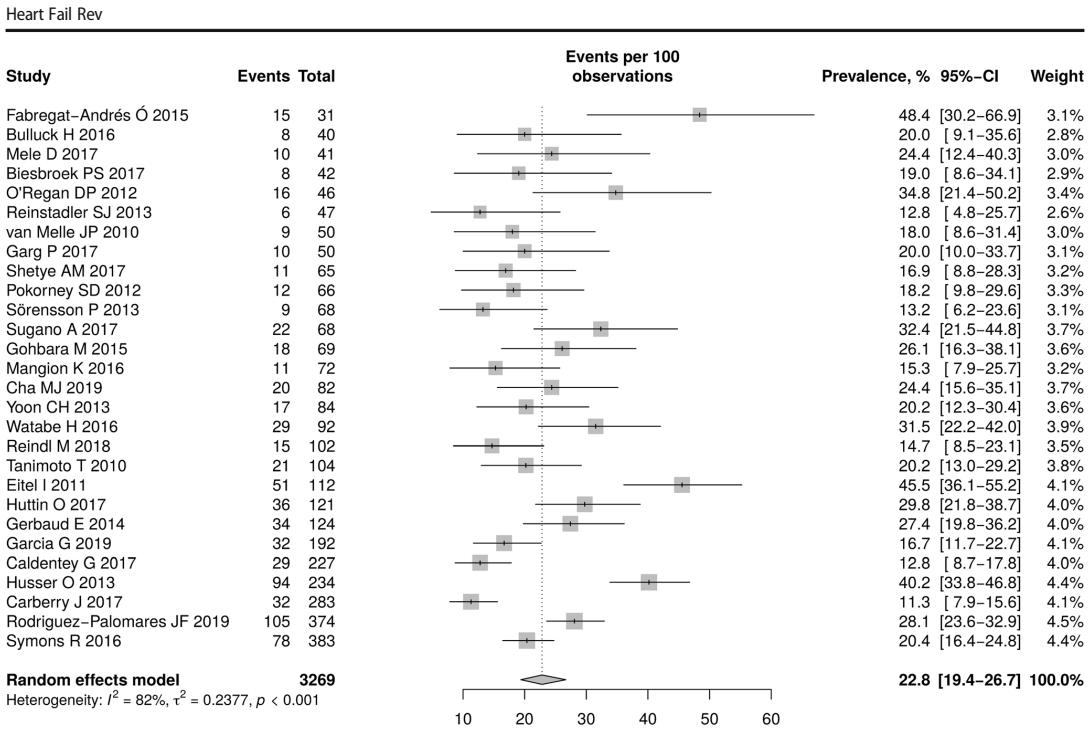


Fig. 3 Meta-analysis of the prevalence of left ventricular remodelling among patients presenting with STEMI using CMR imaging. The square area is proportional to the inverse variance of the estimate

a 10% increase in EDV showed the strongest association with clinical outcomes in 224 patients with STEMI. However, the event-rate was low (13 patients [6%] after a 24-month follow-up). Two recent studies concluded that the follow-up CMR imaging did not add prognostic information upon baseline data, including baseline CMR imaging [34, 49]. Rodriguez-Palomares et al. [34] compiled 374 STEMI patients who had both a baseline and a 6-month CMR imaging. Forty-nine patients presented with the primary endpoint (cardiovascular mortality, hospitalization for HF or ventricular arrhythmia) during a mean follow-up of 72.9 ± 42.8 months. The authors stated that adding remodelling criteria defined as a > 15% increase in EDV and a > 3% decrease in LVEF did not add prognostic value to a model including only baseline CMR data. However, the population of the latter study differ significantly from actual routine STEMI patients because a subset of patients was included > 15 years ago. Two-thirds of patients had percutaneous coronary intervention < 12 h, only 82% were treated with beta-blockers and < 80% with renin-angiotensin-aldosterone system (RAAS) inhibitors at follow-up. Furthermore, the LVEF cut-off suffers from reproducibility issues as it has been demonstrated that the detection of a 3% change in LVEF would require 14 normal subjects or 7 HF patients using CMR imaging [47]. Masci et al. [49] included 492 STEMI patients with both a baseline and a follow-up CMR (median, 4.8 months). Eighty-four patients presented with the primary endpoint (composite of all-death and HF hospitalization), during a mean follow-up of 8.3 years. Both a 20% increase in EDV and a 15% increase in ESV failed to independently predict the primary endpoint. Furthermore, early- (baseline CMR only), deferred- (follow-up CMR only) or repeated-CMR strategies were equivalent for outcome prediction. These results may be interpreted with caution. First, these studies retrospectively compiled databases of previous studies including highly selected patients. Second, the imaging session was performed 6.2 ± 2.6 days [34] and 3 to 6 days (IQR) [49] following STEMI. The baseline CMR imaging is able to quantify infarct size and microvascular obstruction and to improve risk stratification in addition to clinical parameters [50, 51]. Many studies have demonstrated a correlation between infarct size at baseline and LVR, LVEF and infarct size during follow-up. Infarct size is independent of LV volumes, function and loading. However, the assessment of infarct size using CMR has some pitfalls. Infarct size may be overestimated because of inflammatory reactions and it has been demonstrated that there is significant heterogeneity in its assessment using CMR [52, 53]. Also, reversible LV dysfunction

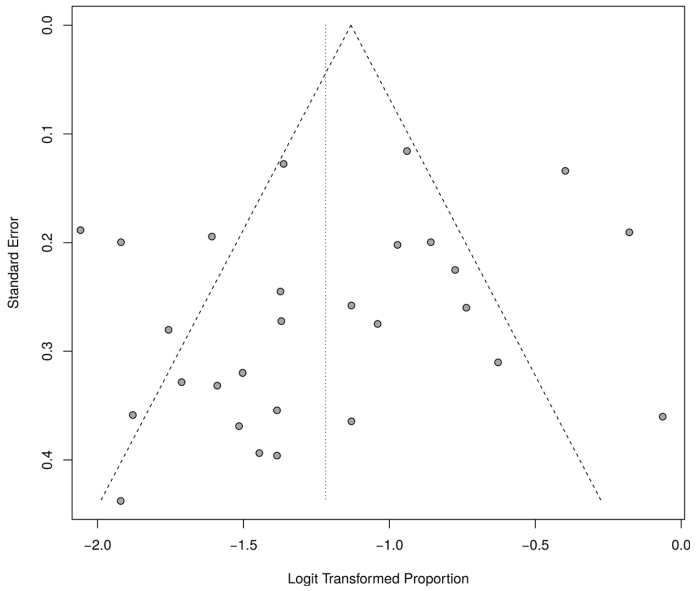


Fig. 4 Funnel plot of standard error by logit transformed proportion of LVR to evaluate publication bias for the prevalence of LVR following STEMI. Egger test: $p = 0.17$

and dilation may be consequences of myocardial stunning. Hence, the first CMR imaging assessing LV volumes and function as well as infarct size may not be performed during the initial week following STEMI, before the end of the stunning time frame and the relative regression of inflammation and oedema [52]. Third, recent data support the usefulness of anti-remodelling drugs following STEMI. A pooled analysis of two large randomized trials demonstrated the benefit of mineralocorticoid receptor antagonists in STEMI (reduction in death and resuscitated sudden death), regardless the existence of heart failure in 2241 patients [54], although LV volumes were not serially assessed.

The definition of LVR states that several mechanisms result in changes in the size, shape and function of the heart and vasculature [1]. The assessment of a single LV volume (either EDV or ESV) does not provide data about LV function. Several CMR studies used a composite definition of LVR, using both EDV and ESV or both EDV and LVEF (Table 1). Bulluck et al. combined the percentage increase in EDV and the percentage increase in ESV for defining different patterns of LVR [55]. A significant increase in EDV may not have the same value whether it is associated with no change in ESV and an increase in LVEF or with a significant increase in ESV with no change or a decrease in LVEF. Previous studies did not evaluate the prognostic value of this combined approach (size, shape and function) for defining LVR. Finally, the present study shows that between-study heterogeneity is low among studies using a follow-up CMR imaging < 6 months and a cut-off value of 15% for ESV and 20% for EDV. Recently, both intra-observer and inter-observer variability were measured in reperfused STEMI patients [55]. Because the minimal detectable change for both EDV and ESV using CMR imaging in STEMI patients was 12% [55], a combine cut-off value of a 12 to 15% increase in ESV and a 12 to 20% increase in EDV might be considered as the most adequate definition of the pattern of adverse LVR following STEMI.

Timing of the follow-up CMR imaging

The timing of the second assessment of LV volumes is also a matter of debate. Identifying LVR early after STEMI may have clinical implications leading to actions to prevent its detrimental effects. However, serial CMR imaging after STEMI showed that LV volumes remained stable during the first month and that ESV decreased significantly at 3 months, leading to a significant improvement in LVEF between 1 and 3 months [56]. Hence, it seems reasonable to perform the follow-up CMR 3 months after STEMI to be able to detect early LVR and potentially allowing the uptitration of antiremodelling drugs.

Limitations

Our study has some limitations that should be acknowledged. First, we chose to include only articles published after 2010 as in older studies the standard of care for STEMI was different. Second, we only included studies using CMR and not

echocardiography. Third, we did not discuss the even more controversial definition of reverse remodelling following STEMI. Fourth, we did not analyse the use of medications or the effect of therapies in patients included as part of randomized trials. Fifth, we did not study the characteristics of the patients included in the CMR studies or analyse individual patient data. Sixth, the studies we included (both randomized controlled trials and cohort studies) demonstrated significant biases such as poor representativeness of all-comers STEMI patients, lack of blinding or small sample size. At last, CMR imaging was performed using the same scanner at baseline and at follow-up. However, it has been demonstrated that the effect of using different scanners did not affect significantly the data reproducibility, despite the variations in radio frequency coil architecture, sequences and software analysis used [57].

Conclusions

LVR definition following STEMI using CMR imaging was highly variable among the studies, which included highly selected patients. Overall, the pooled LVR prevalence was 22.8%, 95% CI [19.4–26.7%]. The most frequent LVR criterion was a 20% increase in EDV or EDVI or a 15% increase in ESV or ESVI. According to the minimal detectable change for both EDV and ESV using CMR imaging in STEMI patients of 12%, a composite cut-off value of a 12 to 15% increase in ESV and a 12 to 20% increase in EDV using a follow-up CMR imaging 3 months after STEMI might be proposed as a consensual cut-off for defining adverse LVR for future CMR studies. There is a need for large-sized, prospective, adequately designed studies with serial CMR imaging and long-term follow-up in unselected patients in order to clarify the optimal LVR definition, the timing of its assessment, its impact on outcomes and strategies to prevent, stabilize or reverse its detrimental effects.

Authors' contributions Damien Legallois extracted and analysed the data and drafted the manuscript. Amir Hodzic extracted the data. Joachim Alexandre, Charles Dolladille, Alain Manrique, Vincent Roule and Paul Milliez participated in data analysis and revised the manuscript for important intellectual content. Eric Saloux and Fabien Labombarda revised the manuscript. Farzin Beygui designed the study, analysed the data and revised the manuscript for important intellectual content.

Data availability All data generated or analysed during this study are included in this published article and its supplementary information files (Online Resource).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval Not applicable.

Consent to participate Not applicable.

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Étude REMOD-TEP

Évaluation de la fonction endothéliale coronaire et de la fibrose myocardique en Tomographie par Émission de Positons (TEP) au décours d'un syndrome coronarien aigu avec sus-décalage du segment ST : relation avec le REMODelage ventriculaire gauche. Investigateur coordinateur : Dr Damien Legallois.

Rationnel

Le phénotype de RVG concerne l'ensemble du myocarde après un SCA (Figure 1). La zone "remote" joue un rôle dans ce RVG post-infarctus (données précliniques) et pourrait même être une cible thérapeutique potentielle [63]. Le rôle de la zone saine sur le RVG est mal connu chez l'homme et l'essentiel de la littérature sur le sujet est récent et postérieur à la date de début de ce travail de thèse [64–66].

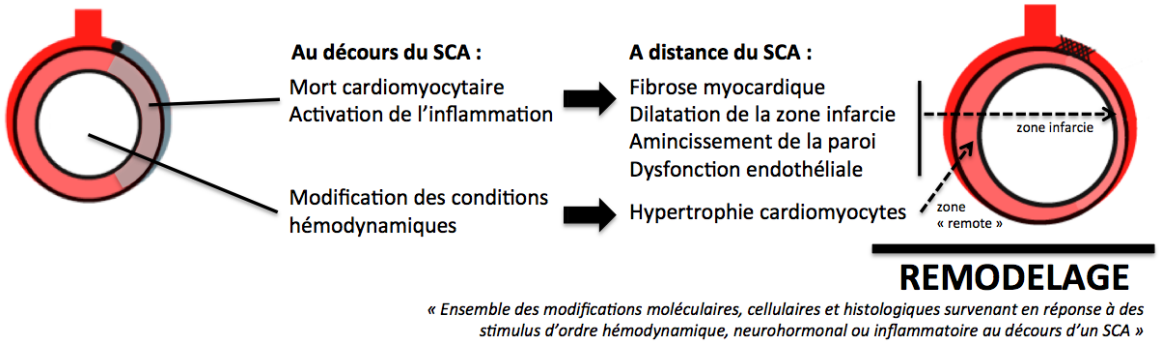

Fig. 1 Le remodelage ventriculaire gauche a pour conséquences une augmentation des volumes ventriculaires, une diminution de la fonction cardiaque et aboutit à l'apparition de signes fonctionnels et cliniques d'IC. La zone remote – controlatérale à l'occlusion coronaire – subit aussi des modifications tissulaires, et donc, un remodelage.

Présentation de l'étude

REMOD-TEP est une étude prospective monocentrique, incluant une partie des patients du registre RESIST pour lesquels les données biologiques et d'imagerie sont plus exhaustives. L'objectif est d'inclure 30 patients pris en charge pour un premier STEMI, ayant une atteinte monotronculaire à la coronarographie et revascularisés à la phase aiguë. Ces patients ont une tomographie par émission de positons à l'eau marquée et test au froid à 3 mois de l'épisode, afin de quantifier dans la zone de l'infarctus et dans la zone remote non directement concernée par l'occlusion coronaire :

- la fonction endothéliale coronaire de façon non invasive. En effet, l'eau marquée est un traceur librement diffusible, permettant de quantifier précisément le débit coronaire local. L'utilisation conjointe d'un test au froid par application d'un coussin glacé sur les jambes permet d'induire une vasodilatation coronaire en cas de fonction endothéliale normale. En cas d'anomalie de la fonction endothéliale, la réponse est atténuée, voire inversée avec mise en évidence d'une vasoconstriction paradoxale.
- la fraction de tissu perfusable, reflet de la fibrose myocardique

Modalités de réalisation de l'examen TEP

Les modalités de l'examen sont similaires à celles de notre précédente étude chez le patient ayant une cardiopathie dilatée non ischémique (Figure 2) [67]. Brièvement, les examens sont réalisés au GIP Cycéron, à Caen. La faible demi-vie de l'oxygène-15 (2,04 minutes) impose que la production d'oxygène-15 (par un cyclotron), la synthèse de l'eau marquée, son administration au patient et l'imagerie TEP se déroule en moins de 10 minutes.

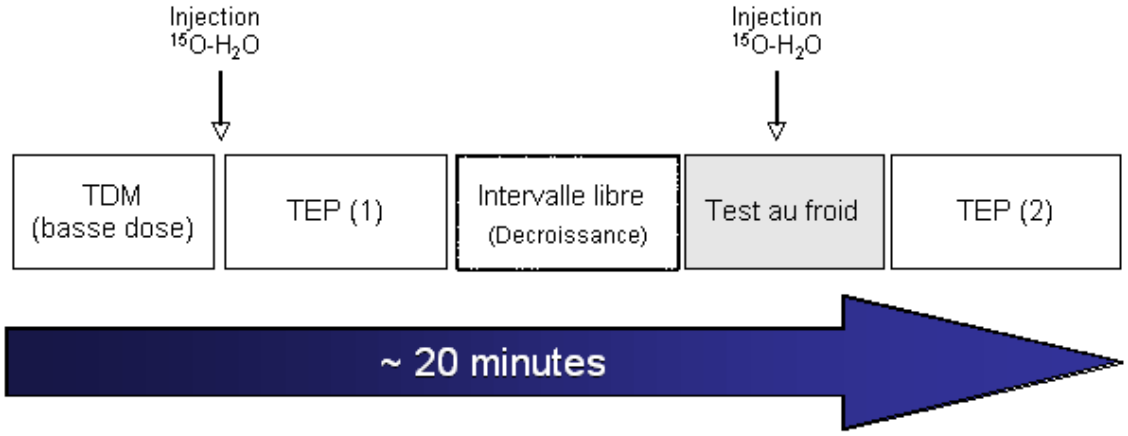

Fig. 2 **REMOD-TEP : modalités de réalisation de l'examen TEP.** TEP, Tomographie par Émission de Positons ; TDM, tomodensitométrie.

Financement du projet

Le budget a été évalué à 58660 euros. Cette étude a été financée (i) par l'appel à projet Emergence du GIRCI Nord-Ouest (octobre 2015) à hauteur de 40000 euros et, (ii) par la bourse "Les syndromes coronariens aigus" de la Société Française de Cardiologie (décembre 2015), pour un montant de 20000 euros.

Réglementaire

- Autorisation d'essai clinique par l'Agence Nationale de Sécurité du Médicament et des produits de santé, le 01 décembre 2015
- Comité de Protection des Personnes Nord-Ouest III, le 09 janvier 2016
- Autorisation de lancement d'étude (CHU de Caen), le 01 mars 2016
- Enregistrement clinicaltrials.gov : NCT02789098
- Début des inclusions le 25 mai 2016

Déroulement de l'étude

La première inclusion a eu lieu le 13 octobre 2016. Le rythme des inclusions a ensuite pu continuer selon le rythme prédéfini. Ainsi, en mai 2017, dix patients – soit un tiers de l'effectif total initial attendu – avaient été inclus.

Malheureusement, une panne va conduire à l'arrêt de la production d'eau marquée durant le printemps 2017. Cette activité est toujours suspendue pour l'heure. Seuls les 4 premiers patients inclus ont pu terminer le protocole avec réalisation de l'examen TEP à 3 mois du SCA. Les 6 autres patients inclus n'ont pu avoir leur examen car la panne est survenue entre leur inclusion et l'imagerie prévue à 3 mois.

Relation entre le strain atrial gauche et le remodelage ventriculaire gauche

Dans le contexte de SCA, la dilatation de l'oreillette gauche (OG) est associée à une augmentation des pressions de remplissage ventriculaire gauche (PRVG) et est un marqueur de mauvais pronostic (mortalité ou hospitalisation pour IC) [68, 69]. Cette étude vise à étudier le lien entre les paramètres de fonction atriale gauche et le RVG chez les patients de la cohorte RESIST pour lesquels nous disposons d'échocardiographie à la phase initiale du STEMI et au cours du suivi.

La méthode utilisée est celle de la mesure du strain de l'OG par speckle tracking [70]. Brièvement, cette technique consiste à suivre la déformation locale du myocarde en analysant le déplacement de marqueurs acoustiques naturels au sein de la paroi myocardique. Il est commun d'étudier 3 composantes au strain de l'OG (Figure 3). Tout d'abord la fonction réservoir, dépendante de la relaxation et de la compliance atriale et de la descente du plancher basal du VG durant la systole ventriculaire. Celle-ci est calculée en mesurant la différence des valeurs de strain entre la fin de la diastole et la réouverture mitrale (et comprend donc les phases de contraction isovolumique, d'éjection ventriculaire et de relaxation isovolumique). La fonction conduit est mesurée entre l'ouverture de la valve mitrale et le début de la contraction de l'OG et est dépendante de la fonction diastolique du VG et notamment de la succion exercée par ce dernier au moment de sa détorsion, en début de diastole. La dernière composante est la composante contractile, fonction de la contractilité atriale gauche, de la compliance du VG et des PRVG. Elle se mesure entre le début de la contraction atriale et la fermeture de la valve mitrale, en fin de diastole.

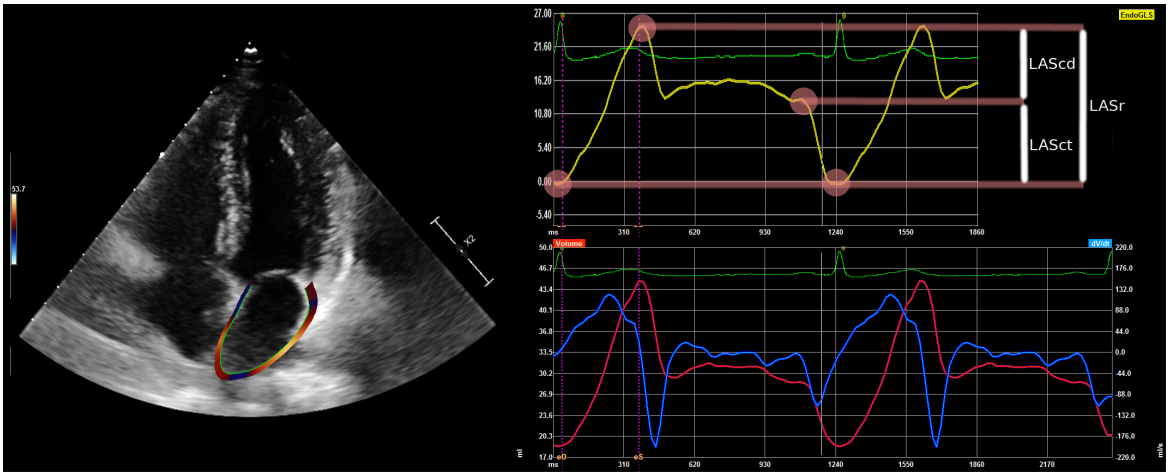

Fig. 3 **Mesure du strain de l'oreillette gauche en échocardiographie.** Il est possible d'individualiser la fonction réservoir (LASr), mesurée entre la fin de la diastole et l'ouverture de la valve mitrale, la fonction conduit (LAScd) entre l'ouverture de la valve mitrale et le début de la contraction de l'OG et la fonction contractile (LASct), entre le début de la contraction atriale et la fermeture de valve mitrale.

Nous avons ainsi mesuré les fonctions réservoir, conduit et pompe de l'OG à la phase aiguë du STEMI et avons étudié leurs relations avec le RVG au cours du suivi à 6 mois dans une population de 121 patients. Les données échocardiographiques ont été traitées suivant les recommandations et documents de consensus [71, 72], notamment en ce qui concerne l'évaluation du strain de l'OG [73].

La comparaison des patients ayant présenté un RVG (défini comme une augmentation d'au moins 20% du volume télédiastolique, mesuré en échocardiographie 3D) avec ceux n'ayant pas présenté de remodelage montre une meilleure fonction pompe dans ce dernier groupe. Cette association persiste après ajustement sur les volumes ventriculaires initiaux. En revanche, il n'y a pas de corrélation entre les valeurs des composantes de strain réservoir ou conduit et l'évolution des volumes ventriculaires gauches au cours du suivi.

Legallois D, Hodzic A, Milliez P, Manrique A, Saloux E, Beygui F.

Left atrial strain quantified after myocardial infarction is associated with ventricular remodeling.

Soumis à American Journal of Cardiology.

Le poster accepté à l'ESC 2020 est reproduit, page 190.

Left atrial strain quantified after myocardial infarction is associated with ventricular remodeling

Short title: Atrial strain and remodeling after AMI

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Total word count: 3036 words

ABSTRACT

Background. Left ventricular remodeling (LVR) is common and associated with adverse outcome after ST-elevation myocardial infarction (STEMI). We aimed to investigate the association between left atrial (LA) mechanical function using speckle tracking imaging and LVR at follow-up in STEMI patients.

Methods. Baseline 3D thoracic echocardiograms were performed within 48 hours following admission and 6 months after STEMI. A >20% increase in the left ventricular end-diastolic volume compared to baseline at 6 months of follow-up was defined as LVR. LA global longitudinal strain was evaluated for the reservoir, conduit, and contraction (LASct) phases.

Results. A total of 121 patients without clinical heart failure were prospectively included (age 58.3±12.5 years, male 98 (81%)). Baseline and follow-up left ventricular ejection fraction (LVEF) were 46.8% [41.0, 52.9] and 52.1% [45.8, 57.0] respectively ($p<0.001$). Compared to other patients, those with LVR had significantly lower values of LASct at baseline (-7.4% [-10.1, -6.5] vs. -9.9% [-12.8, -8.1], $p<0.01$), both on univariate and baseline LV volumes-adjusted analyses. Baseline LA strain for reservoir and conduit phases were not associated with significant LVR at follow-up.

Conclusions. Baseline LASct may help identifying patients without heart failure early after STEMI who are at higher risk of further LVR and subsequent heart failure and who may benefit from more intensive management.

KEYWORDS: ST-elevation myocardial infarction, left ventricular remodeling, left atrial strain

INTRODUCTION

Despite major advances in coronary revascularization for ST-elevation myocardial infarction (STEMI), left ventricular remodeling (LVR) associated with mortality and heart failure (HF) remains common (1). LVR is the consequence of cellular and histological modifications (2), that are induced by deleterious adaptive mechanism involving the infarcted tissue and remote myocardium (3).

Larger left atrial (LA) volume is associated with chronic increased left ventricular (LV) filling pressure and has been described as a predictor of mortality and hospitalization for HF in patients with acute myocardial infarction (AMI) (4,5). However, there are controversial data about the correlation between LA volume and LVR (6,7). Therefore, the assessment of LA mechanical function may have additional prognostic value when compared to conventional echocardiographic measurements (8,9). Direct evaluation of atrial myocardial function using speckle-tracking imaging allows the assessment of active myocardial deformation as a marker of LA function (10,11).

The objective of our study was to investigate the association between LA mechanical function assessed early after STEMI and LVR at follow-up.

MATERIALS AND METHODS

Patient selection and data collection

This study was a prospective, observational study that included consecutive patients admitted for STEMI and successfully treated with either primary percutaneous coronary intervention (pPCI) or fibrinolysis followed by PCI, from June 2015 to October 2018.

Inclusion criteria were: age≥18 years, ischaemic symptoms <12 hours, ECG with ST-segment elevation. Criteria for exclusion were unsuccessful revascularization (residual stenosis>30% in the culprit lesion and/or thombolysis in myocardial infarction flow<3), clinical signs of HF as defined by Killip class ≥II, atrial fibrillation or non-cardiac-related conditions with estimated life expectancy

<12 months and follow-up planned in another center. Informed consent was obtained from all patients. Patients were not involved in setting the research question as echocardiography after STEMI is part of routine clinical practice. The study complied with the Declaration of Helsinki and was approved by the local ethics committee.

Echocardiography

All subjects had 3D transthoracic echocardiogram within 48 hours after admission and at 6 months, using an EPIQ 7G (Phillips Healthcare, Best, Netherlands) equipped with a 1 to 5-MHz transthoracic matrix array transducer (XMATRIX X5-1). Two-dimensional grayscale harmonic images were acquired in the apical plane and in the short axis plane at a frame rate above 50 frames/sec. A 3D full volume was acquired from the apical view with minimum depth to optimize the frame rate. LV end-diastolic (EDV) and end-systolic volumes (ESV) were measured from the resulting three-dimensional volumes and were normalized by body surface area. Color Doppler and tissue Doppler acquisitions were acquired in concordance with the current ASE recommendations (12). Analysis of echocardiographic images was performed offline by two independent observers using dedicated softwares (Intellispace Cardiovascular software [Philips Healthcare, Best, Netherlands] and TomTec software [TomTec Imaging Systems GmbH, Unterschlessheim, Germany]). Diastolic function was assessed as stated in the current ASE/EACVI guidelines (13). LVR at follow-up was defined as a >20% increase in the EDV compared to baseline (14). Depending on the presence or absence of LVR at follow-up, patients were divided into two groups: LV remodeling (LVR+) and no LV remodeling (LVR-).

Analysis of LA volume and function

LA volume was calculated according to the biplane Simpson method. Left atrial emptying fraction (LAEF) was calculated as: (LA volume max-LA volume min)/LA volume max×100 (%). LA

myocardial deformation imaging was assessed following recently published consensus document (10). LA strain was measured using a non-foreshortened apical four chamber view of the left atrium (15), recorded with a frame rate of >40 fps. The user placed two points on the mitral annulus and a third point in the endocardium of the roof of the LA. The software automatically delineated the endocardial contour but could be manually adjusted by the user. The patient was retrospectively excluded if tracking was of poor quality. LA global longitudinal strain was reported separately for the reservoir (inflow during ventricular systole), conduit (passive emptying during ventricular relaxation and diastasis), and contraction phase (active emptying): (i) strain during reservoir phase (LASr) was measured by the difference of strain values at mitral valve opening and at ventricular end-diastole, (ii) strain during conduit phase (LAScd) was measured by the difference of strain values at the onset of atrial contraction and at mitral valve opening, and (iii) strain during contraction phase (LASct) was measured as the difference of strain values at ventricular end-diastole and at the onset of atrial contraction (Figure 1) (10). The time reference to define the zero-baseline for LA strain curves was set to ventricular end-diastole.

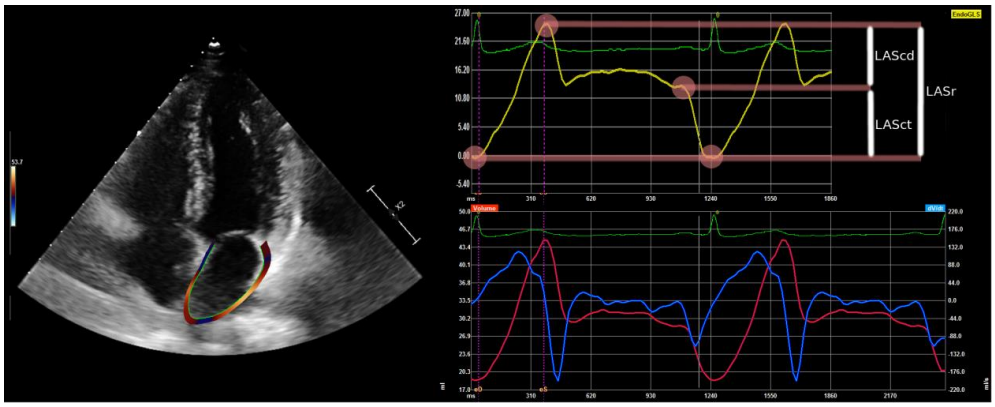

Figure 1. Left atrial strain assessment. Zero strain reference is set at end-diastole. Strain during reservoir phase (LASr) is calculated as the difference between onset of filling and end-diastole, strain during conduit phase (LAScd) is calculated as the difference between onset of atrial contraction and onset of filling and strain during contraction phase (LASct) is calculated as the difference between end-diastole and onset of atrial filling.

Statistical analysis

Continuous data are presented as mean±SD or median [IQR] and categorical data are presented as frequencies and percentages. Differences in characteristics between patient groups were evaluated using the paired Student or Wilcoxon rank sum and $\chi 2$ tests. Un-adjusted and, adjusted on baseline EDV or ESV linear and logistic regression models were carried out to assess the relationship between relative differences in LV volumes as a continuous variable and LVR as a binary variable and, baseline echocardiographic parameters. All statistical analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were 2-sided and used a significance threshold of $p<0.05$.

RESULTS

Study population

Among the 160 patients with complete echocardiogram at baseline, 2 patients died during follow-up and 27 did not attend follow-up echocardiogram (Figure 2). Ten patients were retrospectively

excluded because of poor quality of imaging. Baseline characteristics of the remaining 121 patients are depicted in Table 1. Mean age was 58.3±12.5 years and 98 (81%) were men. The median time between symptom onset to revascularization was 3.8 hours [2.7, 5.2].

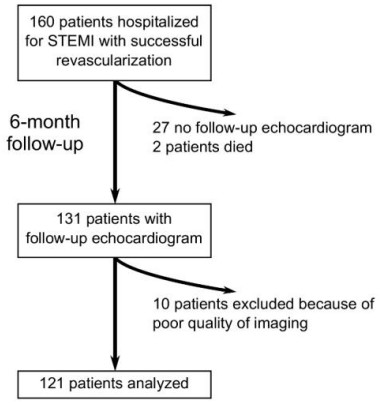

Figure 2. Flow chart.

Left ventricular volumes, function and filling

Baseline left ventricular ejection fraction (LVEF) was 46.8% [41.0, 52.9] and significantly improved to 52.1% [45.8, 57.0] at follow-up, ($p<0.001$, Table 1). At follow-up, there was a significant increase of EDV index (from 56.5 mL/m^2 [47.7, 66.4] to 59.1 mL/m^2 [49.3, 72.4], $p<0.01$) without significant change in ESV index (from 30.3 mL/m^2 [24.1, 36.1] to 27.5 mL/m^2 [20.7, 39.8], $p=0.92$). Median deceleration time of the early mitral inflow was 200 ms [170, 235], E/A ratio was 0.96 [0.84, 1.20] and median E/e' ratio was 8.1 [7.1, 9.9]. Thirty-four patients had LVR at follow-up (28.1%). At follow-up, the improvement of LVEF in patients without LVR (54.0% [48.1, 59.4] vs. 48.2% [41.7, 53.5], $p<0.001$) was driven by a decrease in ESV (24.2 mL/m^2 [19.7, 30.9] vs. 28.8 mL/m^2 [24.4, 36.2], $p<0.001$) without significant change regarding EDV (Table 1). Conversely, both EDV and ESV increased significantly in the LVR+ group (81.4 mL/m^2 [65.3, 92.4] vs. 54.5 mL/m^2 [46.6, 62.9],

p<0.001 and 42.8 mL/m^2 [32.8, 52.9] vs. 31.4 mL/m^2 [24.2, 35.8], p<0.001) without change regarding LVEF.

Relationship between LVR and Left atrial strain volume and function

At baseline, only LASct was significantly different between groups (-7.4% [-10.1, -6.5] in the LVR+ group vs. -9.9% [-12.8, -8.1] in patients without LVR at follow-up (p<0.01, Table 1), demonstrating a better LA pump function at baseline in the latter population. The relationship between the changes in LV volumes and LA pump function is depicted in Figure 3. No other differences were found between groups with respect to baseline LA volume and function, including LASr and LAScd (21.5% [17.0, 24.7] vs. 21.0% [16.8, 26.1], p=0.94 and -12.6% [-15.0, -9.5] vs. -11.4% [-14.5, -8.3], p=0.16, in the LVR+ and LVR- groups, respectively). Adjusted analyses on baseline EDV, ESV and LVEF showed that LASct was associated with LVR independent of baseline LV volumes (Table 2). Sensitivity analysis demonstrated same results (data not shown).

	Overall (n=121)	LVR+ (n=34)	LVR- (n=87)	p value
Age, years	58.3±12.5	57.8±12.9	58.6±12.5	0.76
Gender, male	98 (81.0%)	30 (88.2%)	68 (78.2%)	0.32
Hypertension	43 (35.5%)	9 (26.5%)	34 (39.1%)	0.28
Diabetes mellitus	18 (14.9%)	5 (14.7%)	13 (14.9%)	1
Hypercholesterolemia	51 (42.1%)	16 (47.1%)	35 (40.2%)	0.64
Current smoking	82 (67.8%)	23 (67.6%)	59 (67.8%)	1
Body Mass Index (kg/m^2)	26.0 [24.2, 28.8]	26.0 [24.6, 27.2]	25.9 [23.8, 29.1]	0.76
Symptoms-to-ballon time, hours	3.8 [2.7, 5.2]	3.9 [3.3, 6.1]	3.8 [2.6, 5.2]	0.46
Echocardiography at baseline				
EDV, mL/m^2	56.5 [47.7, 66.4]	54.5 [46.6, 62.9]	58.0 [48.2, 67.6]	0.32
ESV, mL/m^2	30.3 [24.1, 36.1]	31.4 [24.2, 35.8]	28.8 [24.4, 36.2]	0.89
LVEF, %	46.8 [41.0, 52.9]	44.5 [39.1, 50.9]	48.2 [41.7, 53.5]	0.10
E/A ratio	0.96 [0.84, 1.20]	1.00 [0.89, 1.18]	0.96 [0.78, 1.19]	0.27
Deceleration time of early mitral inflow, ms	200 [170, 235]	180 [163, 214]	200 [170, 240]	0.08
Mean E/e' ratio	8.1 [7.1, 9.9]	8.4 [7.0, 10.8]	8.0 [7.1, 9.6]	0.54
Left atrial volume, mL/m^2	32.1 [26.5, 38.9]	32.9 [27.6, 39.6]	32.0 [26.2, 38.5]	0.51
LAEF, %	51.7±10.0	51.2±9.9	51.9±10.1	0.75
LASr, %	21.4 [16.8, 25.8]	21.5 [17.0, 24.7]	21.0 [16.8, 26.1]	0.94
LAScd, %	-12.0 [-14.5, -8.8]	-12.6 [-15.0, -9.5]	-11.4 [-14.5, -8.3]	0.16
LASct, %	-9.4 [-12.3, -7.1]	-7.4 [-10.1, -6.5]	-9.9 [-12.8, -8.1]	<0.01
Echocardiography at follow-up				
EDV, mL/m^2	59.1 [49.3, 72.4]†	81.4 [65.3, 92.4]‡	54.2 [47.0, 67.1]	<0.001
ESV, mL/m^2	27.5 [20.7, 39.8]	42.8 [32.8, 52.9]‡	24.2 [19.7, 30.9]‡	<0.001
LVEF, %	52.1 [45.8, 57.0]‡	47.2 [39.3, 53.6]	54.0 [48.1, 59.4]‡	0.001

Table 1. Baseline characteristics and echocardiographic data according to LVR status. A: peak velocity of atrial diastolic filling, E: peak velocity of early diastolic filling, e': early mitral annular velocity, EDV: end-diastolic volume, ESV: end-systolic volume, LAEF: LA emptying fraction, LAScd: strain during conduit phase, LASct: strain during contraction phase, LASr: strain during reservoir phase, LVEF: LV ejection fraction, and STEMI: ST-elevation myocardial infarction. †p<0.01 and ‡p<0.001 vs. baseline.

			EDV-adjusted model		ESV-adjusted model		EF-adjusted model	
	OR, [95%CI]	Un-adjusted p.value	Adjusted OR, [95%CI]	Adjusted p.value	Adjusted OR, [95%CI]	Adjusted p.value	Adjusted OR, [95%CI]	Adjusted p.value
DT, per 10 ms	0.92 [0.85, 1.00]	0.0495	0.92 [0.85, 1.00]	0.07	0.92 [0.85, 1.00]	0.049	0.93 [0.86, 1.01]	0.07
LASr, %	0.99 [0.94, 1.04]	0.63	0.98 [0.93, 1.04]	0.58	0.99 [0.93, 1.04]	0.63	1.00 [0.94, 1.06]	0.99
LAScd, %	0.96 [0.90, 1.03]	0.23	0.96 [0.90, 1.03]	0.26	0.96 [0.90, 1.02]	0.22	0.94 [0.88, 1.01]	0.22
LASct, %	1.19 [1.05, 1.34]	<0.01	1.19 [1.05, 1.34]	<0.01	1.19 [1.05, 1.34]	<0.01	1.17 [1.04, 1.33]	0.02

Table 2. Association between LA parameters at baseline and LVR at follow-up. Univariate and bivariate analysis (adjusted for baseline LV volumes). DT: deceleration time of early mitral inflow, EDV: end-diastolic volume, EF: ejection fraction, ESV: end-systolic volume, LAScd: strain during conduit phase, LASct: strain during contraction phase, LASr: strain during reservoir phase.

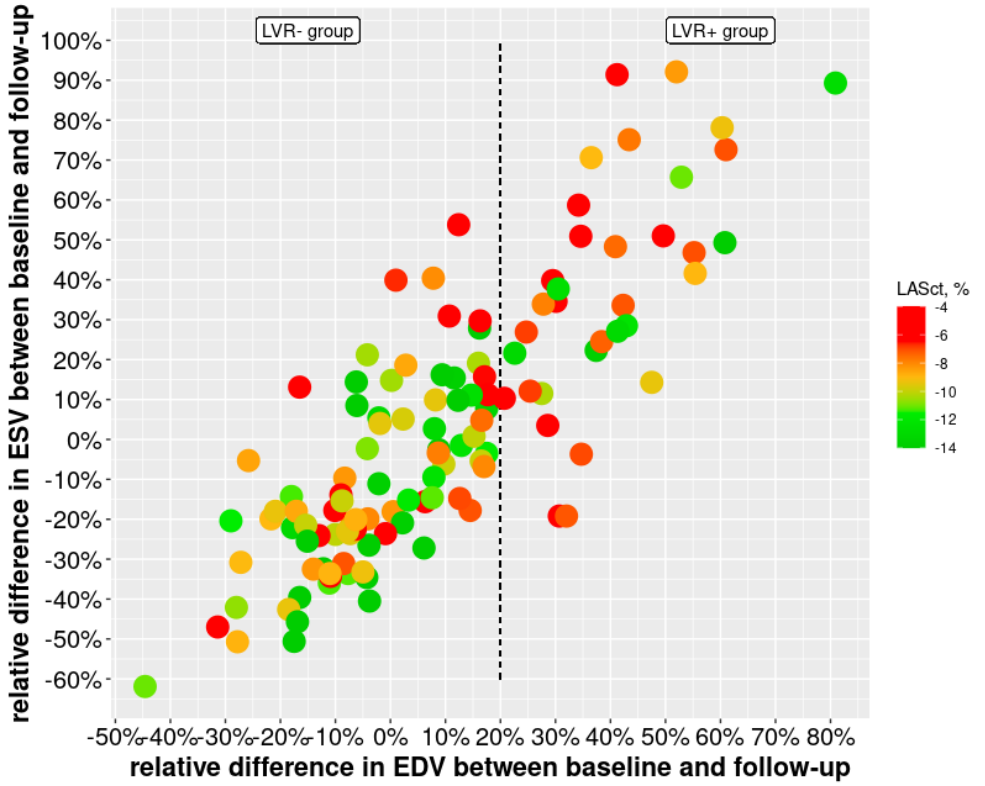

Figure 3. Relationship between left atrial strain during contraction phase (LASct) and LVR, defined as a >20% increase in the EDV compared to baseline. EDV: end-diastolic volume, ESV: end-systolic volume. LASct is expressed as %.

DISCUSSION

This study shows that baseline LA mechanical function using LASct assessment is independently associated with LVR at follow-up in STEMI patients. Close physiological interactions link LA and LV functions during cardiac cycle. The LA is a blood reservoir during LV systole. This function depends on both LA relaxation and compliance (16) and, LV systolic function through the descent of the LV base (17,18). During early diastole, LA and LV are directly connected and coupled. LAScd is reliant on LV diastolic function, including both the suction force dependent on LV relaxation and LV chamber stiffness (19,20). LA also acts as an active pump during late LV diastole. The latter LA booster function (LASct) is based on intrinsic LA contractility, LV compliance and LV end-diastolic pressure (LVEDP), as LA preload reserve decreases when LV filling pressures increase (11).

Altered LA function has been described in AMI (16,21). The aforementioned interactions between LA and LV are more complex after AMI where a preserved LASr can withstand the impact of the increased LA pressure due to LV dysfunction and maintain an adequate LV filling (22). A low LASr leads to impaired LV diastolic filling and reduced LV stroke volume (23,24). Both LA reservoir dysfunction and elevated LVEDP contribute to LA enlargement especially when combined. LA pump function contributes to up to 30% of total LV stroke volume in normal individuals and its contribution to LV filling and stroke volume is higher in patients with AMI (25). As reduced LVEF has been described as an independent determinant of impaired LA pump function (26), post-STEMI altered LVEF may lead to reduced LASct. LA passive ejection is altered in patients with AMI, which may be compensated by an increase in active contractile function of the LA (27). As a result, LV stroke volume can be maintained despite LV dysfunction (28). However, such conditions are associated with LA pressure overload, leading to both LA enlargement and dysfunction.

This study demonstrated that baseline LASct is associated with the changes of LV volumes at follow-up in a STEMI population with successful reperfusion and without clinical signs of HF. Few studies have assessed the relationship between LA function and the change of LV volumes and function after STEMI. A prior study assessing LA and LV functions within 48 hours and 12 months after admission

for AMI (22) showed that ESV and EDV decreased significantly, resulting in an increase in LVEF, regardless of the existence of LA remodeling. However, the relationship between LA strain at baseline and the changes of LV volumes and function during follow-up were not described. In our study, the association between low values of LASct and LVR may be a consequence of the aforementioned interactions between LV and LA. Reduced LASct may be an early sub-clinical and sub-anatomic marker of more extensive myocardial damage leading to reduced LV compliance and increased LVEDP. Such conditions as well as the subsequent modified interactions between LA booster function and LV function (29) may initiate the deleterious adaptive mechanical and neurohormonal responses (30) which ultimately leads to LVR. It has been described that reduced LVEF is an independent determinant of impaired LA pump function (26). As a consequence, it could be hypothesized that LV systolic dysfunction and LA pump function impairment may worsen each other in the setting of AMI. However, the present study argued that LA impairment may be the primary driver as we showed that (i) LASct was associated to LVR, independently of baseline LV volumes and, (ii) LA mechanical function impairment precedes LVR.

The present study has several limitations. The population is highly selected including only patients with successful myocardial reperfusion and revascularization, without HF and who had complete 3D-transthoracic echocardiogram at 2 timepoints. The measurement of LA strain is software dependent and our results may not be generalized to other softwares. Finally, as in all cohort studies the cause-effect relationship may only be speculative and the impact of known or unknown covariables not analyzed in the present study on the LV remodeling remains unassessed.

CONCLUSIONS

Our study showed that after STEMI, in patients with successful myocardial reperfusion and no clinical sign of HF, the contractile component of baseline LA strain was significantly associated with dynamic increase of EDV, indicating LVR. These findings suggest that there is a relationship between

LA function, LV function and adverse LVR after STEMI. Low values of LASct at baseline may be a sensitive sub-clinical and sub-anatomic marker of the extent of LV damage, helpful for identifying a subgroup of patients at higher risk of further LVR and HF.

Competing Interests statement

D. Legallois reports grant from Pfizer and personal fees from Astrazeneca, outside the submitted work. F. Beygui reports grants and non-financial support from Medtronic, grants and non-financial support from Biosensor, personal fees and non-financial support from BMS, outside the submitted work. There is no other competing interest to declare.

Contributorship Statement

D. Legallois: Data curation, Formal analysis, Writing - original draft;

A. Hodzic: Investigation, Writing - review & editing

P. Milliez: Supervision, Writing - review & editing

A. Manrique: Writing - review & editing

E. Saloux: Investigation, Software, Writing - review & editing

F. Beygui: Conceptualization, Methodology, Supervision, Writing - review & editing and Validation

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Relation entre gradient de pression intraventriculaire diastolique et remodelage ventriculaire gauche

Un grand nombre d'études ont évalué la valeur prédictrice de paramètres échocardiographiques pour la survenue d'un RVG en post-infarctus. Il a ainsi été montré que le strain longitudinal global [55, 56, 74], le *wall motion score index* (évaluant la qualité de la contraction myocardique segmentaire) [56, 74, 75] et certains paramètres de rotation et de twist [57, 74, 75] sont associés à la survenue d'un RVG après SCA. En revanche, les données de la littérature sont moins formelles concernant la valeur prédictrice de l'évolution vers un RVG des paramètres de fonction diastolique comme le volume de l'OG [55, 76], le ratio $\frac{E}{A}$ [55, 75, 77], le temps de décélération de l'onde E [76, 77] ou encore le ratio $\frac{E}{e'}$ [75, 76].

Une dysfonction diastolique est retrouvée dans un grand nombre de pathologies cardiovasculaires, y compris l'infarctus du myocarde, et est associée à une augmentation du risque de réhospitalisation au décours de l'épisode initial [78, 79]. La dysfonction diastolique précède parfois l'altération de la fonction systolique VG, conduisant à des symptômes d'IC chez des patients ayant une FEVG préservée [80]. La détorsion du VG est un mécanisme important de la fonction diastolique [81]. La contraction du VG puis la phase de relaxation active qui suit en début de diastole a pour conséquence la création d'une hétérogénéité de pression au sein de ce dernier. Ce gradient de pression négatif entre la valve mitrale et l'apex du VG est responsable d'un phénomène de succion qui va aspirer le sang de l'OG vers le VG en début de diastole [82]. Il a été précédemment montré que ce gradient de pression est corrélé aux indices de relaxation VG [83, 84], en faisant ainsi un paramètre d'évaluation de la fonction diastolique. Il a été montré que l'échocardiographie en mode

TM avec Doppler couleur permet la quantification non invasive de ce gradient de pression intraventriculaire diastolique (GPIVD), aussi bien dans les études précliniques que chez l'homme [85, 80, 86]. De nombreuses situations sont susceptibles de diminuer le GPIVD parmi lesquelles l'ischémie myocardique [87]. En revanche, la relation entre GPIVD et RVG n'est pas connue. Nous avons donc étudié l'association entre le GPIVD à la phase aiguë de l'infarctus et la survenue d'un RVG lors du suivi chez des patients pris en charge pour un STEMI, traités par angioplastie coronaire et sans signe clinique d'IC.

Matériels et Méthodes

Sélection des patients

Cette étude est une étude prospective, observationnelle ayant inclus des patients consécutivement admis pour STEMI et traités soit par angioplastie primaire soit par fibrinolyse puis angioplastie coronaire, entre juin 2015 et octobre 2018. Les critères d'inclusion sont: âge$\geq$18 ans, douleur datant de moins de 12 heures, présence d'un sus-décalage du segment ST sur l'électrocardiogramme qualifiant. Les critères d'exclusion sont: revascularisation incomplète (persistance d'une sténose résiduelle $>$30% en regard de la lésion coupable et/ou score TIMI<3), signes cliniques d'IC définis par une classe Killip $\geq$II, fibrillation atriale, pathologie responsable d'une espérance de vie estimée à moins de 12 mois ou suivi planifié dans un autre établissement. Un consentement éclairé écrit a été recueilli pour tous les patients et le protocole a été approuvé par le Comité de Protection des Personnes Nord-Ouest III.

Échocardiographie

Une échocardiographie cardiaque 3D est réalisée chez tous les patients dans les 48 heures suivant l'admission et à 6 mois, au moyen d'un échocardiographe EPIQ 7G (Philips Healthcare, Best, Pays-Bas), équipé d'une sonde 1 à 5-MHz (XMATRIX X5-1). Les acquisitions sont réalisées en décubitus latéral gauche et en apnée, durant 3 cycles cardiaques. Le volume télédiastolique (VTD) et le volume télésystolique (VTS) VG sont mesurés à partir des acquisitions 3D et normalisés par la surface corporelle [88]. Le volume de l'OG est mesuré selon la méthode biplan en télésystole et est également normalisé à la surface corporelle. La fonction diastolique est mesurée selon les recommandations actuelles ASE/EACVI [72], comprenant la quantification de l'onde E et de l'onde A sur le flux Doppler transmitral, la mesure du pic de vitesse de l'anneau mitral (e') en doppler tissulaire (moyenne des pics en septal et en latéral). L'existence d'un RVG au cours du suivi est défini par une augmentation $\geq$20% du VTD par rapport à sa valeur initiale [89]. La quantification de ces paramètres sont réalisés au décours de l'examen, sur une station dédiée, par deux opérateurs indépendants, au moyen des logiciels Intellispace Cardiovascular [Philips Healthcare, Best, Pays-Bas], TomTec [TomTec Imaging Systems GmbH, Unterschlessheim, Allemagne] et un programme dédié au calcul du GPIVD développé dans Mathlab [version R2020a].

Quantification du gradient de pression intraventriculaire diastolique

Le flux à travers une valve mitrale normale peut être étudié par l'équation de Navier-Stokes pour les fluides incompressibles, la masse volumique du sang ne dépendant pas de la pression ou de la température dans les conditions d'acquisition [80]. La composante gravitationnelle peut être négligée, de même que la composante visqueuse, considérant que le flux observé en doppler couleur n'est pas au contact des parois valvulaires. Si on considère

ensuite l'analyse d'un flux le long de la ligne Doppler, on aboutit alors à l'équation d'Euler (équation 1) où P représente la pression, v la vitesse Doppler, s la coordonnée le long de l'axe TM, t le temps et ρ, la masse volumique du sang.

$$\frac{\partial P}{\partial s} = -\rho \left[\frac{\partial v}{\partial t} + v \frac{\partial v}{\partial s} \right] \tag{1}$$

L'intégration de cette équation fait apparaître plus clairement les deux composantes restantes à la variation de pression : la composante convective et la composante inertielle (respectivement en bleu et en rouge dans l'équation 2, équation de Bernoulli) [85]. La composante convective correspond à la perte de pression consécutive à l'augmentation de l'énergie cinétique quand le flux passe à travers un orifice. La composante inertielle correspond à la variation de pression nécessaire pour accélérer une masse de sang. Le GPIVD correspond à la somme de ces deux composantes.

$$P_{base} - P_{apex} = \frac{1}{2} \rho \left(v_{apex}^2 - v_{base}^2 \right) + \rho \int_{base}^{apex} \frac{\partial v}{\partial t} \partial s \tag{2}$$

Le flux mitral est enregistré en mode TM et Doppler couleur en vue apicale 4 cavités durant une brève apnée. Les données sont stockées au format Dicom, comprenant les données natives, et sont affichées au format JPEG (Joint Photographic Experts Group). Les images sont traitées au décours de l'examen par notre logiciel précédemment publié [86] afin d'estimer la différence instantanée de pression entre la base du VG et l'apex. Afin de pouvoir quantifier le GPIVD, l'alignement de l'acquisition Doppler doit être dans l'axe du flux sanguin, les structures anatomiques du VG et surtout la valve mitrale doivent être visibles et il ne doit pas y avoir d'obstruction au flux sanguin. Le logiciel est automatique permettant

d'avoir une meilleure reproductibilité inter-opérateur. En revanche, si l'utilisateur juge que le plan de l'ouverture mitrale n'est pas positionné de façon adéquate, il est possible de réajuster sa position manuellement. La résolution temporelle est définie à 75 mm/s mais peut être modifiée en fonction de la fréquence cardiaque afin d'avoir 3 cycles consécutifs et moyenner les mesures. Brièvement, le logiciel traite l'image en réalisant un désaliasing [90, 91] puis un lissage avant de pouvoir déterminer les composantes convectives et inertielles et donc le GPIVD. Un exemple du processus est représenté sur la Figure 4.

Analyse statistique

Les variables continues sont représentées sous forme de moyenne $\pm$ écart-type ou médiane et espace interquartile selon la distribution du paramètre. Les variables qualitatives sont présentées sous forme de nombre et pourcentages. Les patients sont répartis en deux groupes selon l'existence (RVG$\oplus$) ou non (RVG$\ominus$) d'un RVG au cours du suivi. Les caractéristiques de ces deux groupes sont comparées par le test *t* de Student ou le test de Mann-Whitney. Nous avons utilisé des modèles de régression linéaire et logistique pour étudier la relation entre l'évolution des volumes VG en tant que variable continue et l'existence d'un RVG en tant que variable binaire respectivement et les paramètres échocardiographiques à la phase initiale. Ces analyses ont été réaliseés sans ajustement et après ajustement sur les VTD et VTS initiaux. Le logiciel utilisé est R version 3.6.3 (R Foundation for Statistical Computing, Vienne, Autriche). Les tests utilisés sont bilatéraux avec un seuil de significativité fixé à 0,05.

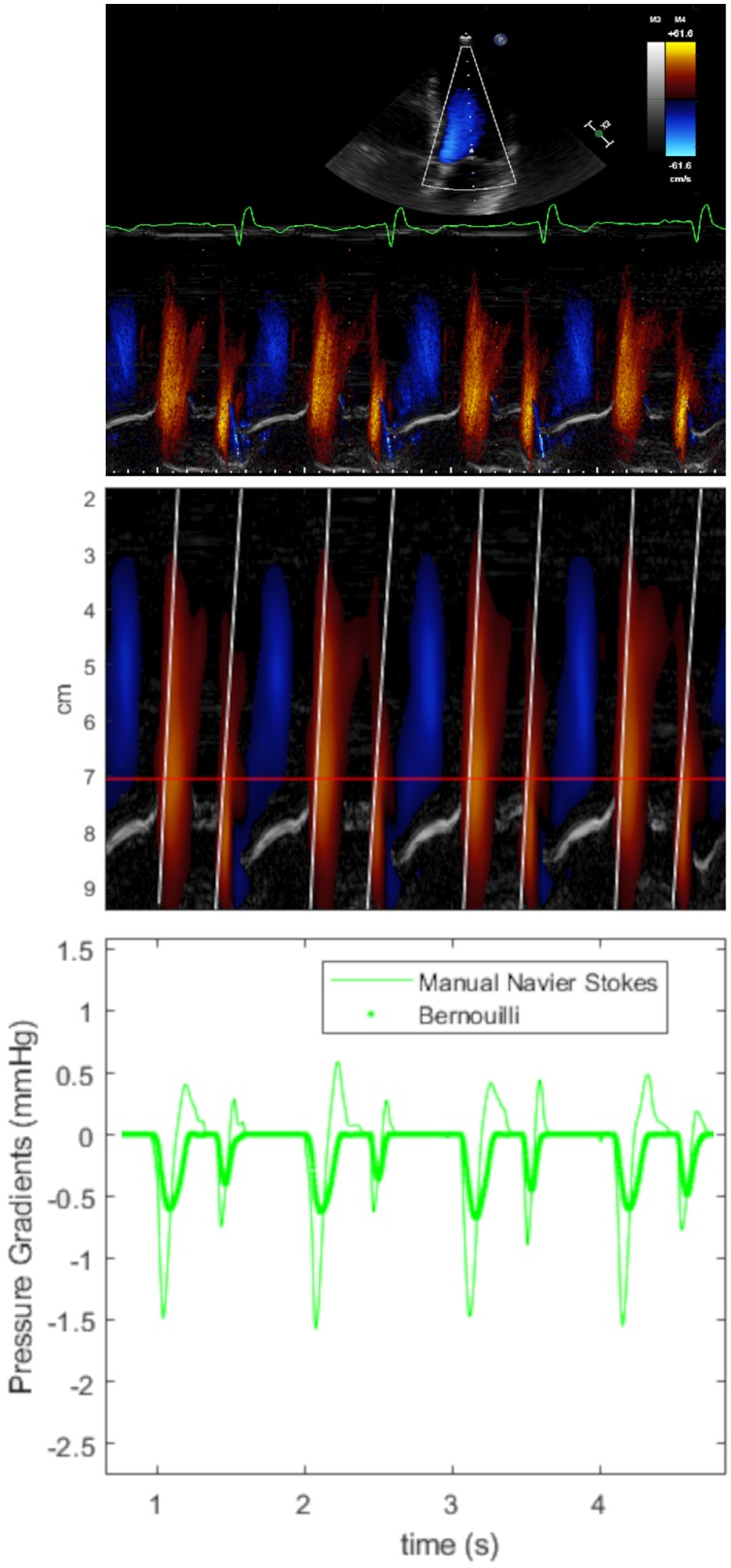

Fig. 4 **Mesure du gradient de pression intraventriculaire diastolique.** En haut: image TM doppler couleur centré sur le flux mitral, vitesse de défilement: 75mm/s. Au milieu: traitement de l'image (désaliasing et lissage). En bas: courbe de valeur du gradient de pression intraventriculaire diastolique (équation de Navier Stokes): -1,4 à -1,5 mmHg selon les mesures.

Résultats

Population de l'étude

Parmi les 205 patients qui ont eu une échocardiographie complète à la phase initiale de l'infarctus, 4 sont décédés au cours du suivi, avant la réalisation de la seconde échocardiographie. Trente-neuf patients n'ont pas été revus au décours de l'hospitalisation initiale, majoritairement en raison d'un suivi organisé en dehors du centre (Figure 5). Enfin, 29 patients ont été rétrospectivement exclus en raison d'une qualité insuffisante des acquisitions échocardiographiques (TM avec Doppler couleur ou acquisition 3D pour la mesure des volumes VG). Les caractéristiques des 133 patients inclus dans l'analyse sont décrites dans la Table 3. L'âge moyen est de 56,9 ans [49,4 – 67,5] et 113 (85%) sont de sexe masculin. La durée médiane entre le début de la symptomatologie et la revascularisation coronaire est de 4,1 heures [2,9 – 7,0].

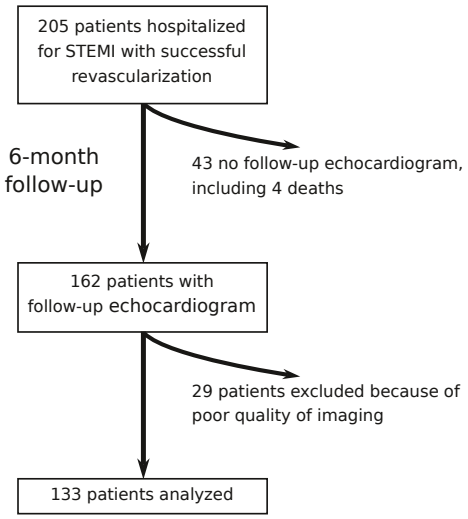

Fig. 5 **Flow chart.**

Table 3 : Caractéristiques de la population.

	Population générale n=133	LVR⊕ n=38	LVR⊖ n=95	valeur de p
Age, années	56,9 [49,4 – 67,5]	62,5 [50,9 – 68,8]	56,0 [49,3 – 66,8]	0,41
Sexe masculin	113 (85,0%)	35 (92,1%)	78 (82,1%)	0,24
Hypertension artérielle	48 (36,1%)	12 (31,6%)	36 (37,9%)	0,63
Diabète de type 2	20 (15,0%)	7 (18,4%)	13 (13,7%)	0,68
Hypercholestérolémie	53 (39,8%)	19 (50,0%)	34 (35,8%)	0,19
Tabagisme	83 (62,4%)	22 (57,9%)	61 (64,2%)	0,63
IMC, kg/m^2	26,1 [24,2 – 29,0]	26,0 [24,6 – 27,4]	26,2 [24,0 – 29,1]	0,44
Délai de reperfusion†, heures	4,1 [2,9 – 7,0]	4,0 [3,3 – 6,7]	4,2 [2,9 – 7,9]	0,84
Infarctus antérieur	57 (42,9%)	16 (42,1%)	41 (43,2%)	1
A l'admission				
FC, bpm	75 ± 17	73 ± 19	75 ± 17	0,57
PAS, mmHg	140 [119 – 156]	133 [115 – 150]	141 [119 – 159]	0,43
PAD, mmHg	80 [70 – 94]	80 [66 – 89]	80 [70 – 97]	0,26
DFG estimé, mL/min/1,73 m^2	93 [80 – 106]	88 [77 – 101]	97 [80 – 107]	0,17
Echocardiographie initiale				
VTD indexé, mL/m^2	57,9 [47,7 – 66,3]	56,8 [47,4 – 66,3]	58,0 [47,8 – 66,3]	0,78
VTS indexé, mL/m^2	30,6 [24,6 – 37,4]	32,8 [24,8 – 38,2]	28,7 [24,6 – 34,8]	0,19
FEVG, %	46,5 [40,1 – 53,2]	42,9 [37,8 – 47,8]	48,3 [41,0 – 53,8]	<0,01
Rapport $\frac{E}{A}$	0,96 [0,83 – 1,18]	0,98 [0,85 – 1,18]	0,96 [0,79 – 1,17]	0,53
Temps de décélération de l'onde E, ms	200 [170 – 235]	180 [153 – 230]	200 [170 – 240]	0,046
Rapport $\frac{E}{e'}$ moyen	8,1 [7,0 – 9,9]	8,1 [6,7 – 9,3]	8,1 [7,1 – 9,9]	0,75
Volume de l'OG, mL/m^2	31,4 [26,4 – 37,6]	32,0 [27,3 – 39,0]	31,2 [26,2 – 37,5]	0,41
GPIVD (valeurs absolues), mmHg	1,28 [0,96 – 1,85]	1,26 [1,02 – 1,95]	1,28 [0,92 – 1,85]	0,52
Echocardiographie de suivi				
VTD indexé, mL/m^2	59,2 [49,8 – 71,7]**	83,0 [67,1 – 92,1]***	54,9 [47,5 – 64,9]*	<0,001
VTS indexé, mL/m^2	27,5 [21,1 – 40,2]	43,0 [35,0 – 52,9]***	23,8 [19,7 – 30,5]***	<0,001
FEVG, %	52,1 [44,2 – 57,1]***	47,1 [41,6 – 51,1]	54,0 [47,1 – 59,6]***	<0,01

DFG, débit de filtration glomérulaire ; FC, fréquence cardiaque ; FEVG, fraction d'éjection ventriculaire gauche ; GPIVD, gradient de pression intraventriculaire diastolique ; IMC, indice de masse corporelle ; OG, oreillette gauche ; PAD, pression artérielle diastolique ; PAS, pression artérielle systolique ; VTD, volume télédiastolique ; VTS, volume télésystolique. †délai compris entre le début de la symptomatologie et la revascularisation (succès de fibrinolyse, angioplastie primaire ou de sauvetage) *p<0,05 ; **p<0,01 ; ***p<0,001.

Volumes et fonction du ventricule gauche

Trente-huit patients (28,6%) ont présenté un RVG au cours du suivi. Il n'y a pas de différence entre les groupes LVR$\oplus$ et LVR$\ominus$ concernant les valeurs initiales de VTD indexé (56,8 mL/m^2 [47,4 – 66,3] et 58,0 mL/m^2 [47,8 – 66,3] respectivement ; p=0,78 ; Table 3) et de VTS indexé (32,8 mL/m^2 [24,8 – 38,2] et 28,7 mL/m^2 [24,6 – 34,8] ; p=0,19). En revanche, les patients du groupe LVR$\oplus$ ont une FEVG plus basse lors de l'échocardiographie initiale (42,9% [37,8 – 47,8] et 48,3% [41,0 – 53,8] respectivement ; p<0.01). Lors de l'échocardiographie de suivi, les valeurs de VTD et VTS sont plus élevées dans le groupe LVR$\oplus$, comme attendu (83,0 mL/m^2 [67,1 – 92,1] et 54,9 mL/m^2 [47,5 – 64,9] ; p<0.01 pour le VTD et 43,0 mL/m^2 [35,0 – 52,9] et 23,8 mL/m^2 [19,7 – 30,5] ; p<0,001 pour le VTS). La FEVG augmente significativement dans le groupe LVR$\ominus$ lors du suivi mais pas dans le groupe LVR$\oplus$ (p<0,001 et p=0,12 respectivement).

Paramètres de fonction diastolique

Le temps de décélération de l'onde E mitrale est plus long dans le groupe LVR$\ominus$ par rapport au groupe LVR$\oplus$ (200 ms [170 – 240] et 180 ms [153 – 230] ; p<0.05). Le rapport $\frac{E}{A}$ est similaire dans les deux groupes (0,98 [0,85 – 1,18 dans le groupe LVR$\oplus$ et 0,96 [0,79 – 1,17] dans le groupe LVR$\ominus$; p=0,53). Il n'existe pas de différence du rapport $\frac{E}{e'}$ entre les groupes (8,1 [6,7 – 9,3] dans le groupe LVR$\oplus$ et 8,1 [7,1 – 9,9] dans le groupe LVR$\ominus$; p=0,75).

Relations entre le gradient de pression intraventriculaire diastolique, les paramètres de fonction diastolique et le remodelage ventriculaire gauche

Le gradient de pression intraventriculaire diastolique est similaire dans les deux groupes lors de l'examen initial (1,26 mmHg [1,02 – 1,95] dans le groupe LVR$\oplus$ et 1,28 mmHg [0,92 – 1,85] dans le groupe LVR$\ominus$; p=0,52). Ce résultat est retrouvé même après ajustement

sur la FEVG ou les volumes VG initiaux. Nous n'avons pas retrouvé de relation entre la variation du GPIVD et la variation de la FEVG (p=0,56) ou le RVG (p=0,72) au cours du suivi (Figure 6). Il existe une corrélation significative entre le GPIVD et les paramètres de fonction diastolique mesurés sur l'échocardiographie initiale, et notamment: (i) le rapport $\frac{E}{A}$ (r=-0,26 ; p<0,01) ; (ii) le rapport $\frac{E}{e'}$ (r=-0,24 ; p<0,01) et (iii) le pic de vélocité de l'onde E mitrale (r=0,63 ; p<0,001 ; Figure 7). Concernant la relation entre le GPIVD et la fonction diastolique, il existe une tendance non significative à une valeur plus faible (en valeur absolue) du GPIVD chez les patients ayant une dysfonction diastolique de grade 1 par rapport à ceux ayant une dysfonction diastolique de grade intéterminé (1,15 mmHg [0,88 – 1,75] et 1,39 mmHg [1,05 – 2,00] respectivement ; p=0,07 ; Figure 8).

Discussion

Notre étude n'a pas permis de montrer d'association significative entre le GPIVD calculé sur l'échocardiographie initiale et la survenue d'un RVG au cours du suivi. En revanche, il existe une association entre le GPIVD et certains paramètres de fonction diastolique, notamment le pic de vélocité de l'onde E mitrale mais aussi dans une moindre mesure les rapports $\frac{E}{A}$ et $\frac{E}{e'}$. Il existe également une tendance pour une relation entre GPIVD et le grade de dysfonction diastolique.

Le remplissage VG est un phénomène complexe qui dépend de plusieurs paramètres : la relaxation des fibres myocardiques, la pression de l'OG et sa contractilité, la pression du VG en fin de diastole, sa fonction systolique et sa compliance [81]. La détorsion du VG durant la phase de relaxation isovolumique est un mécanisme-clé du remplissage VG précoce. Le retour du VG à sa conformation pré-éjection permet de libérer l'énergie stockée lors de la systole dans les éléments élastiques du tissu [81, 92] et contribue à générer un gradient de

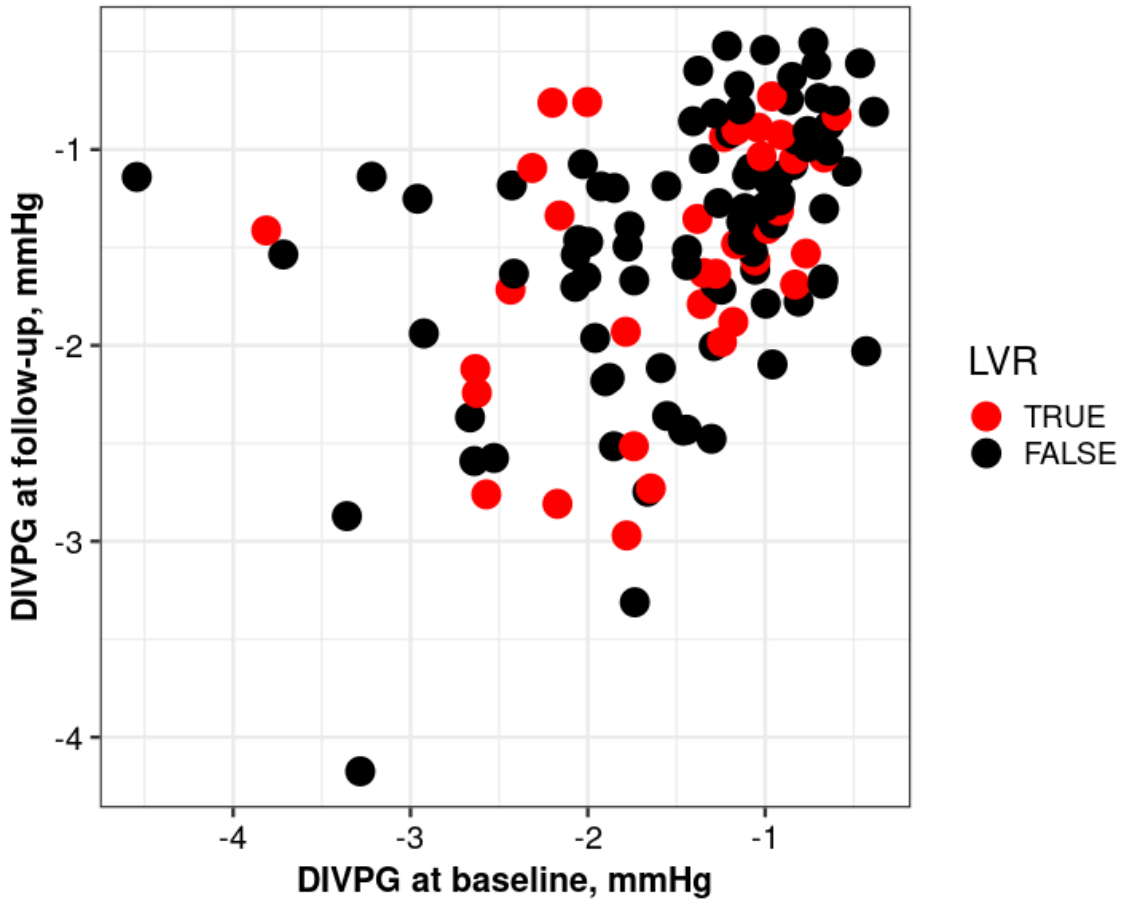

Fig. 6 **Relation entre la variation du gradient de pression intraventriculaire diastolique et le remodelage ventriculaire gauche au cours du suivi.** Le remodelage ventriculaire gauche (LVR) est défini par une augmentation $\geq$20% du volume télédiastolique au cours du suivi.

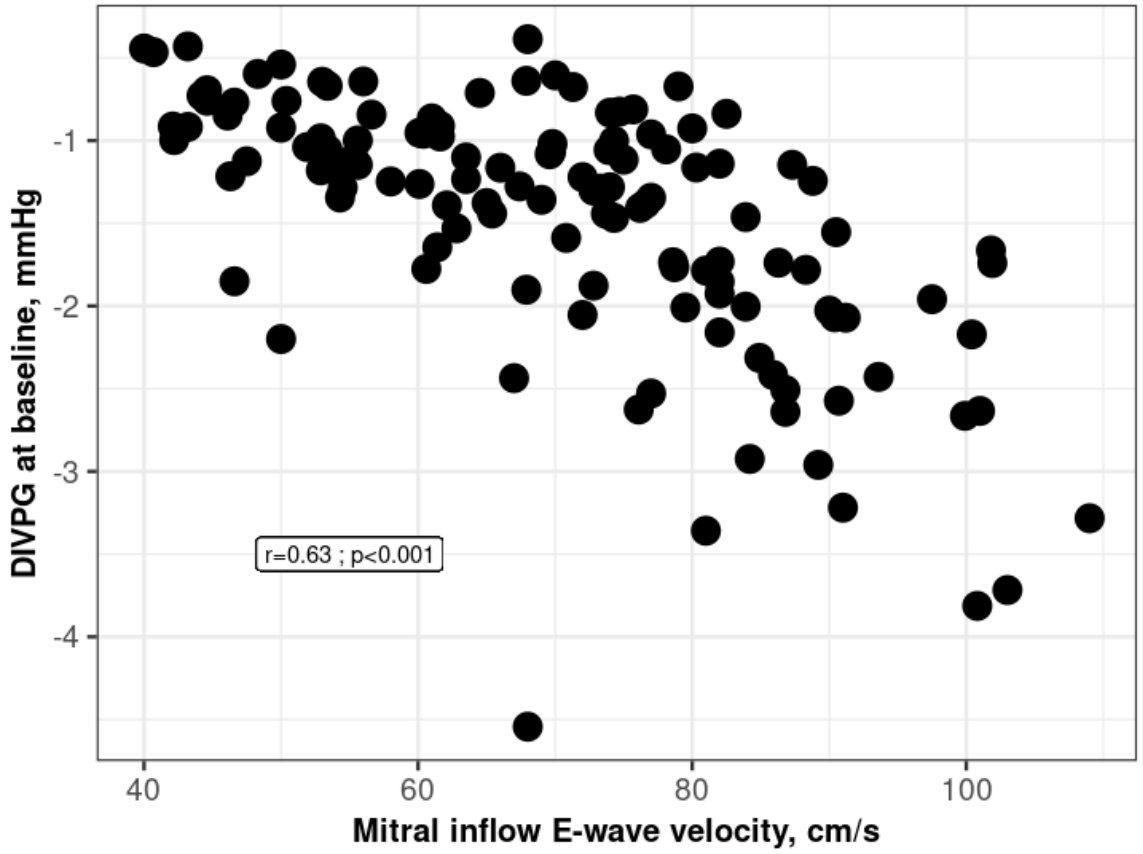

Fig. 7 **Relation entre le gradient de pression intraventriculaire diastolique et le pic de vélocité de l'onde E mitrale.**

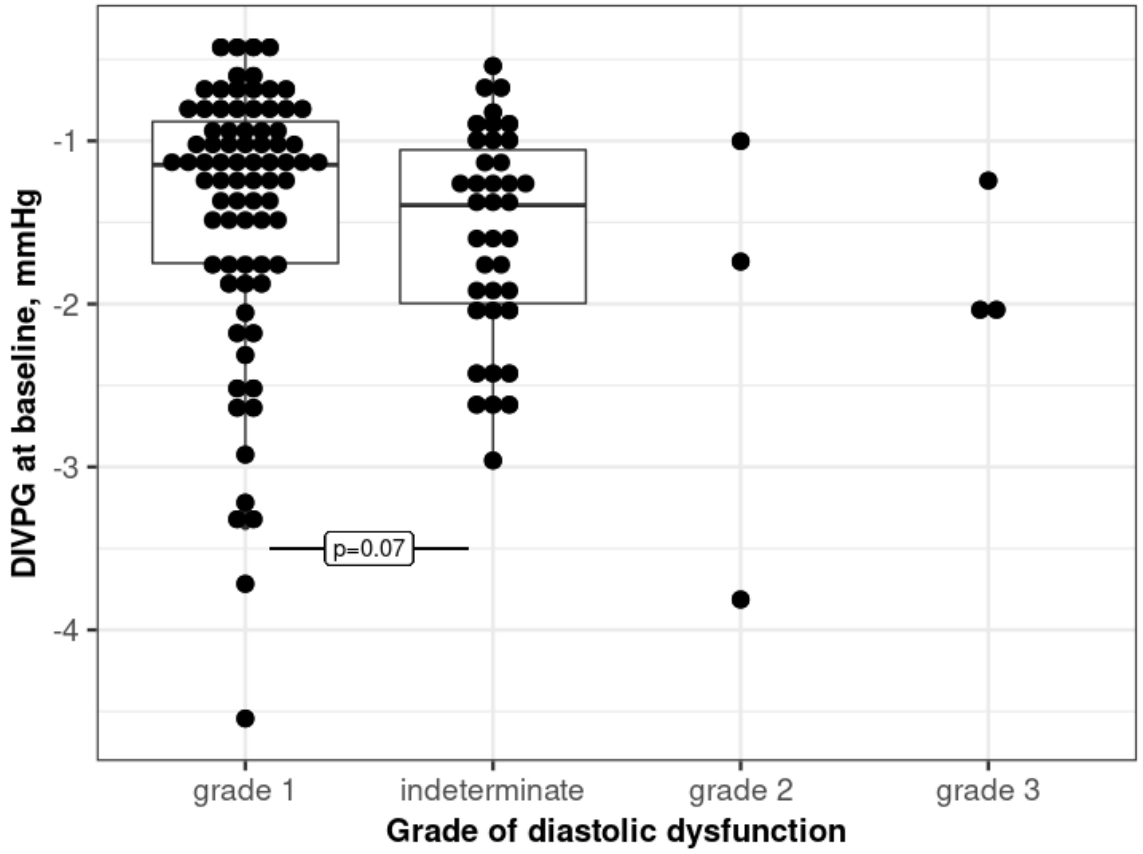

Fig. 8 **Relation entre le gradient de pression intraventriculaire diastolique et le grade de dysfonction diastolique.**

pression intraventriculaire qui va créer une succion du sang vers le VG. Ce gradient est mesurable de façon non-invasive [86].

Dans notre étude, le GPIVD moyen est de 1,28 mmHg [0,96 – 1,85] dans les 24 à 48 heures suivant le STEMI, en utilisant une acquisition TM centrée sur la valve mitrale et la fonction Doppler couleur. Notre équipe a mis en évidence des valeurs de GPIVD plus élevées chez des volontaires sains (3,2 mmHg $\pm$ 1,0 mmHg) [86]. Plusieurs explications peuvent être avancées pour expliquer cette différence. Premièrement, il a été mis en évidence dans des études précliniques que l'ischémie est une situation qui diminue le GPIVD [87]. Il existe des modifications marquées du profil de remplissage dans des situations comme l'ischémie myocardique ou l'IC, que ce soit dans des études précliniques [83, 93] ou chez l'homme [84]. Deuxièmement, la rigidité du VG augmente avec l'âge et les patients que nous avons inclus sont plus âgés que dans la littérature [94]. Troisièmement, un facteur déterminant du remplissage VG est sa fonction systolique. Les anomalies régionales de la fonction systolique VG que l'on observe dans l'infarctus du myocarde va induire une diminution de l'énergie stockée durant la systole et donc une diminution de l'énergie relâchée en début de diastole [87], diminuant ainsi le GPIVD. Aussi, il a été proposé que les anomalies de la torsion du VG conduise à une augmentation de la demande en oxygène par un mécanisme de diminution de l'efficacité de la contraction myocardique (par une perte de l'uniformité du stress sur les fibres myocardiques [95]). Cette augmentation de la demande en oxygène toucherait alors également les zones *remote* du myocarde et conduirait à terme à une altération de la contractilité et au RVG [96].

Il existe des données contradictoires dans la littérature sur l'association entre la torsion VG et le RVG. La torsion VG mesurée à la phase aiguë n'est pas associée à la survenue d'un RVG chez 75 patients avec STEMI antérieur [75]. Une autre étude a montré que les

patients ayant présenté un RVG au cours du suivi ont des paramètres plus bas de torsion VG au décours immédiat de l'infarctus [97]. Dans cette même étude, il existe une association significative entre FEVG et torsion VG, qui n'est pas retrouvée comme un facteur prédictif indépendant de RVG. D'autres auteurs ont montré que la torsion VG est associée significativement à la FEVG et à la taille de l'infarctus mais aussi au RVG, en analyse multivariée [74]. Il existe moins de données sur la relation entre la détorsion du VG et le RVG. Dans une étude ayant inclus 208 patients avec STEMI mais avec une FEVG et des paramètres de torsion VG meilleurs que dans l'étude précédente, les paramètres de détorsion ne sont pas associés à la survenue d'un RVG au cours du suivi [76].

Il existe également des données divergentes sur la valeur prédictrice des paramètres plus conventionnels de fonction diastolique quant à la survenue d'un RVG au décours d'un STEMI. Il n'existe pas d'association entre un profil restrictif du remplissage VG et la survenue d'un RVG chez 109 patients pris en charge pour un STEMI [98]. En revanche, la mise en évidence d'un profil restrictif – défini par un temps de décélération de l'onde E mitrale $\leq$130 ms – est associé à l'absence de survenue d'un remodelage "reverse", défini dans l'étude par une diminution $>$10% du VTS VG dans une population de 184 patients, à 6 mois de l'épisode initial [99]. Dans une étude post-hoc de l'étude TIPTOP, une dysfonction diastolique de grade 3, définie par un rapport $\frac{E}{A} \geq$2 conformément aux recommandations en vigueur [72], est associée à une plus grande augmentation du VTS et une moindre amélioration de la FEVG au cours du suivi [100]. Le GPIVD n'est pas associé à la survenue d'un RVG dans notre étude. Il existe des différences entre l'étude post-hoc de TIPTOP précédemment citée et la notre qui peuvent expliquer ces résultats. Premièrement, nous avons inclus un nombre limité de patients. Deuxièmement, les patients inclus dans leur étude ont une fonction systolique VG plus altérée que dans notre population [100]. La FEVG médiane est de 39% [32 – 44] dans le groupe doxycycline et 37% [33 – 43] dans le groupe contrôle de cet essai randomisé contre

46,5% [40,1 – 53,2] dans notre étude. Leur cohorte a également une fonction diastolique plus altérée. Près de deux tiers de leurs patients ont une dysfonction diastolique de grade 3, synonyme d'élévation de la pression OG alors que ce type de profil mitral est retrouvé chez seulement 3 de nos patients (2,4%). Nous avons observé que le GPIVD est plus bas chez les patients ayant une dysfonction diastolique de grade 1 et est corrélé avec le pic de vélocité de l'onde E mitrale. Une précédente étude a montré des résultats similaires, où le GPIVD est plus bas chez les patients ayant une dysfonction diastolique de grade 1 par rapport aux patients ayant une dysfonction diastolique de grade 2 ou 3 [84]. Étant donné ces résultats d'une part et l'observation de valeurs plus élevées de GPIVD chez des sujets sains d'autre part, il est possible de faire l'hypothèse que la relation entre les grades de fonction diastolique et le GPIVD suive une courbe en J, similaire à celle du rapport $\frac{E}{A}$. En effet, les patients ayant une dysfonction diastolique de grade 1 ont un rapport $\frac{E}{A}$ plus bas que les patients sans anomalie de la fonction diastolique ou avec une dysfonction diastolique de grade 2 [72]. Ceci peut expliquer les résultats discordants concernant la valeur prédictrice du rapport $\frac{E}{A}$ pour la survenue d'un RVG au décours d'un STEMI. En effet, l'existence – ou non – d'une association dépend de la typologie des patients inclus. Une étude a inclus 964 patients avec STEMI et une FEVG moyenne de $47\% \pm 9\%$. Le rapport $\frac{E}{A}$ est de 0,88 [0,69 – 1,10] dans le sous-groupe de patients ayant présenté un remodelage ventriculaire et 0,92 [0,75 – 1,10] dans le sous-groupe de patients sans RVG (association négative ; p=0,04) [101]. A l'inverse, une association positive est décrite dans une autre étude ayant inclus 194 patients [102]. L'âge moyen des patients inclus est similiare mais la FEVG à l'inclusion est de $60\% \pm 11\%$ et le rapport $\frac{E}{A}$ est de $1,2 \pm 0,8$ dans la population de patients ayant présenté un RVG contre $1,1 \pm 0,4$ dans le reste de la population (p=0,005). Étant donné que le GPIVD est corrélé au pic de vélocité de l'onde E mitrale dans notre étude, il est possible

que l'inclusion de patients ayant un grade de dysfonction diastolique plus élevé que ceux que nous avons inclus aurait conduit à des résultats différents de ceux que nous avons observé.

Ainsi, les données contradictoires de la littérature concernant l'association entre les paramètres de fonction diastolique – dont le GPIVD – et le RVG est probablement à mettre en rapport avec l'hétérogénéité des populations incluses dans les différentes études. En effet, ces paramètres de fonction diastolique ne sont pas associés à l'existence d'un RVG dans le suivi quand les patients inclus ont une FEVG relativement conservée, un faible grade de dysfonction diastolique et donc des pressions non élevées dans l'OG [76, 103]. A l'inverse, une association entre paramètres de fonction diastolique et RVG est retrouvée dans les études ayant inclus des patients ayant une altération de la FEVG ou une atteinte plus sévère de la fonction diastolique [74, 100, 55].

Notre étude présente plusieurs limites. Tout d'abord, notre population est petite et sélectionnée dans la mesure où nous avons inclus uniquement des patients revascularisés à la phase aiguë et sans signe clinique d'insuffisance cardiaque lors de l'hospitalisation initiale. Nos résultats ne peuvent donc pas être extrapolés à l'ensemble des patients pris en charge pour un STEMI. Il existe par ailleurs une variabilité de la mesure du GPIVD selon le logiciel et le matériel utilisés [82]. Cette information doit être prise en compte lors de la comparaison des valeurs de GPIVD entre différentes cohortes. Enfin, la méthodologie d'acquisition des images n'est pas standardisée. La majeure partie des acquisitions des images échocardiographiques a eu lieu entre 2016 et 2018, sans standardisation de la vitesse de défilement de l'image ou du gain. Or, il a récemment été démontré que plus le gain de l'image est augmenté, plus l'enveloppe du Doppler couleur est réduite et ceci, de façon très significative [82]. Dans

la mesure où le logiciel que nous avons utilisé travaille à partir de l'image JPEG, l'absence de standardisation du gain doit nous conduire à interpréter avec prudence les mesures de GPIVD.

Conclusion

Notre étude a montré que dans une population de patients revascularisés à la phase aiguë d'un STEMI et sans signe clinique d'IC, la quantification du GPIVD, un paramètre associé à la détorsion VG, n'est pas associé à la survenue d'un RVG au cours du suivi. Avant de généraliser ces résultats à l'ensemble des patients pris en charge pour un STEMI, il est nécessaire d'étudier la relation entre le GPIVD, les paramètres de fonction diastolique et la survenue d'un RVG dans une population non sélectionnée de patients hospitalisés pour STEMI et en utilisant une méthodologie standardisée.

Axe biomarqueurs et remodelage ventriculaire gauche en post-infarctus

Biomarqueurs et remodelage ventriculaire gauche : revue de la littérature

De très nombreux biomarqueurs ont été décrits comme pouvant potentiellement prédire la survenue du RVG au décours d'un STEMI. Ces biomarqueurs d'intérêt avaient été colligés dans une publication lilloise, parue en 2012 [104]. Les auteurs avaient sélectionné 59 publications, concernant 52 biomarqueurs différents. Depuis, de très nombreux travaux ont porté sur cette même thématique. Avant toute nouvelle étude sur le sujet, il paraissait donc licite de refaire un point sur les données précédemment acquises.

Au total, nous avons retrouvé 134 publications décrivant 457 relations concernant plus d'une centaine de biomarqueurs différents. Parmi ces biomarqueurs, certains ont été étudiés à plusieurs reprises avec des résultats reproductibles quant à leur capacité à prédire le RVG au cours du suivi. Il s'agit surtout des marqueurs de nécrose myocardique, des peptides natriurétiques, ou encore des marqueurs d'inflammation ou des molécules intervenant sur la matrice extracellulaire. Ces biomarqueurs d'intérêt s'inscrivent donc dans la physiopathologie du RVG après SCA telle que nous l'avons brièvement rappelée au début de ce manuscrit (partie Introduction, page 2).

Ce travail montre également trois autres résultats. Premièrement, il existe une grande quantité de marqueurs biologiques décrits comme étant associés à la survenue d'un RVG au cours du suivi. Ces biomarqueurs ne sont pas réalisés en routine et les résultats manquent souvent de reproductibilité, le caractère prédictif d'un biomarqueur particulier étant souvent l'apanage d'une seule étude. Deuxièmement, un grand nombre de ces études sont des petites cohortes (le nombre médian de patients est de 88). Troisièmement, l'hétérogénéité des résultats obtenus pour certains biomarqueurs est potentiellement en rapport avec les modalités de prélèvement et de sa quantification. Le délai entre l'occlusion coronaire et le prélèvement sanguin servant à mesurer le biomarqueur doit être défini pour chaque biomarqueur, en fonction du mécanisme qu'il étudie dans la physiopathologie du SCA.

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The relationship between circulating biomarkers and left ventricular remodeling after myocardial infarction: an updated review.

Soumis à Disease Markers.

Les données supplémentaires de cet article sont disponibles dans les annexes, page 192.

The relationship between circulating biomarkers and left ventricular remodeling after myocardial infarction: an updated review

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ABSTRACT

Left ventricular remodeling (LVR) is common in patients with ST-elevation myocardial infarction (STEMI) and is associated with worse outcomes. Numerous clinical, imaging and biological parameters have been proposed as prognostic factor for the existence of LVR after STEMI. We performed a systematic review of the published evidence about the association of biomarkers with LVR after STEMI. Overall, 131 publications investigating 452 relations were studied. Some biomarkers were more likely to be associated with LVR at follow-up: infarct size-related biomarkers, natriuretic peptides levels (especially at discharge), white blood cells count, C-reactive protein or high-sensitivity C-reactive protein and matrix metalloproteinase-9, reflecting myocardial damage, inflammation, neurohormonal activation or matrix turnover, which are important drivers of LVR. Additionally, we found numerous articles about the relationship between 64 biomarkers that are not assessed routinely and LVR. A significant proportion of these studies showed a significant correlation but these isolated data have to be confirmed in further studies. To note, there is a high heterogeneity in the literature regarding LVR definition, timeframe of the follow-up imaging session or timing of the blood samples. The latter point is particularly important, depending of the pathophysiology of the studied biomarker. Some biomarkers reflecting myocardial damage, neurohormonal activation, inflammation and matrix turnover have been associated with LVR in past studies. Further studies using a standardized methodology to define LVR should focus on the interest of a multimarker approach to predict LVR in non-selected patients.

KEYWORDS: left ventricular remodeling ; acute myocardial infarction ; biomarkers ; ST-elevation myocardial infarction

INTRODUCTION

Despite major advances in coronary revascularization for ST-elevation myocardial infarction (STEMI), left ventricular remodeling (LVR) associated with mortality and heart failure (HF) remains common [1,2]. LVR is the consequence of cellular and histological modifications [3], that are induced by deleterious adaptive mechanism involving the infarcted tissue and remote myocardium [4]. LVR has been extensively studied in clinical studies, and it is now accepted that it is influenced by several factors (e.g. infarct size or neurohormonal activation). The assessment of biomarkers at the acute phase of myocardial infarction may reflect some of these mechanisms and predict LVR in STEMI patients.

Ten years ago, Fertin et al. performed a systematic overview of 59 articles about the relationship between 52 different biomarkers and LVR after acute myocardial infarction (AMI) [5]. During the last decade, a growing number of studies brought new data about the relationship between some biomarkers and LVR. In the present study, we aim to perform an update of published evidence on the association of circulating biomarkers, assessed at the acute phase of STEMI, with LVR.

METHODS

Search strategy

We conducted a computerized Medline search of published articles through July 2020, using the following combined criteria: (i) (« remodeling »[Title/Abstract] OR « remodelling »[Title/Abstract] OR «volume »[Title/Abstract]) AND (ii) « myocardial infarction »[Title/Abstract]) AND (iii) (« follow-up »[Title/Abstract] or « months »[Title/Abstract] or « month »[Title/Abstract]). The third part of the combined search was set to exclude studies with no follow-up after the index STEMI. Review articles and bibliographies of all relevant articles were searched manually for additional articles. Eligible studies had to fulfil the following criteria: (i) patients were admitted with STEMI or AMI but the proportion of patients with STEMI is described, (ii) the baseline imaging session was performed within 10 days following STEMI, (iii) the follow-up imaging session was performed >1 month after STEMI, (iv) the number of included patients was ≥30, (v) the biomarkers of interest were measured during the index admission, (vi) LVR was defined or the relationship between the biomarkers and the change regarding left ventricular volumes was available, and (vii) the article was written in English.

Statistical analysis

We anticipated a significant heterogeneity regarding included population, timeframe of biomarkers and imaging sessions and the definition of LVR from one study to another. As a consequence, it was not possible to conduct a formal meta-analysis. The correlation between a biomarker level and LVR was defined as positive if a high level of the biomarker was significantly associated ($p<0.05$) with either the definition of LVR used in the study or with left ventricular dilation at follow-up if no definition of LVR was provided. Conversely, the correlation was defined as negative if a low level of biomarker was significantly associated ($p<0.05$) with LVR or left ventricular dilation. Otherwise, there was no correlation between the level of the biomarker and LVR.

RESULTS

The relationship between LVR and a wide spectrum of potential biomarkers have been studied after STEMI. Unless otherwise indicated, the tables in the present document contain only data about biomarkers that have been studied more than twice in the literature, with significant association with LVR. The full dataset including isolated studies regarding a specific biomarker or biomarkers that were never associated with LVR in past studies is available as Supplementary materials. The median number of patients per study was 88 (range: 30, 1995) in the 131 selected publications. The median follow-up duration was 6 months (range: 1, 44). Forty studies (30.5%) used cardiac magnetic resonance (CMR) imaging and 85 (64.9%) used transthoracic echocardiography. Eighty-nine studies used a cut-off value for LVR (67.9%) and 5 (3.8%) defined reverse LVR as a 10 to 15% decrease in ESV during follow-up. When LVR was defined as a dichotomous criterion, the prevalence of LVR ranged from 12.5% to 51.8%. The cut-off values of a ≥20% increase in left ventricular end-diastolic volume and a ≥15% increase in left ventricular end-systolic volume were the two most common criteria (55 [42.0%] and 8 [6.0%] studies, respectively). Eighty-seven studies described a relationship between biomarkers used to assess infarct size (e.g. troponin or creatine phosphokinase) and LVR (Supplementary Table). Among the 129 associations, a positive correlation was reported in 79 cases (61.2%, and 19 were positive in multivariate analysis [14.7%]), a negative correlation in

2 cases (but related to the same publication [6]), a variable or borderline (p=0.05) correlation in 2 cases and no correlation in 46 cases (35.7%).

Natriuretic peptides

The 46 studies that described a relationship between natriuretic peptides and LVR are presented in Table 1. A positive association was reported in 19 studies (41.3%). Among these studies, 6 described a positive relationship in multivariate analysis whereas the association was no longer present in multivariate analysis in 5 studies. A variable association, depending of the timing of the measurement of the biomarker was described in 7 studies. The only study that reported a negative association showed no longer association in multivariate analysis. The 18 remaining studies reported no significant association between natriuretic peptides levels and LVR.

Complete blood count, biochemistry and lipid profile

The relationship between complete blood count parameters and LVR are depicted in Table 2. Among the 6 studies that investigated the association between hemoglobin levels and LVR, only 2 studies found that there was a positive correlation between hemoglobin and LVR [47,48]. However, these studies were conducted by the same team and used a nonconventional definition of LVR (>20mL/m^2 increase in EDVi, and any increase in EDVi, respectively). Regarding white blood cells, we selected 14 publications and found 17 associations. Among these associations, 4 failed to demonstrate a significant association in multivariate analysis whereas a fifth study showed that the positive association remains after multivariate analysis. The relationship between renal function and LVR has been described in 25 studies. Among these studies, only two described that low kidney function is associated with LVR at follow-up (Supplementary Table, (i) Buono et al. [60]: estimated glomerular filtration rate: 94±20 mL/min/1.73m^2 in patients without LVR vs. 85±21 mL/min/1.73m^2 in patients with LVR [p=0.032], and (ii) Liu et al. [30]: OR=0.939 in both univariate [p<0.0001] and multivariate [p=0.0137] analysis for renal function). One third of the 15 studies described a significant positive correlation between glucose levels and LVR (Table 3). However, it is likely that there is no significant association between baseline lipid profile after STEMI and LVR as only one study showed a positive correlation between high-density lipoprotein cholesterol and LVR (Supplementary Data).

Inflammation, fibrosis and extracellular matrix

The Table 4 shows the relationship between markers of inflammation and LVR. Twenty-nine studies investigated the association between inflammation markers (mainly C-reactive protein or high-sensibility C-reactive protein) and LVR: there was no correlation in 14 cases (48.3%), a positive correlation in 9 cases (31.0%, with 3 positive correlation using multivariate analysis and 4 studies without significant relationship after multivariate or propensity-matched analysis) and a variable correlation in 2 cases, depending of the timing of the assessment of the biological parameter: no correlation at admission and positive association at 24 hours or at discharge. Regarding 14 fibrosis and extracellular matrix-related biomarkers, MMP-9 was the most investigated (Table 5). MMP-9 levels was associated with LVR as 6 studies demonstrated significant positive correlation between MMP-9 and LVR.

Other biomarkers

The relationship between 64 other biomarkers (including 12 miRNA) and LVR is depicted in Supplementary Table. A significant proportion of these studies demonstrated an association between biomarker level and LVR, but it may be taken with care as most of the data of the latter studies were isolated studies. The Table 6 described data about some biomarkers that have been reported twice or more (galectin-3 [29,51], hepatocyte growth factor [76,77], myeloperoxidase [71,78,79], osteoprotegerin [80,81] and suppression of tumorigenicity-2 [33,40]).

DISCUSSION

The results of the present review could be synthetized as following: (i) there is a massive literature about the relationship between circulating biomarkers and LVR in STEMI patients but there is no standardized cut-offs to define LVR and no standardized method for the assessment of biomarkers, allowing to draw definitive conclusions about the latter associations, (ii) there is data supporting that LVR is associated with baseline levels of some biomarkers related to infarct size, neurohormonal activation, inflammation, and matrix turnover and, (iii) it is of utmost importance to perform blood samples according to the pathophysiology of the biomarker of interest (e.g. biomarkers of neurohormonal activation at admission are poorly correlated to

LVR compared to discharge levels). A greater area of infarcted tissue may lead to higher levels of inflammation, a higher impairment of left vetricular function and, as a consequence, a higher neurohormonal activation to maintain adequate hemodynamics. In the end, there is higher levels of matrix turnover biomarkers due to a larger area of infarcted myocardium and LVR (Figure 1).

The timing of the blood samples is particularly important when assessing the relationship between a biomarker and LVR. After an AMI, the expression of biomarkers is time dependent and is related to the pathophysiology of the studied mechanism. As an example, the markers of cardiac injury (e.g. troponin) rapidly peak post-AMI and then taper off. Most of the studies we included investigating the relationship between troponins levels and LVR showed a positive association (Supplementary Table). These studies assessed either the peak of troponin using serial assessments or baseline troponin within 24 hours after primary percutaneous coronary intervention as an estimate of the area of myocardial infarction. Conversely, the studies that assessed myocardial damage either only at the very acute phase of STEMI (e.g. during primary percutaneous coronary intervention) [9,50,51,82] or only at discharge [30,35,83] were more likely to fail to demonstrate a significant association with LVR. Regarding natriuretic peptides, very early assessment is poorly associated with LVR [9,13,15,27,40,51,55] as its levels reflects neurohormonal activation and is enhanced by elevated intracardiac pressure. The latter phenomenon arises in the days following STEMI and, as a consequence, elevated natriuretic peptide levels at discharge [19,22,30,37,44] is a better marker of cardiac injury and neurohormonal activation and therefore a better prognostic factor of LVR. Some studies we included assessed natriuretic peptides both at baseline and at discharge and found no association between baseline natriuretic peptides levels and LVR but a positive correlation when assessing discharge levels [11,17,26,31,42,43]. The blockade of neurohormonal activation is already a key target after AMI [84]. The ability of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to reduce cardiovascular remodeling after AMI in clinical studies is well documented [85,86]. Regarding inflammation and matrix remodeling biomarkers, their ability to predict LVR at follow-up may also be variable, depending of the timing of the assays (C-reactive protein [17], matrix turnover protein levels like metalloproteinase [42,69,71], tissue inhibitor of metalloproteinase [70,71] or N-terminal type I procollagen [42]). These results are consistent with pathophysiology as inflammatory response, including neutrophils and

macrophages activation do not peak before week 1 [87]. Then, the duration and the magnitude of the inflammation and its resolution [88] and the appropriate reactive fibrosis deposition during matrix remodeling [89] are determinants of the quality of wound healing.

The Table 6 showed the relationship between biomarkers that are not used routinely and LVR. These results are useful in a hypothesis-generating approach. However, the latter results suffer from a lack of reproducibility and external validation. Conversely to conventional biochemical assays, the latter biomarkers may not have standardized methodology: (i) antibodies may be different from a kit to another one, (ii) there is no quality check as compared to routine biomarkers, (iii) interexperiment variability may occur, (iv) there is no normal value to compare with. The present review underlines that there is a need for incoming studies investigating the interest of a multimarker approach (including simple biomarkers related to infarct size, neurohormonal activation, inflammation, and matrix turnover), possibly associated with baseline clinical and imaging data, to predict LVR and improve risk stratification in non-selected STEMI patients. The upcoming studies have to avoid classical pitfalls commonly observed in the studies investigating the relationship between biomarkers and LVR in the setting of AMI. First, LVR is commonly defined as an increase of LV volumes between a baseline and a follow-up imaging session in the setting of AMI. However, the definition of LVR is highly variable regarding the timeframe of the follow-up imaging session and the used cut-off [90]. Moreover, the patients included in these studies are highly selected [90]. Second, there are some methodological issues that have to be taken into consideration. In most of the studies we included, the assessment of biomarkers levels is not the primary objective of the study at the time of the inclusion of the patients. The published results are post-hoc analysis, based on retrospective measurements in patients included prospectively. Also, the sample size of included studies was small. The overall consequence of these methodological issues is a lack of reproducibility of the results.

There are some additional limitations regarding the data we reviewed. We did not analyse the characteristics of the included patients nor the use of medications. The relationship between biomarkers and LVR may only be speculative and the impact of known or unknown covariables were not analysed. Further studies focusing on the modulation of implicated pathways may be of particular interest.

CONCLUSION

There is growing evidence about the relationship between biomarkers and LVR in STEMI patients. Our review showed that some biomarkers reflecting myocardial damage, neurohormonal activation, inflammation and matrix turnover may be associated with LVR. Further studies should focus on the interest of a multimarker approach to predict LVR in non-selected patients in order to help to refine risk stratification and to evaluate the interest of a more aggressive therapy (e.g. neurohormonal modulation) in high-risk patients. However, it is of utmost importance to perform blood samples according to the pathophysiology of the biomarker of interest and to use a standardized methodology to define LVR.

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FIGURE LEGENDS

Figure 1. Evolution of biomarkers levels after STEMI in case of small infarct area (lower panel) and large infarct area (upper panel). A larger infarcted myocardium leads to a higher level of biomarkers of myocardial damage and enhanced inflammation, activation of neurohormonal activation and matrix turnover and then, adverse left ventricular remodeling. LV: left ventricular, STEMI: ST-elevation myocardial infarction.

TABLES

Table 1. Association between natriuretic peptides levels and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; BNP, brain natriuretic peptide ; CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV(i), (indexed) end-systolic volume ; LVR, left ventricular remodeling ; MI, myocardial infarction ; PCI, percutaneous coronary intervention ; SPECT, single positron emission computed tomography ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

Table 2. Association between complete blood test data and LVR at follow-up in STEMI patients. CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV, end-systolic volume ; LVR, left ventricular remodeling ; MI, myocardial infarction ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

Table 3. Association between glucose levels and LVR at follow-up in STEMI patients. CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV, end-systolic volume ; LVR, left ventricular remodeling ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

Table 4. Association between biomarkers of inflammation and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; CMR, cardiac magnetic resonance ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

Table 5. Association between biomarkers involved in the turnover of matrix and collagen synthesis and degradation and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV(i), (indexed) end-systolic volume ; LVR, left ventricular remodeling ; MI, myocardial infarction ; MMP, matrix metalloproteinase ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TIMP, tissue inhibitor of metalloproteinase ; TTE, transthoracic echocardiography.

Table 6. Association between remaining circulating biomarkers not included in previous tables and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction ; CMR, cardiac magnetic resonance ; EDV(i), (indexed) end-diastolic volume ; ESV(i), (indexed) end-systolic volume ; LVG, left ventriculography ; LVR, left ventricular remodeling ; MI, myocardial infarction ; PCI, percutaneous coronary intervention ; STEMI, ST-elevation myocardial infarction ; TTE, transthoracic echocardiography.

Table 1

	sample size	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	relationship	comments
BNP								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Caldentey et al. (7)	227	48 hours after admission	CMR, 6 mo	ΔEDV≥20 %	29 (16%)	none	140±107 vs. 146±114 ; p=0.859	pg/mL
Crilley et al. (8)	126	day 3 to 7	TTE, 2 mo	ΔESVI>10%	45 (36%)	positive	p=0.034	
Dominguez-Rodriguez et al. (9)	97	at admission	TTE, 12 mo	ΔEDV>20%	21 (21.6%)	none	450 (421-485) vs. 473 (406-415) ; p=0.18	pg/mL
Hsu et al. (10)	97 (61 % STEMI)	day 2, day 7	TTE, 6 mo	ΔEDV>20%	24 (32.9%)	none none	322.0±440.2 vs. 342.1±369.5 ; p=0.841 224.7±305.7 vs. 327.8±256.1 ; p=0.148	pg/mL, day 2 pg/mL, day 7
Meng et al. (11)	31 (67 % STEMI)	at admission, day 3 and day 7	TTE, 3 mo	ΔEDV>20%	7 (22.6%)	none positive	135.8 (13.0 - 725.6) vs. 255 (14.0-2378) ; p=0.277 121.1 (26.6-585.8) vs. 935 (51.9-2287) ; p=0.033	admission day 7
Ortiz-Perez et al. (12)	88	48 hours	CMR, 6.4 mo	ΔEDVI≥20%	15 (16.9%)	none	115.2 [51.5-204.1] vs. 87.0 [45.9-178.4] ; p=NS	
Yoshitomi et al. (13)	33	at admission	LVG, 3 mo	ΔEDVI≥8%	14 (42.4%)	none	27±33 vs 58±101 ; p=NS	pg/mL
logistic regression								
Choi et al. (14)	131	at admission, day 2 to 5	TTE, 6 mo	ΔEDV>20%	42 (32%)	variable, multivariate positive, multivariate	OR range : 1,005-1,008 ; p range 0.01-0.08 OR range : 1,011-1,013 ; p<0,01 (all models)	on admission day 2 to 5
Dominguez-Rodriguez et al. (15)	108	before primary PCI	TTE, 12 mo	ΔEDV>20%	21 (19%)	none	OR 1.006, 95%CI [0.999, 1.013] ; p=0.07	
Gohbara et al. (16)	69	at admission, 6 hours, daily until discharge	CMR, 7 mo	ΔEDVI≥20%	18 (26.1%)	negative none, multivariate	OR 0.977, 95%CI [0.955, 0.999] ; p=0.045 OR 0.978, 95%CI [0.951, 1.007] ; p=0.136	per 1 pg/mL
Swiatkiewicz et al. (17)	198	at admission, discharge	TTE, 6 mo	ΔEDV>20%	55 (27.8%)	none positive positive, multivariate	OR 1.08, 95%CI [0.88, 1.33] ; p=NS OR 1.14, 95%CI [1.02, 1.28] ; p<0.05 OR 1.21, 95%CI [1.05, 1,39] ; p<0.01	admission, discharge, per 100 pg/mL
linear regression								
Cerisano et al. (18)	56	day 1, day 3	TTE, 6 mo	ΔLVEDVI > 2 times the SD of baseline values	17 (30%)	positive none, multivariate	beta coefficient 1.001, 95%CI [1.001, 1.007] ; p=0.02 beta coefficient 0.992, 95%CI [0.983, 1.000] ; p=0.06	
Fertin et al. (19)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	positive (all time points)	beta coefficient 0.207 ; p=0.002	
Garcia-Alvarez et al. (20)	78	within the first 24 to 96 hours after the onset of symptoms	TTE and CMR, 6 mo	ΔEDV>20%	26 (31.7%)	positive positive, multivariate	B coefficient 0.07, 95%CI [0.01, 0.13] ; p=0.01 B coefficient 0.08, 95%CI [0.01, 0.15] ; p=0.04	
Türkoğlu et al. (21)	255	at admission, 24 hours	TTE, 6 mo	ΔEDV≥20%	60 (23.5%)	positive, multivariate	beta coefficient 4.996, 95%CI [2.703, 9.232] ; p<0.001	pg/mL
ROC curve								
Sato et al. (22)	105	day 5	SPECT, 44 mo	ΔEDV≥20%	25 (23.8%)	positive	AUC 0.817, cut-off value 138 pg/mL, sensitivity 92 %, specificity 71 %	day 5
not described								
Bauters et al. (23)	226 (Q-wave MI)	at admission	TTE, 12 mo	percent change in LVEDV	NA	positive, multivariate		
Peak BNP								
Wu et al. (24)	104	day 1, day 3, day 5 and day 7	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	223.7±213.5 vs. 168.4±129.8 ; p=0.35	pg/mL
log BNP								
Hsiao et al. (25)	54	immediately, 8 hours, 16 hours	TTE, 6 mo	ΔESV>15%	19 (35.2%)	positive	OR 2.89, 95%CI [1.06, 7.88] ; p=0.04	log ng/L

NT-proBNP								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
López Haldón et al. (26)	159	before PCI and discharge	TTE, 6 mo	ΔEDV≥20 %	31 (19.5%)	none positive	374±799 vs. 460±941 ; p=0,66 945±1630 vs.1957±2000 ; p=0,016	pg/mL, admission pg/mL, discharge
Garcia et al. (27)	64	48h [IQR 24;72]	CMR, 3/12 mo	ΔESV>10%	NA	none	1375±1630 vs. 1844±1882 ; p=0,23	ng/L
Na et al. (28)	208	unavailable	TTE, 6 mo	ΔEDV>20%	53 (25.5%)	none	594±1312 vs. 525±1217 ; p=0.759	pg/mL
logistic regression								
Di Tano et al. (29)	92	baseline	TTE, 6 mo	ΔESV≥15 %	26 (28.2%)	positive none, multivariate	OR 1.15, 95%CI [1.04, 1.27] ; p=0.007 p=NS	per 1000 ng/mL
Liu et al. (30)	198	day 5	TTE, 12 mo	ΔEDV≥20 %	56 (28.3%)	positive none, multivariate	OR 1.003, 95%CI [1.001, 1.004] ; p<0.0001 OR 1.001, 95%CI [0.999, 1.002] ; p=0.2915	
Urbano-Moral et al. (31)	112	during PCI and discharge	TTE, 6 mo	ΔEDV>20%	24 (21.4%)	none positive positive, multivariate	OR 1.000, 95%CI [1.000, 1.001] ; p=0.2 OR 1.000, 95%CI [1.000, 1.001] ; p=0.008 OR 1.000, 95%CI [1.000, 1.001] ; p=0.8 OR 1.001, 95%CI [1.000, 1.001] ; p=0.1 (adjusted)	pg/mL, enrolment pg/mL, discharge
linear regression								
Giallauria et al. (32)	61	baseline	TTE, 6 mo	changes in EDVI	NA	positive, multivariate	beta coefficient 0.358 ; r2=0.814 ; p<0.001	
Kercheva et al. (33)	31	day 1, 3, and 7	TTE, 6 mo	ΔEDV or ESV>20%	14 (45.2%)	none	beta coefficient 0.005 ; p=0.97	
ROC curve								
Reindl et al. (34)	88	unavailable	CMR, 4 mo	ΔEDV≥20 %	11 (12.5%)	positive none, multivariate	AUC 0.74, 95%CI [0.57, 0.90] ; sensitivity 56%, specificity 88%, PPV 41%, NPV 93% OR 9.8, 95%CI [2.4, 39.4] ; p=0.001 p=NS	cut-off value 2155 pg/mL
Devaux et al. (35)	60 (derivation cohort) 30 (validation cohort)	day 3-4 (before discharge)	TTE, 176 d (derivation) CMR, 121 d (validation)	increase in LVEDV	30 (50%)	none	AUC 0.60, [0.39, 0.80]	
Lv et al. (36)	359 (AMI)	at admission	TTE, 6 mo	ΔEDV>10%	116 (32.3%)	positive	AUC 0.704, 95%CI [0.654, 0.751] ; p<0.001	
Reinstadler et al. (37)	123	at admission and daily between day 1 and day 4	CMR, 4 mo	ΔEDV≥20 %	16 (13.0%)	none	AUC 0.68, 95%CI [0.59, 0.76] sensitivity 50 %, specificity 86 %	cut-off 1931 ng/L admission
Xiaozhou et al. (38)	106	unavailable	TTE, 3 mo	ΔEDV≥20 %	22 (20.8%)	positive	AUC 0.894 ; sensitivity 83.3 %, specificity 81.8 %	cut-off 952 pg/mL
correlation (Pearson or Spearman)								
Kelly et al. (39)	404 (81 % STEMI)	pre-discharge	TTE, 10 mo	ΔEDV/ESV, increased EDV	142 (48.6%)	none	r=0.019 ; p=0.753 (change in EDV) r=0.008 ; p=0.895 (change in ESV)	
not described								
Bière et al. (40)	66	baseline	CMR, 3 and 12 mo	ΔESV>10%	33 (20%)	none		
Kelly et al. (41)	91 (85 % STEMI)	0-12h, 12-24h, 24-48h, and 24h intervals until discharge	TTE, 6 mo	change in LV volumes	NA	none		
Manhenke et al. (42)	42	prior to PCI, day 2 and week 1	CMR, 2 and 12 mo	none	NA	variable		
Mather et al. (43)	48	day 2, day 7	CMR, 1 and 3 mo	none	NA	variable (day 2) positive (day 7)		
Peak NT-proBNP								
ROC curve								

Reinstadler et al. (44)	47	before PCI, every 6 hours during 24 hours then daily	CMR, 4 mo	ΔEDV≥20 %	6 (12.8%)	positive	AUC 0.75, 95%CI [0.52, 0.99] sensibility 66 %, specificity 83 %	cut-off 1916 ng/L
correlation (Pearson or Spearman)								
Feistritzer et al. (45)	89	serially	CMR, 4 mo	ΔEDV≥20 %	14 (15.7%)	none none, multivariate	r=0.204 ; p=0.061 r=0.03 ; p=0.787	
Log NT-proBNP								
logistic regression								
Kim et al. (46)	262	unavailable	TTE, 6 mo	ΔEDV≥20 %	66 (25.2%)	positive, multivariate	OR range : 1.28, 95%CI [1.02, 1.61] ; p=0.03 to 1.34, 95%CI [1.09, 1.64] ; p=0.005	multiple models
linear regression								
Lin et al. (47)	264	day 2	TTE, 6 mo	ΔEDVI>20 ml/m²	unavailable	positive	standardized coefficient 2.352 ; p=0.012	
Liu et al. (48)	331	unavailable	TTE, 6 mo	increase in LVEDVi	NA	positive none, multivariate	coefficient 7.049 ; p=0.006 coefficient 2.853 ; p=0.305	
not described								
Nilsson et al. (49)	42	1 week,	CMR, 1, 3, 6 and 12 mo	none	NA	positive, multivariate		
proBNP								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Khurelsukh et al. (50)	35	at admission	TTE, 2 and 12 mo	ΔEDV≥20 %	14 (40%)	none	587±1311 vs. 626±1280 ; p=0.24	pg/mL
Andrejic et al. (51)	57	during PCI	TTE, 6 mo	ΔESV≥20 %	22 (38.6%)	none	250 [179, 2071] vs. 1577 [309.5, 4926] ; p=0.182	pg/mL

Table 2

	sample size	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	relationship	comments
Hemoglobin								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Barberato et al. (52)	55	baseline	TTE, 2 mo	ΔESV≥15%	13 (24%)	none	13±2 vs. 13±2 ; p=0.80	g/dL
Na et al. (28)	208	unavailable	TTE, 6 mo	ΔEDV>20%	53 (25.5%)	none	14.8±1.8 vs. 14.6±1.8 ; p=0.515	g/dL
Wu et al. (24)	104	before and after PCI	TTE, 6 mo	≥15% decrease in ESV (reverse remodeling)	56 (53.8%,) reverse	none	13.6±1.4 vs. 13.7±1.5 ; p=0.19	g/dL
Andrejic et al. (51)	57	during PCI	TTE, 6 mo	ΔESV≥20%	22 (38.6%)	none	142 [132, 142] vs. 130.5 [112.5, 154.5] ; p=0.397	g/L
linear regression								
Lin et al. (47)	264	day 2	TTE, 6 mo	ΔEDVI>20 ml/m²	unavailable	positive	standardized coefficient : 1.333 ; p=0.007	
Liu et al. (48)	331	unavailable	TTE, 6 mo	increase in EDVi	NA	positive none, multivariate	coefficient : 1.464 ; p=0.026 coefficient : 0.394 ; p=0.567	
White blood cells								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Abdel Hamid et al. (53)	62	within 24 hours	TTE, 1 mo	ΔEDV≥20%	16 (26%)	none	11.6±4.4 vs. 14.0±3.8 ; p=0.065	10^3 cells/mL
Bonios et al. (54)	42	baseline	TTE, 3 mo	ΔESV>15 %	13 (31%)	positive	11.5±3.0 vs. 16.0±3.0 ; p<0.05	cells/L
Garcia et al. (27)	64	48h [IQR 24;72]	CMR, 3 and12 mo	ΔESV>10%	NA	positive	10,346±3,626 vs. 12,028±2,593 ; p=0.028	
Andrejic et al. (51)	57	during PCI	TTE, 6 mo	ΔESV≥20%	22 (38.6%)	positive	9.0 [8.3, 11.7] vs. 9.5 [9.17, 12.6] ; p=0.016 ; Z=2.404	10^{12}/L
Garcia et al. (27)	64	48h [IQR 24;72]	CMR, 3 and 12 mo	ΔESV>10%	NA	positive	7,596±3,822 vs. 9,035±3,036 ; p<0.001	neutrophils
Caldentey et al. (55)	227	day 1, day 7, 6 months	CMR, 6 mo	ΔEDV≥20%	29 (16%)	none none	0.59±0.55 vs. 0.60±0.26 ; p=0.924 0.79±0.98 vs. 1.19±2.09 ; p=0.210	G/L, day 1 G/L, day 7 monocytes
logistic regression								
Bochenek et al. (56)	66	Upon admission, 6, 12 and 24h	TTE, 3 mo	ΔEDV>20%	22 (33%)	positive, bivariate	OR 1.31, 95%CI [1.08, 1.58] ; p=0.01	per 1/L
Liu et al. (30)	198	day 5	TTE, 12 mo	ΔEDV≥20%	56 (28.3%)	positive none, multivariate	OR 1.065, 95%CI [1.001, 1.133] ; p=0.0467 OR 0.955, 95%CI [0.857, 1.065] ; p=0.4101	
Swiatkiewicz et al. (17)	198	at admission, 24 hours	TTE, 6 mo	ΔEDV>20%	55 (27.8%)	none none	OR 1.10, 95%CI [0.97, 1.22] ; p=0.068 OR 1.09, 95%CI [0.97, 1.23] ; p=NS	admission at 24h per 10^3 increase
Aoki et al. (57)	131	at presentation and every 24 h for at least 5 days	LVG, 6 mo	ΔEDVI≥10%	48 (37%)	positive none, multivariate	p=0.017 OR 1.198 95%CI [0.196, 7.333] ; p=0.845	cut-off≥12000/mm3 Peak WBC
Aoki et al. (57)	131	at presentation and every 24 h for at least 5 days	LVG, 6 mo	ΔEDVI≥10%	48 (37%)	positive none, multivariate	p=0.082 OR 0.412, 95%CI [0.07, 2.404] ; p=0.324	cut-off≥8900/mm3 peak neutrophils
Aoki et al. (57)	131	at presentation and every 24 h for at least 5 days	LVG, 6 mo	ΔEDVI≥10%	48 (37%)	positive none, multivariate	p=0.001 OR 2.741, 95%CI [0.995, 7.554] ; p=0.051	cut-off≥830/mm3 peak monocytes
linear regression								
Lin et al. (47)	264	day 2	TTE, 6 mo	ΔEDVI>20 ml/m²	unavailable	positive	standardized coefficient : 1.099 ; p=0.042	

Zaliaduonyte-Peksiene et al. (58)	141	unavailable	TTE, 4 mo	ΔEDV≥20%	49 (34.8%)	positive positive, multivariate	OR 1.16, 95%CI [1.00, 1.35] ; p=0.038 OR 1.12, 95CI [1.00, 1.28] ; p=0.04
Liu et al. (48)	331	unavailable	TTE, 6 mo	increase in EDVi	NA	none none, multivariate	coefficient : 0.694 ; p=0.058 coefficient : 0.266 ; p=0.447
ROC curve							
Karuzas et al. (59)	75	every 6 h after admission until peak values	TTE, 6 mo	ΔEDV≥15%	22 (29.3%)	none	AUC 0.497 ; p=0.567 ; cut-off value 13.4x10^9/L sensitivity 28 % ; specificity 61 %
not described							
Bauters et al. (23)	226 (Q-wave MI)	at admission	TTE, 12 mo	change in EDV	NA	positive	

Table 3.

	sample size	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	relationship	comments
Glucose								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Buono et al. (60)	109	once daily during hospitalization	TTE, 17 mo	ΔEDVI≥20%	30 (28%)	none	134±62 vs. 125±46 ; p=0.507	mg/dL, fasting
Wu et al. (24)	104	in the morning of the first day after admission	TTE, 6 mo	≥15% decrease in ESV (reverse remodeling)	56 (53.8%) reverse	none	8.44±4.96 vs. 8.42±4.63 ; p=0.50	mmol/L, fasting
Barberato et al. (52)	55	baseline	TTE, 2 mo	ΔESV≥15 %	13 (24%)	none	126±55 vs. 129±29 ; p=0.9	mg/dL
Reindl et al. (61)	143	unavailable	CMR, 4 mo	ΔEDVI≥15%	29 (20%)	none	134 [114, 153] vs. 136 [118, 165] ; p=0.36	mg/dL
Swiatkiewicz et al. (17)	198	at admission	TTE, 6 mo	ΔEDV>20%	55 (27.8%)	none	7.4 [6.7, 9.2] vs. 7.8 [6.8, 9.6] ; p=NS	mmol/L, admission
Türkoğlu et al. (21)	255	at admission, 24 hours	TTE, 6 mo	ΔEDV≥20%	60 (23.5%)	none	145.9±70.0 vs. 150.0±89.4 ; p=0.722	mg/dL
Andrejic et al. (51)	57	during PCI	TTE, 6 mo	ΔESV≥20%	22 (38.6%)	none	6.00 [5.10, 8.10] vs. 5.50 [4.63, 9.60] ; p=0.525 ; Z=0.635	
logistic regression								
Aoki et al. (57)	131	at presentation	LVG, 6 mo	ΔEDVI≥10%	48 (37%)	positive positive, multivariate	p=0.003 OR 3.020, 95%CI [1.329, 6.866] ; p=0.008	cut-off 130 mg/dL, fasting
Gohbara et al. (16)	69	at admission	CMR, 7 mo	ΔEDVI≥20%	18 (26.1%)	none none	OR 1.007, 95%CI [0.996, 1.018] ; p=0.196 OR 1.016, 95%CI [0.999, 1.034 ; p=0.065	per 1 mg/dL
Joyce et al. (62)	964	unavailable	TTE, 6 mo	ΔEDV≥20%	296 (30.7%)	positive none multivariate	OR 1.08, 95%CI [1.03, 1.13] ; p=0.001 p=NS	mmol/L
Piestrzeniewicz et al. (63)	75	at admission	TTE, 12 mo	ΔEDVI≥20%	15 (20%)	positive	OR 1.0228, 95%CI [1.008, 1.0378] ; p=0.0024	
Urbano-Moral et al. (31)	112	during PCI	TTE, 6 mo	ΔEDV≥20%	24 (21.4%)	none	OR 0.998, 95%CI [0.990, 1.006] ; p=0.60	at enrolment
linear regression								
Bauters et al. (64)	137	at admission	TTE, 12 mo	ΔEDV>20%	44 (32%)	positive, multivariate positive, multivariate	beta coefficient 0.218 ; p=0.009 beta coefficient 0.173 ; p=0.03	cut-off glucose admission 7 mM glucose : quantitative values
correlation (Pearson or Spearman)								
Feistritzer et al. (45)	89	at admission	CMR, 4 mo	ΔEDV≥20%	14 (15.7%)	none	r=0.020 ; p=0.852	mg/dL, admission
not described								
Nicolau et al. (65)	52	at admission	Radionuclide ventriculography, 6 mo	none	NA	positive		

Table 4.

	sample size	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	relationship	comments
Peak C-reactive protein								
logistic regression								
Aoki et al. (57)	131	at presentation and every 24 h for at least 5 days	LV, 6 mo	ΔEDVI≥10%	48 (37%)	none none, multivariate	p=0.095 OR 1.417, 95%CI [0.606, 3.316] ; p=0.422	cut-off 10.2 mg/dL
Gohbara et al. (16)	69	at admission, every 3h during 24 h, every 6h the next 2 days then daily	CMR, 7 mo	ΔEDVI≥20%	18 (26.1%)	none	OR 1.019, 95%CI [0.887, 1.171] ; p=0.787 OR 1.038, 95%CI [0.835, 1.291] ; p=0.736	per 1mg/dL
correlation (Pearson or Spearman)								
Feistritzer et al. (45)	89	serially	CMR, 4 mo	ΔEDV≥20%	14 (15.7%)	none	r=0.042 ; p=0.698	mg/dL
C-reactive protein								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Caldentey et al. (55)	227	day 1, day 7	CMR, 6 mo	ΔEDV≥20%	29 (16%)	none none	87.8±185.9 vs. 76.8±117.0 ; p=0.781 75.7±173.6 vs. 52.8±103.7 ; p=0.535	ng/mL, day 1 ng/mL, day 7
Zaliaduonyte-Peksiene et al. (58)	141	unavailable	TTE, 4 mo	ΔEDV≥20%	49 (34.8%)	none	4.7 [2.85, 16.32] vs. 10.58 [2.2, 24.5] ; p=NS	mg/L
Garcia et al. (27)	64	48h [IQR 24;72]	CMR, 3 and 12 mo	ΔESV>10%	NA	positive	21.7±30.4 vs. 35.9±44.3 ; p=0.02	mg/L
logistic regression								
Dominguez-Rodriguez et al. (15)	108	before primary PCI	TTE, 12 mo	ΔEDV>20%	21 (19%)	none	OR 1.369, 95%CI [0.638, 2.940] ; p=0.42	
Liu et al. (30)	198	day 5	TTE, 12 mo	ΔEDV≥20%	56 (28.3%)	positive none, multivariate	OR 1.218, 95%CI [1.077, 1.377] ; p=0.0017 OR 1.012, 95%CI [0.803, 1.275] ; p=0.9222	
Piestrzeniewicz et al. (63)	75	unavailable	TTE, 12 mo	ΔEDVI≥20%	15 (20%)	positive	OR 1.145, 95%CI [1.037, 1.264] ; p=0.0072	
Swiatkiewicz et al. (17)	198	at admission, 24 hours, discharge	TTE, 6 mo	ΔEDV>20%	55 (27.8%)	none positive none positive, multivariate	OR 2.99, 95%CI [0.60, 14.92] ; p=NS OR 1.29, 95%CI [1.08, 1.56] ; p<0.01 OR 1.05, 95%CI [0.86, 1.30] ; p=NS OR 1.29, 95%CI [1.04, 1.60] ; p<0.05	admission 24h admission discharge discharge for a 10 mg/L increase
linear regression								
Fertin et al. (19)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	positive	beta coefficient: 0.185 ; p=0.006	baseline
ROC curve								
Karuzas et al. (59)	75	every 6 h after admission until peak values	TTE, 6 mo	ΔEDV≥15%	22 (29.3%)	none	AUC 0.601 ; cut-off 13.9 mg/L ; p=0.108 sensitiviy 48 % ; specificity 78 %	
correlation (Pearson or Spearman)								
Schoos et al. (66)	55	day 1-2, day 4, day 7	CMR, 6 mo	change in EDV and/or ESV	NA	none none	R=-0.073 ; p=0.61 R=-0.028 ; p=0.92	for ΔESV for ΔEDV
Peak high-sensitivity C-reactive protein								
logistic regression								
Reindl et al. (61)	143	unavailable	CMR, 4 mo	ΔEDV≥15%	29 (20%)	positive positive, multivariate	OR 4.39, 95%CI [1.86, 10.31] ; p=0.001 OR 2.66, 95%CI [1.05, 6.71] ; p=0.04	cut-off 31 mg/L
linear regression								
Reindl et al. (67)	102	unavailable	CMR, 4 mo	ΔEDV≥20%	15 (14.7%)	positive none, multivariate	OR 4.29, 95%CI [1.26, 14.56] ; p=0.02 p=NS	cut-off 23 mg/L

High-sensitivity C-reactive protein								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Buono et al. (60)	109	day 2, after a 12-hour overnight fast	TTE, 17 mo	ΔEDVI≥20%	30 (28%)	none	11±18 vs. 17±25 ; p=0.281	mg/L
Hsu et al. (10)	97 (61% STEMI)	at first 3 days	TTE, 6 mo	ΔEDV>20%	24 (32.9%)	none	33.3±36.2 vs. 37.5±44.2 ; p=0.662	mg/L
Khurelsukh et al. (50)	35	at admission	TTE, 2 and 12 mo	ΔEDVI≥20% (2 mo)	14 (40%)	positive	0.18±0.20 vs. 0.38±0.38 ; p=0.046	ng/dL
Na et al. (28)	208	unavailable	TTE, 6 mo	ΔEDV>20%	53 (25.5%)	none	0.94±2.40 vs. 0.67±1.14 ; p=0.276	mg/L
Choe et al. (68)	1237	unavailable	TTE, 6 mo	>10% decrease in ESV (reverse remodeling)	466 (37,7%) reverse	positive none (propensity-matched)	0.6 [0.2, 0.8] vs. 0.7 [0.3, 0.6] ; p=0.046 0.6 [0.1, 2.9] vs. 0.8 [0.3, 4.6] ; p=0.111	mg/L
Wu et al. (24)	104	before and after PCI	TTE, 6 mo	≥15% decrease in ESV (reverse remodeling)	56 (53.8%) reverse	none	0.57±0.34 vs. 0.56±0.39 ; p=0.87	mg/L
Andrejic et al. (51)	57	during PCI	TTE, 6 mo	ΔEDV≥20%	22 (38.6%)	positive	3.4 [1.35, 7.3] vs. 13.50 [4.70, 87.20] ; p=0.035 ; Z=2.112	mg/L
logistic regression								
Urbano-Moral et al. (31)	112	at discharge	TTE, 6 mo	ΔEDV≥20%	24 (21.4%)	positive positive, multivariate positive, multivariate	OR 1.022, 95%CI [1.006, 1.038] ; p=0.006 OR 1.016, 95%CI [1.000, 1.032] ; p=0.04 OR 1.040, 95%CI [1.000, 10.081] ; p=0.04	mg/L, discharge mg/L, discharge, unadjusted mg/L, discharge, adjusted
ROC curve								
Reindl et al. (34)	88	unavailable	CMR, 4 mo	ΔEDV≥20%	11 (12.5%)	positive none, multivariate	AUC 0.68, 95%CI [0.52, 0.84] ; cut-off 23mg/L Se 73 % ; Sp 63 % ; PPV 23 % ; NPV 94 % p=NS	
Reinstadler et al. (37)	123	at admission and daily between day 1 and day 4	CMR, 4 mo	ΔEDV≥20%	16 (13.0%)	none	AUC 0.63, 95%CI [0.54, 0.72] ; cut-off 22,5 mg/L sensitivity 88 %, specificity 48 %	admission
Xiaozhou et al. (38)	106	unavailable	TTE, 3 mo	ΔEDV≥20%	22 (20.8%)	positive	AUC 0.825, cut-off 12.4 pg/mL sensitivity 76.2 % ; specificity 81.8 %	
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	variable		
Mather et al. (43)	48	day 2, day 7	CMR, 1 and 3 mo	none	NA	positive (day 2), multivariate		
log high-sensitivity C-reactive protein								
logistic regression								
Hsiao et al. (25)	54	immadiately, 8 hours, 16 hours	TTE, 3 and 6 mo	ΔESV>15% (6 mo)	19 (35.2%)	none		

Table 5.

	sample size	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	relationship	comments
MMP-2								
linear regression								
Fertin et al. (69)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	none	regression coefficient: 0.018 ; p=NS	
correlation (Pearson or Spearman)								
Cerisano et al. (70)	106	early after PCI and at days 1, 7	TTE, 6 mo	change in EDVi	NA	none		
Nilsson et al. (71)	46	before PCI, 12 hours, 24 hours and 48 hours	CMR, 4 mo	change in EDVi and ESVi	NA	none	r range from -0.123 to 0.031 ; p=NS r range from -0.151 to 0.152 ; p=NS	change in EDVi change in ESVi
Webb et al. (72)	32 (84 % STEMI)	at enrollment, days 2 to 5	TTE, 3 and 6 mo	change in EDV	NA	none	r = 0.27 ; p=0.20	
not described								
Kelly et al. (41)	91 (85 % STEMI)	0-12 h, 12-24 h, 24-48 h, and 24 h intervals thereafter, until discharge	TTE, 6 mo	change in LV volumes	NA	none		
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	variable		
MMP-3								
linear regression								
Fertin et al. (69)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	none	regression coefficient: 0.007 ; p=NS	
correlation (Pearson or Spearman)								
Kelly et al. (73)	382 (81.2 % STEMI)	0-12hrs, 12-24hrs and subsequent 24hr periods during the index admission	TTE, 5 mo	change in ESV and EDV	NA	positive	r = 0.123 ; p=0.041	change in ESV
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	variable		
MMP-8								
linear regression								
Fertin et al. (69)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	positive positive, multivariate	regression coefficient: 0.168 ; p=0.01 standardized beta coefficient: 0.162 ; p=0.025	
correlation (Pearson or Spearman)								
Cerisano et al. (70)	106	early after PCI and at days 1, 7	TTE, 6 mo	change in EDVi	NA	none		
Nilsson et al. (71)	46	before PCI, 12 hours, 24 hours and 48 hours	CMR, 4 months	change in EDVi and ESVi	NA	variable : negative/none none	r=-0.322 ; p<0.05 ; p=NS otherwise (r range : -0.125 to 0.022) r range from -0.282 to -0.08 ; p=NS	at 12 hours, change in EDV change in ESV
Webb et al. (72)	32 (84 % STEMI)	at enrollment, , days 2 to 5	TTE, 3 and 6 mo	change in EDV	NA	none	r=0.04 ; p>0.20	
MMP-9								
logistic regression								

Urbano-Moral et al. (31)	112	at discharge	TTE, 6 mo	ΔEDV≥20 %	24 (21.4%)	positive positive, multivariate positive, multivariate	OR 1.001, 95%CI [1.000, 1.001] ; p=0.004 OR 1.000, 95%CI [1.000, 1.001] ; p=0.03 OR 1.001, 95%CI [1.000, 1.001] ; p=0.04	ng/mL ng/mL, unadjusted ng/mL, adjusted
linear regression								
Fertin et al. (69)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	positive (baseline)	regression coefficient: 0.153 ; p=0.02 standardized beta coefficient: 0.131 ; p=0.07	
correlation (Pearson or Spearman)								
Cerisano et al. (70)	106	early after PCI and at days 1, 7	TTE, 6 mo	change in EDVi	NA	none		
Kelly et al. (41)	91 (85 % STEMI)	0-12 h, 12-24 h, 24-48 h, and 24 h intervals thereafter, until discharge	TTE, 6 mo	change in LV volumes	NA	positive positive, multivariate positive, multivariate	r=0.3 ; p=0.016 p=0.007 p=0.005	change in EDV change in EDV change in ESV
Kelly et al. (39)	404 (81 % STEMI)	within 24 h of admission	TTE, 10 mo	change in EDV and ESV, increased EDV	142 (48.6%)	positive none	r=0.174 ; p=0.005 r=0.04 ; p=0.520	change in EDV change in ESV
Nilsson et al. (71)	46	before PCI, 12 hours, 24 hours and 48 hours	CMR, 4 mo	change in EDVi and ESVi	NA	positive none	r range from -0.288 to 0.033 ; p=NS r range from -0.228 to -0.027 ; p=NS	change in EDV change in ESV
Webb et al. (72)	32 (84 % STEMI)	at enrollment, , days 2 to 5	TTE, 3 and 6 mo	change in EDV	NA	positive	r=0.63 ; p=0.03	
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	none		
TIMP-1								
linear regression								
Fertin et al. (69)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	none	regression coefficient: 0.116 ; p=NS	
correlation (Pearson or Spearman)								
Cerisano et al. (70)	106	early after PCI and at days 1, 7	TTE, 6 mo	unavailable	NA	none none none	r=-0.06 ; p=0.60 r=-0.03 ; p=0.81 r=-0.12 ; p=0.28	baseline day 1 day 7
Kelly et al. (39)	404 (81 % STEMI)	pre-discharge	TTE, 10 mo	change in EDV and ESV, increased EDV	142 (48.6%)	variable	r=0.124 ; p=0.036 r=0.116 ; p=0.05	change in EDV change in ESV
Nilsson et al. (71)	46	before PCI, 12 hours, 24 hours and 48 hours	CMR, 4 mo	change in EDVi and ESVi	NA	variable none	r=-0.305 ; p<0.05 ; p=NS otherwise r range from -0.261 to -0.076 ; p=NS	at 48h, change in EDV change in ESV
Webb et al. (72)	32 (84 % STEMI)	at enrollment, , days 2 to 5	TTE, 3 and 6 mo	change in EDV	NA	none	r=-0.20 ; p>0.20	
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	none		
TIMP-2								
linear regression								
Fertin et al. (69)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	ΔEDV>20%	87 (38%)	none	regression coefficient: 0.066 ; p=NS	
correlation (Pearson or Spearman)								
Cerisano et al. (70)	106	early after PCI and at days 1, 7	TTE, 6 mo	change in EDVi	NA	none none negative	r=0.09 ; p=0.42 r=0.05 ; p=0.63 r=-0.24 ; p=0.03	baseline day 1 day 7
Nilsson et al. (71)	46	before PCI, 12 hours, 24 hours and 48 hours	CMR, 4 mo	change in EDVi and ESVi	NA	none none	r range from -0.043 to 0.044 ; p=NS r range from 0.015 to 0.092 ; p=NS	change in EDV change in ESV

Webb et al. (72)	32 (84 % STEMI)	at enrollment, , days 2 to 5	TTE, 3 and 6 mo	change in EDV	NA	none	r=-0.24 ; p>0.20	
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	none		
N-terminal type I procollagen (PINP)								
logistic regression								
Urbano-Moral et al. (31)	112	at discharge	TTE, 6 mo	ΔEDV≥20 %	24 (21.4%)	none	OR 1.003, 95%CI [0.969, 1.038] ; p=0.90	µg/l
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	variable		
N-terminal type III procollagen (PIIINP)								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Radovan et al. (74)	30	at admission, day 2, day 4, day 7	TTE, 1 and 6 mo	none	NA	positive	ΔEDVI = 4.67±0.95 mL/m2 (PIIINP4≤4.0µg/L) vs. 12.84±1.23 mL/m2 ; p<0.0001	
correlation (Pearson or Spearman)								
Poulsen et al. (75)	47	at admission, once a day during the following 3 days	TTE, 3 and 12 mo	none	NA	positive	r=0.50 ; p<0.001	day 4
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	none		
carboxy-terminal telopeptide of procollagen type I (ICTP)								
linear regression								
Cerisano et al. (18)	56	day 1, day 3	TTE, 6 mo	ΔLVEDVI > 2 times the SD of baseline values	17 (30%)	positive positive, multivariate	beta coefficient : 1.388 [1.082, 1.781] ; p=0.01 beta coefficient : 2.140 [1.120, 3.550] ; p=0.01	
not described								
Manhenke et al. (42)	42	prior to PCI, day 2, week 1	CMR, 2 and 12 mo	none	NA	none		
carboxy-terminal propeptide of procollagen type (PICP)								
between groups comparison (t-test, wilcoxon sum test or Mann-Whitney test) : LVR- vs. LVR+								
Cerisano et al. (18)	56	day 1, day 3	TTE, 6 mo	ΔLVEDVI > 2 times the SD of baseline values	17 (30%)	none	99±31 vs. 86±34 ; p=0.197	ng/mL
Radovan et al. (74)	30	at admission, day 2, day 4, day 7	TTE, 1 and 6 mo	none	NA	positive	ΔEDVI = 3.96±1.01 mL/m2 (PICP4≤110.0µg/L) vs. 8.93±1.68 mL/m2 ; p=0.02	

Table 6.

	sample size	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	relationship	comments
Copeptin								
Kelly et al. (91)	274 (84 % STEMI)	day 3 to 5	TTE, 5 mo	change in EDV and ESV	88 (32.1%)	positive	ΔEDV: r=0.171, p=0.015 ; ΔESV: r=0.186, p=0.008.	
Reinstadler et al. (44)	47	day 2	CMR, 4 mo	ΔEDV≥20%	6 (12.8%)	positive	AUC 0.79 , 95%CI [0.59, 0.98] , cut-off value 16.7 pmol/L sensitivity: 67% ; specificity: 88 %	pmol/L
Galectin-3								
Di Tano et al. (29)	92	Baseline	TTE, 6 mo	ΔESV≥15%	26 (28.2%)	positive positive, multivariate	OR 1.22, 95%CI [1.09, 1.38] ; p=0,0001 OR 1.22, 95%CI [1.06, 1.39] ; p=0.005	per 1ng/mL change
Andrejic et al. (51)	57	day 1	TTE, 6 mo	ΔESV≥20%	22 (38.6%)	positive	8.22±2.34 vs. 10.34±3.81 ; t=2.589 ; p=0.012	ng/mL
Hepatocyte Growth Factor								
Lamblin et al. (76)	226 (Q-wave MI)	at discharge (day 3 to day 7)	TTE, 12 mo	increase in EDV and ESV	NA	none		
Soeki et al. (77)	40 (AMI)	at admission, day 7	LVG, 3 mo	ΔEDVi ≥5 ml/m2	15 (37.5%)	variable	0.33±0.08 vs. 0.34±0.12 ; p=0.640 0.47±0.13 vs. 0.36±0.09 ; p=0.003	ng/mL, day 1 ng/mL, day 7
Myeloperoxidase								
Nilsson et al. (71)	46	before PCI, 12 hours, 24 hours and 48 hours	CMR, 4 mo	change in EDVi and ESVi	NA	none variable	correlation : r range from -0.199 to -0.109 ; p=NS correlation : r range from -0.347 to -0.033 ; p<0.05 at 48 hours (r=-0.347) ; p=NS otherwise	change in EDV change in ESV
Stamboul et al. (78)	40	before and during PCI	CMR, 6 mo	ΔESV>10%	19 (47.5%)	none	MPO <640ng/mL : LVR 6/20 patients vs. MPO >640pg/mL : LVR 13/20 patients ; p=0.066	
Yunoki et al. (79)	160	at admission	LVG, 6 mo	none	NA	positive	correlation : r=0.230 ; p<0.05	
Helseth et al. (92)	272	before and immadiately after PCI and day 1	CMR, 4 mo	change in EDVI or ESVI	NA	none		myeloperoxidase DNA
Osteoprotegerin								
Erkol et al. (80)	80	at admission	TTE, 6 mo	ΔEDV≥20 %	29 (36.3%)	positive positive, multivariate	OR 4.07, 95%CI [1.51, 10.94] ; p=0.005 OR 4.05, 95%CI [1.06, 15.38] ; p=0.04	cut-off>132 pg/mL
Shetelig et al. (81)	272	before and immediately after PCI, day 1	CMR, 4 mo	change in EDV	NA	none	ΔEDV : 9.0 (-8.3, 24.8) mL (OPG<median) vs. 9.0 (-7.0, 27.0) mL (OPG>median) ; p=0.61	
ST2 (suppression of tumorigenicity-2)								
Bière et al. (40)	66	baseline	CMR, 3 and 12 mo	ΔESV>10%	33 (20%)	none		
Kercheva et al. (33)	31	day 1, day 3, day 7	TTE, 6 mo	ΔEDV and/or ΔESV>20%	14 (45.2%)	positive (day 1 and day 3, none otherwise)	42 (28, 262) ng/mL vs. 162 (36, 279) ng/mL; p=0.015 33 (17,61) ng/mL vs. 81 (29, 191) ng/mL ; p=0.021 25 (14, 44) ng/mL vs. 39 (24, 113) ng/mL ; p>0.05	day 1 day 3 day 7

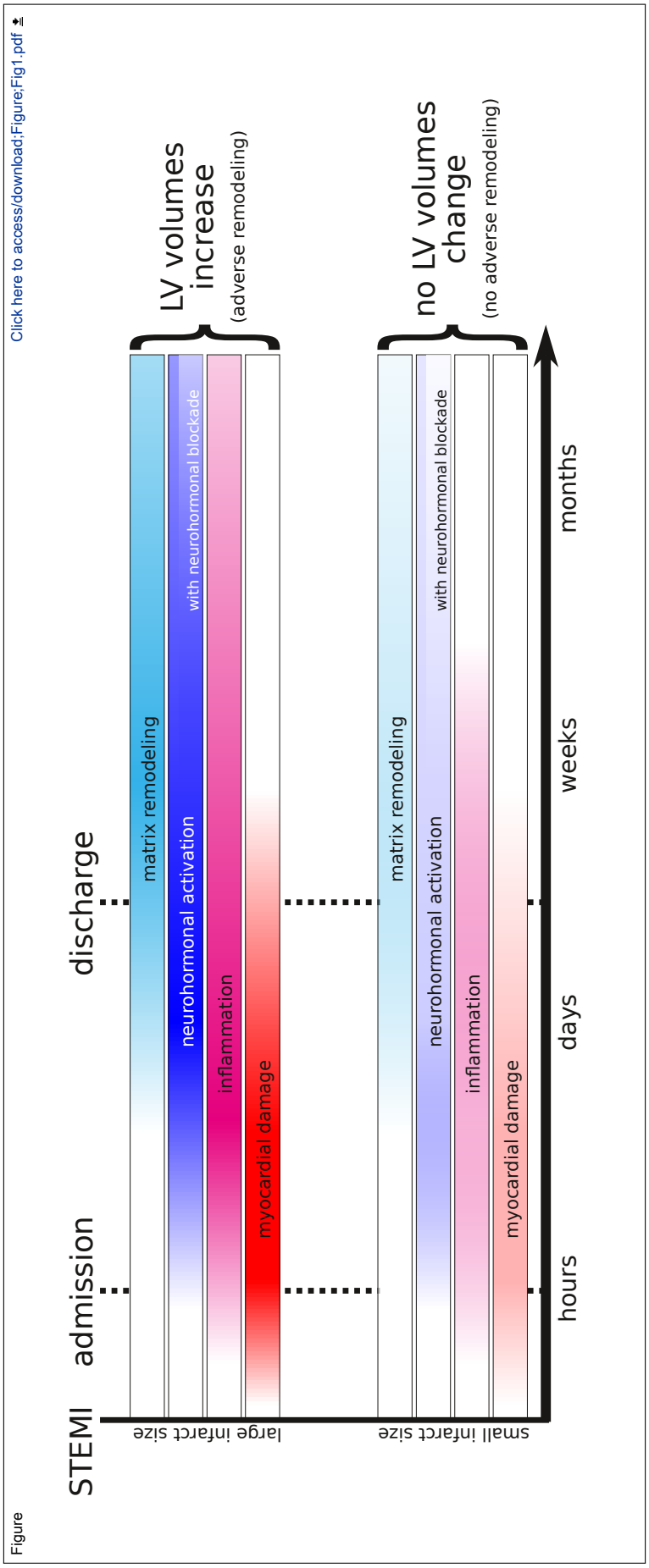
Figure
Click here to access/download;Figure;Fig1.pdf
STEMI
admission
discharge
matrix remodeling
neurohormonal activation
with neurohormonal blockade
inflammation
myocardial damage
large infarct size
LV volumes increase
(adverse remodeling)
small infarct size
no LV volumes change
(no adverse remodeling)
hours
days
weeks
months

Relation entre taux de néprilysine et remodelage ventriculaire gauche

Les systèmes neuro-hormonaux jouent un rôle fondamental dans la survenue du RVG après SCA. La relation entre certains biomarqueurs en lien avec l'activation neuro-hormonale et le RVG ont déjà été décrits. La néprilysine est une endopeptidase capable de dégrader de nombreux substrats tels que la bradykinine, les peptides natriurétiques ou encore l'adrénomédulline [105, 106]. Son inhibition par le sacubitril, associée à un traitement par valsartan forme ce qu'on appelle un inhibiteur de la néprilysine (angiotensin receptor-neprilysin inhibitor) (ARNI) et a permis de diminuer la mortalité et les réhospitalisations pour IC par rapport à l'enalapril, dans une population de patients ayant une IC à FEVG altérée [107]. L'inhibition du SRAA permet de limiter le RVG [108] et de diminuer la mortalité après un STEMI [109]. Dans ce contexte, l'objectif de ce travail est donc d'étudier la relation entre les niveaux plasmatiques de néprilysine et le RVG au décours d'un STEMI.

Le dosage de néprilysine a été réalisé chez 68 patients de la cohorte RESIST pour lesquels nous disposions de prélèvements sanguins sur tubes EDTA et d'échocardiographies permettant d'évaluer les volumes VG en 3D, à la phase initiale et durant le suivi (7 mois, minimum: 6 mois, maximum: 10 mois). Les taux de néprilysine étaient faibles, $\leq$125 pg/mL (point d'entrée de la gamme de dosage) pour 38 patients. Nous avons donc formé un premier groupe de patients ayant un taux plasmatique de néprilysine $\leq$125 pg/mL et les trente autres patients ont été répartis dans deux autres groupes en fonction de la médiane des valeurs de néprilysine chez ces patients (valeur médiane: 450 pg/mL).

Les patients ayant les taux les plus élevés de néprilysine avaient aussi la FEVG la plus basse à la phase aiguë (39,1% $\pm$ 6,9% vs. 46,4% $\pm$ 8,3% dans le groupe $\leq$125 pg/mL et vs 47,1% $\pm$ 8,1% dans le groupe intermédiaire [126 – 450 pg/mL], p<0,01). Au cours du suivi, la récupération de la FEVG était meilleure dans le groupe néprilysine >450 pg/mL, conduisant à l'absence de différence significative sur la FEVG par rapport aux autres groupes au terme du suivi (50,4% $\pm$ 9,9% vs 53,0% $\pm$ 8,9% et 50,6% $\pm$ 9,7% ; p=0.55). Le taux de néprilysine initial est ainsi positivement associé à un stunning en analyse univariée et multivariée. En revanche, nous n'avons pas mis en évidence de corrélation significative avec le volume télédiastolique ventriculaire gauche ou son évolution au cours du suivi.

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BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction

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Abstract

Background: Left ventricular remodeling following ST-elevation myocardial infarction (STEMI) is associated with poor outcome, including heart failure (HF). Neprilysin inhibition leads to improved outcome in patients with altered left ventricular ejection fraction (LVEF).

Methods: We aimed to assess the association between serum levels of neprilysin and left ventricular (LV) volumes, function and remodeling in STEMI patients with successful myocardial reperfusion and no clinical sign of HF. Sixty-eight patients were admitted for STEMI and had both plasma neprilysin measurement at baseline and 3D transthoracic echocardiogram at baseline and after a median follow-up of 7 months. We compared 3 groups: a group with a low-level of plasma neprilysin (< 125 pg/mL, i.e. the lower limit of detection of the assay) and the two other groups were defined as being below or above the median value of the remaining samples.

Results: Median age was 58.5 ± 12.8 years and 56 (82.4%) were men. Median LVEF was 45.0 ± 8.5%. Baseline characteristics were comparable between groups (low-level of neprilysin group [≤125 pg/mL, $n = 38$], medium-level of neprilysin group [126–450 pg/mL, $n = 15$] and a high-level group [> 450 pg/mL, n = 15]). At baseline there was a non-significant trend towards lower end-diastolic volume ($p = 0.07$) but significantly lower LVEF in the high neprilysin group (46.4 ± 8.3%, 47.1 ± 8.1% and 39.1 ± 6.9%, $p < 0.01$). At follow-up, the magnitude of LVEF increase was significantly more important in the high neprilysin group compared to the other groups ($p = 0.022$ for relative change in LVEF and 6.6 ± 7.3%, 3.6 ± 9.0% and 11.3 ± 8.4%, $p = 0.031$ for absolute change in LVEF) resulting in similar LVEF levels at follow-up between all groups (53.0 ± 8.9%, 50.6 ± 9.7% and 50.4 ± 9.9%, $p = 0.55$).

Conclusions: Initial high neprilysin levels may identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up. Future studies will have to assess the role of neprilysin in the setting of STEMI and the potential benefit of its blockade.

Keywords: Neprilysin, ST-elevation myocardial infarction, Left ventricular remodeling

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Background

Despite widespread urgent coronary revascularization in the setting of ST-elevation myocardial infarction (STEMI), subsequent left ventricular remodeling (LVR) remains common [1, 2] and associated with mortality, heart failure (HF) and ventricular arrhythmia [3]. LVR is the consequence of cellular and histological modifications, such as myocyte hypertrophy, apoptosis and extracellular matrix remodeling [4]. These phenomena are induced by deleterious adaptive mechanical and neurohormonal responses, including the renin-angiotensin-aldosterone system (RAAS) [5]. Early angiotensin-converting enzyme (ACE) inhibition following STEMI associated with a significant reduction in mortality [6] and decreased LVR through suppression of the activity of the RAAS [7] is to be considered in all STEMI patients [8]. Neprilysin is a neutral endopeptidase that degrades several endogenous vasoactive peptides, such as bradykinin, natriuretic peptides and adrenomedullin [9, 10]. Its inhibition interacts with the RAAS, increasing angiotensin-II blood concentrations as compared with placebo, indicative of blockade of the angiotensin-II receptor type 1 (AT1) receptor [11]. In the PARADIGM-HF trial [12], neprilysin inhibition combined with inhibition of AT1 receptors was superior to ACE inhibition by enalapril in reducing both the risks of death and hospitalization for HF in patients with HF and reduced LVEF. In a recent study, the use of an angiotensin receptor-neprilysin inhibitor yielded a significant decrease in left ventricular (LV) volumes at 4 months in the same HF population [13]. There is no data available about the relationship between baseline neprilysin levels and LVR after STEMI. The aim of the present study was to assess the association between serum levels of neprilysin and LV volumes, function and remodeling in STEMI patients at baseline and 6 ± 1 month follow-up.

Methods

This study was a prospective, observational multicenter study that included consecutive patients admitted for STEMI and treated with either primary percutaneous coronary intervention (pPCI) or rescue PCI after unsuccessful fibrinolysis therapy, from January 2017 to October 2018. Inclusion criteria were as follows: age ≥ 18 years, chest pain associated with an ECG with ST-segment elevation (either > 1 mm in ≥2 contiguous limb leads or > 2 mm in ≥2 contiguous precordial leads or new left bundle branch block or new significant Q wave). Criteria for exclusion were unsuccessful revascularization (residual stenosis > 30% in the culprit lesion and/or thombolysis in myocardial infarction flow < 3), clinical signs of HF as defined by Killip Kimball class≥II, non-related heart conditions with estimated life expectancy < 12 months and follow-up planned in another center. Informed consent was obtained from the patients. The study complied with the Declaration of Helsinki and was approved by the local ethics committee (protocol number A14-D17-VOL.20).

On admission, routine blood samples were drawn and collected in tubes containing lithium heparin, ethylenediaminetetraacetic acid or spray-coated silica, centrifuged for 12 min at 2000 g at room temperature then assayed for routine biological measurement. The remaining plasma and serum were stored at − 80 °C until use. Neprilysin was measured on remaining plasma samples in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (Human Neprilysin DuoSet ELISA, RD systems, Minneapolis, USA) according to the manufacturer's instructions. Data were linearized by plotting the log of neprilysin concentrations versus the log of the optical density and the best fit line was determined by regression analysis. Other measurements specific to the present study included high-sensitivity cardiac troponin I (hs-cTnI) (Dxi Beckman Coulter) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Cobas e-411, Roche). Minimum sensitivity and upper limit of detection were 2.3–27027 pg/mL for hs-cTnI, 5–35000 pg/mL for NT-proBNP, and 125–8000 pg/mL for neprilysin; values higher than the upper limit of detection were manually diluted for neprilysin. The highest intra- and inter-assay coefficients of variation were 3.9 and 5.1% for hs-cTnI and 2,7% and 4,6% for NT-proBNP. The recommended diagnostic threshold for the diagnosis of acute myocardial infarction was hs-cTnI > 17.5 pg/mL.

A total of 94 patients with STEMI underwent successful revascularization during the inclusion period. All included subjects had a complete 3D-transthoracic echocardiogram within 48 h. Transthoracic echocardiograms was planned at 6 months after STEMI, as a part of routine follow-up. All echocardiograms were performed using an ultrasonic device system (EPIQ 7G, Phillips Healthcare, Best, Netherlands) and were obtained by experienced ultrasonographers who were unaware of neprilysin measurement results. A standard imaging protocol was used with 4-chamber, 2-chamber apical, and long and short axis parasternal views. Left ventricle end-diastolic volume (EDV), left ventricle end-systolic volume (ESV)) and LVEF were measured with 3D method, using Intellispace Cardiovascular software (Philips Healthcare, Best, Netherlands) and TomTec software (TomTec Imaging Systems GmbH, Unterschlessheim, Germany).

The sample size was estimated based on the assumption of a normal distribution for most variables, either as such or after log-transformation by the inclusion of ≥60 patients. The study was designed to compare 3 groups based on the tertiles of neprilysin concentration in our population. However, because of the skewed distribution of neprilysin values, we decided to define the lowest

group by those with levels < 125 pg/mL (i.e. the lower limit of detection of the essay) and to divide the remaining patients into two other groups according to median neprilysin concentration value (450 pg/mL) when quantifiable. Qualitative variables are shown as count and frequency (%). Quantitative variables are presented as mean ± SD or median and interquartile ranges when they had a skewed distribution. Continuous variables were compared using either ANOVA or Kruskall-Wallis test and categorical variables were compared by the $\chi 2$ test or Fisher's exact test, where adapted. Biomarkers levels with skewed distribution were log-transformed before being used as continuous variables in statistical analyses. Spearman correlation coefficient was used to assess the correlation between non-normally distributed quantitative parameters. Statistical tests were 2-sided and used a significance threshold of $p < 0.05$. All statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Among the 94 patients with complete 3D-transthoracic echocardiogram at baseline, two patients died during follow-up. Out of the remaining 92 patients, 14 did not attend follow-up echocardiogram, 3 were excluded due to poor quality of echocardiographic images and 7 were retrospectively excluded because of a loss of blood samples (Fig. 1). A total of 68 patients with complete biological data and both initial and follow-up echocardiography was included in the analyis. Baseline characteristics are depicted in Table 1. Median age was 58.5 ± 12.8 years and 56 (82.4%) were men. Baseline LVEF was 45.0 ± 8.5% (Table 2). Drug therapy at baseline and at follow-up is depicted in Table 3. The mean follow-up time was 7 months [6 to 10 months].

As shown in Table 1, baseline characteristics were comparable between groups (low-level of neprilysin group [≤125 pg/mL, $n = 38$], medium-level of neprilysin group [126–450 pg/mL, $n = 15$] and a high-level group [> 450 pg/mL, n = 15]). Similarly, as shown in Table 2, baseline NT-proBNP levels and hs-cTnI levels were similarly distributed between groups with no correlation between the levels of the two latter and neprilysin levels (r = 0.06 and r = 0.08, respectively). The relationship between neprilysin levels and the changes of LV volumes between baseline and follow-up is depicted in Fig. 2. There were no significant correlation between levels of NT-proBNP, hs-cTnI or neprilysin and the EDV change between baseline and follow-up (r = 0.07, r = 0.09 and r = 0.07, respectively). At baseline there was a non-significant trend towards lower EDV but significantly lower LVEF in the high neprilysin group ($p = 0.07$ and $p < 0.01$, respectively, vs. other groups, Table 2 and Figs. 3 and 4). During follow-up, LVEF increased in both low and the high neprilysin level groups (46.4 ± 8.3% to 53.0 ± 8.9%, $p < 0.001$; and 39.1 ± 6.9% to 50.4 ± 9.9%, $p < 0.001$ respectively). The magnitude of LVEF increase during follow-up was significantly more important in the high neprilysin group compared to the other groups ($p = 0.022$ for relative and $p = 0.031$ for absolute change in

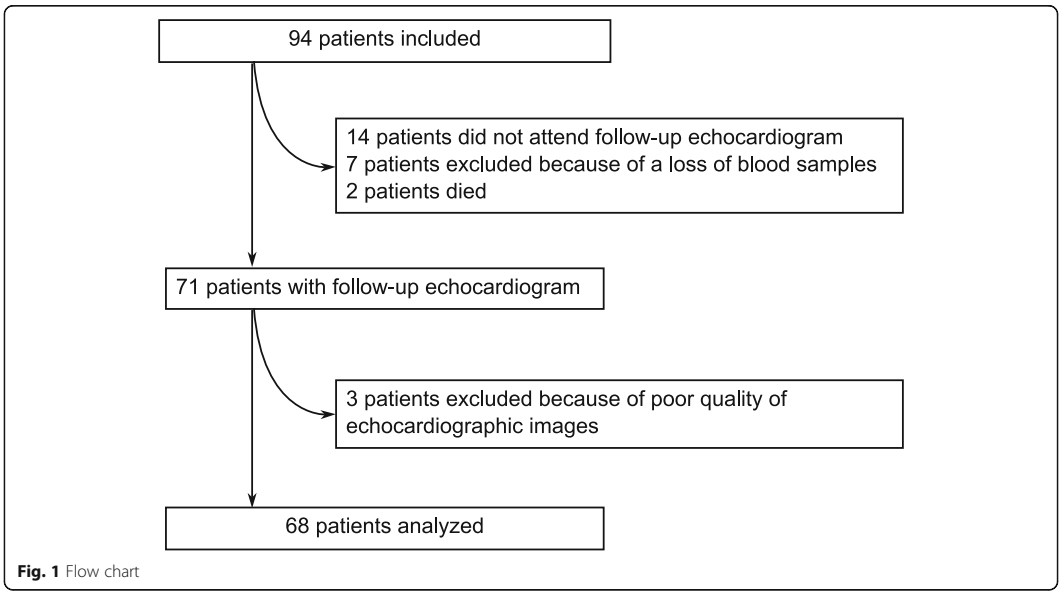

Fig. 1 Flow chart

Table 1 Baseline characteristics according to neprilysin levels

	Overall ($n = 68$)	Neprilysin level ≤ 125 pg/mL ($n = 38$)	Neprilysin level 126–450 pg/mL ($n = 15$)	Neprilysin level > 450 pg/mL ($n = 15$)	Overall *p*.value	Highest-level vs. lower groups *p*.value
Age, years	58.5 ± 12.8	59.8 ± 11.7	54.8 ± 9.8	60.5 ± 16.8	0.37	0.58
Gender, male	56 (82.4%)	31 (81.6%)	13 (86.7%)	12 (80.0%)	0.88	1
Hypertension	25 (36.8%)	11 (28.9%)	6 (40.0%)	8 (53.3%)	0.25	0.23
Diabetes mellitus	13 (19.1%)	7 (18.4%)	3 (20.0%)	3 (20.0%)	0.99	1
Hypercholesterolemia	33 (48.5%)	19 (50.0%)	6 (40.0%)	8 (53.3%)	0.74	0.90
Current smoking	43 (63.2%)	26 (86.4%)	8 (53.3%)	9 (60.0%)	0.57	1
Body Mass Index, kg/m2	26.1 [24.0, 29.4]	26.0 [23.6, 29.3]	28.5 [26.3, 29.3]	25.8 [23.4, 30.0]	0.45	0.75
Heart rate, bpm	77 ± 17	75 ± 15	80 ± 19	78 ± 20	0.62	0.77
Systolic BP, mmHg	142 ± 25	145 ± 28	134 ± 22	145 ± 22	0.39	0.65
Diastolic BP, mmHg	85 ± 19	87 ± 16	78 ± 21	86 ± 22	0.26	0.83
Anterior STEMI	27 (39.7%)	15 (39.5%)	6 (40.0%)	6 (40.0%)	1	1
Symptoms to balloon, hours	4.7 [3.1, 8.7]	4.5 [3.2, 6.0]	3.7 [2.7, 8.6]	6.8 [3.9, 10.8]	0.36	0.18
Thrombolysis	2 (2.9%)	1 (2.6%)	0	1 (6.7%)	0.69	0.40
GFR, mL/min/1.73m^2	93 ± 17	91 ± 16	96 ± 19	93 ± 16	0.65	0.88

BP blood pressure, *GFR* glomerular filtration rate, *STEMI* ST-elevation myocardial infarction

LVEF, Table 2) resulting in similar LVEF levels at follow-up between all groups. Neprilysin values were independently associated with an improvement of LVEF during follow-up in multivariate analysis (Table 4). There was no ischemic event during follow-up. Six patients underwent planned coronary revascularization after the index hospitalization.

Discussion

The present study is the first to show that after admission for STEMI highest levels of plasma neprilysin are associated with lower LVEF and a trend towards lower EDV at baseline, and higher magnitude of improvement of LVEF at follow-up when compared to other groups. These findings suggest that high neprilysin levels may

Table 2 Biological and echocardiographic data according to neprilysin levels. ***$p < 0.001$ vs. baseline

	Overall ($n = 68$)	Neprilysin level ≤ 125 pg/mL ($n = 38$)	Neprilysin level 126–450 pg/mL ($n = 15$)	Neprilysin level > 450 pg/mL ($n = 15$)	Overall *p*.value	Highest-level vs. lower groups *p*.value
At baseline						
NT-proBNP, pg/mL	187 [64, 790]	184 [66, 1155]	287 [87, 566]	217 [65, 1103]	0.77	0.47
hs-cTnI, pg/mL	1947 [159, 9948]	1511 [156, 9794]	1136 [327, 6711]	2765 [574, 10,492]	0.64	0.38
Neprilysin, pg/mL	125 [125, 432]	–	350 [183, 411]	1070 [781, 1824]		
At baseline						
EDV, mL/m^2	53.8 ± 13.0	55.1 ± 12.4	56.0 ± 13.5	48.3 ± 13.3	0.18	0.07
ESV, mL/m^2	28.2 [22.4, 34.7]	27.8 [23.2, 34.9]	28.8 [24.3, 32.8]	28.5 [21.1, 36.0]	0.97	0.82
LVEF, %	45.0 ± 8.5	46.4 ± 8.3	47.1 ± 8.1	39.1 ± 6.9	< 0.01	< 0.01
At follow-up						
EDV, mL/m^2	56.6 ± 15.0	57.8 ± 13.6	58.7 ± 19.9	51.6 ± 12.6	0.35	0.15
%increase in EDV	4.6 [−8.6, 18.6]	−0.1 [8.9, 17.4]	5.9 [−11.4, 22.1]	10.7 [−5.3, 20.5]	0.69	0.39
ΔEDV, mL/m^2	5.4 ± 23.2	5.5 ± 22.7	5.4 ± 28.6	5.1 ± 20.0	1	0.96
ESV, mL/m^2	25.4 [19.0, 34.8]	25.8 [19.6, 32.7]	25.9 [18.9, 36.5]	25.1 [19.1, 32.3]	0.91	0.66
%increase in ESV	−14.3 [−23.3, 10.5]	−10.9 [−22.1, 9.7]	−11.1 [−27.0, 28.8]	−15.2 [−24.2, 1.6]	0.69	0.44
ΔESV, mL/m^2	−4.2 ± 17.7	−3.7 ± 17.3	−0.8 ± 20.9	−8.9 ± 15.4	0.46	0.26
LVEF, %	51.9 ± 9.2***	53.0 ± 8.9***	50.6 ± 9.7	50.4 ± 9.9***	0.55	0.49
%increase in LVEF	17.7 ± 22.0	16.0 ± 19.4	9.1 ± 21.5	30.3 ± 24.5	0.022	0.01
ΔLVEF, %	7.0 ± 8.3	6.6 ± 7.3	3.6 ± 9.0	11.3 ± 8.4	0.031	0.02

EDV end-diastolic volume, *ESV* end-systolic volume, *hs-cTnI* high-sensibility cardiac troponin I, *LVEF* left ventricular ejection fraction

Table 3 Drug therapy according to neprilysin levels, at baseline and at follow-up

	Overall ($n = 68$)	Neprilysin level ≤ 125 pg/mL ($n = 38$)	Neprilysin level 126–450 pg/mL ($n = 15$)	Neprilysin level > 450 pg/mL ($n = 15$)	Overall *p*.value	Highest-level vs. lower groups *p*.value
At baseline						
antiplatelet agent	6 (8.8%)	2 (5.3%)	1 (6.7%)	3 (20.0%)	0.23	0.23
beta-blocker	3 (4.4%)	2 (5.3%)	0	1 (6.7%)	0.63	1
ACEI/ARB/MRA	18 (26.5%)	8 (21.1%)	5 (33.3%)	5 (33.3%)	0.53	0.73
statins	17 (25.0%)	9 (23.7%)	4 (26.7%)	4 (26.7%)	0.97	1
diuretics	7 (10.3%)	3 (7.9%)	2 (13.3%)	2 (13.3%)	0.77	1
At follow-up						
antiplatelet agent	68 (100.0%)	38 (100.0%)	15 (100.0%)	15 (100.0)%	–	
beta-blocker	64 (94.1%)	36 (94.7%)	14 (93.3%)	14 (93.3%)	0.98	1
ACEI/ARB/MRA	52 (76.5%)	30 (78.9%)	12 (80.0%)	10 (66.7%)	0.60	0.51
statins	65 (95.6%)	37 (97.4%)	15 (100.0%)	13 (86.7%)	0.15	0.24
diuretics	11 (16.2%)	7 (18.4%)	2 (13.3%)	2 (13.3%)	0.86	1

identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up.

Neprilysin is a neutral endopeptidase that degrades several endogenous vasoactive peptides, such as natriuretic peptides, Angiotensin-II, Endothelin-1, bradykinin, substance P and adrenomedullin [9, 10] which may be involved in the post STEMI neurohormonal activation. More than half of the patients (55.9%) had a very low levels of neprilysin at baseline, below the measurement threshold of 125 pg/mL in the present study. Serial measurements of serum neprilysin concentration following STEMI in a prior study have shown comparable results to our study with a median initial neprilysin level of 88.3 pg/mL [IQR: 14, 375.5]) [14]. Low levels of neprilysin have been reported to be associated with cardiovasciular risk factors such as hypertension and smoking as well as diastolic left ventricular dysfunction in a large community-based cohort of 1536 participants without known cardiovascular disease (median of 3.9 ng/mL [IQR: 1.0, 43.0 ng/mL] [15]). The latter two studies failed to show an impact of neprilysin levels on outcome. These

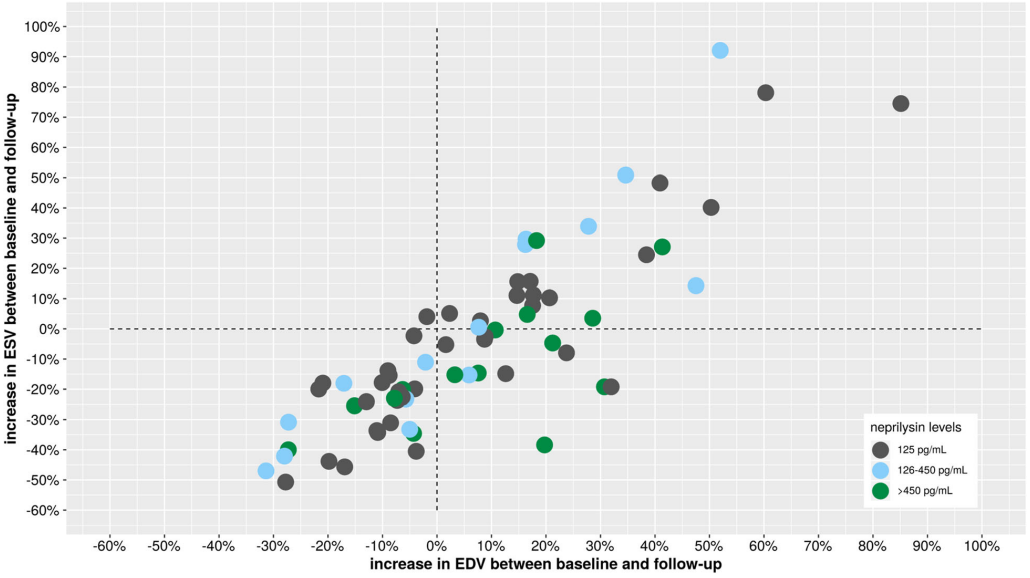

Fig. 2 Relationship between plasma neprilysin level at admission and changes regarding left ventricular volumes between baseline and follow-up

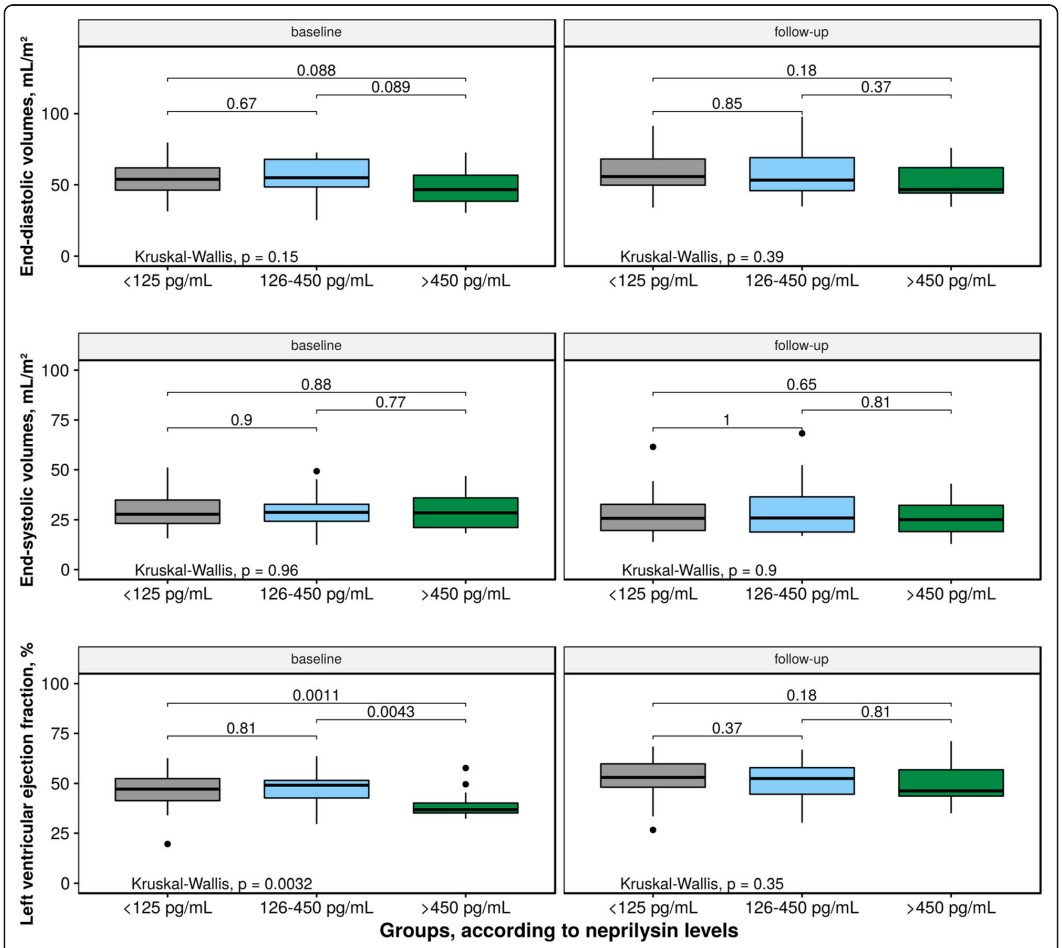

Fig. 3 Left ventricular volumes and ejection fraction at baseline and during follow-up

data support a complex relationship between neprilysin levels and cardiac functional or structural compromise in possibly different directions in different conditions. Such complex relationship is not paradoxical as neprilysin degrades effectors with opposite effects. Its action, up- or down-regulation, and maybe inhibition may therefore lead potentially to either beneficial or detrimental effects.

After STEMI, early neurohormonal activation occurs in order to maintain hemodynamic homeostasis [16]. Our study was limited to patients without HF or severely reduced LVEF. We found a mild increase in natriuretic peptides levels and mildy reduced LVEF in the study population. Neprilysin catalyzes the degradation of several vasodilator peptides, especially natriuretic peptides but also bradykinin, substance P, and adrenomedullin [17]. It is likely that the increase of the level of these peptides is at least partly related to a decrease of plasma neprilysin concentrations although the direction of such relationship could not be identified. In the above mentioned large community-based cohort, excluding patients with a LVEF< 45%, low neprilysin levels were associated with higher prevalence of smokers, hypertension, dyslipidemia and impaired diastolic function [15]). Although the level of plasma neprilysin were not available before the onset of STEMI in our study, it may be speculated that most patients included in our analysis, with cardiovascular risk factors, may have had low levels of neprilysin prior to acute myocardial infarction.

The associations between low soluble neprilysin levels and an adverse cardiometabolic and smoking profile in

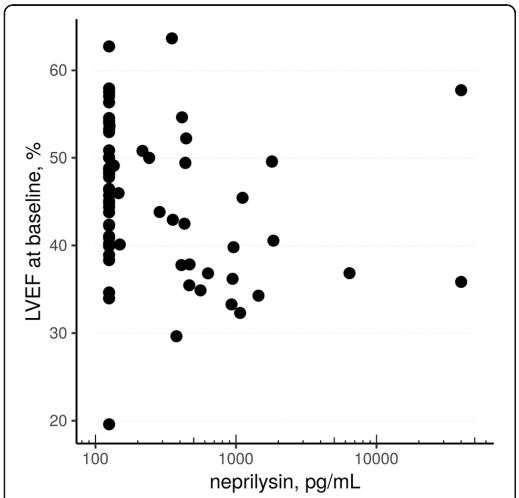

Fig. 4 Correlation between neprilysin levels and LVEF at baseline

the general population on one hand and the association between high levels and poor outcome [18–20] as well as the beneficial effect of simultaneous neprylisin and angiotensinII inhibition in HF with altered LVEF populations [12] may be explained by different populations and different levels and patterns of neurohormonal activation. Endothelial dysfunction and the subsequent vasoconstriction, are common findings in patients with coronary artery disease risk factors (hypertension, smoking, dyslipidemia) [21]. Neprilysin degrades atrial natriuretic peptide which is a key signaling pathway in blood pressure regulation [22]. The association between such risk factors and the lower levels of neprilysin in the general population may be explained by the down-regulation of neprilysin in this setting to counteract impaired vasomotion, while in the setting of HF, high levels of neprilysin, upregulated by the increase of natriuretic peptides levels, are associated with detrimental effects which may be prevented by its inhibition [12].

The present STEMI population is different from both the general population and the chronic or acute HF patient populations. Hemodynamic status and the evolution of cardiac volumes and function are obviously different between patients without cardiovascular disease, with subclinical diastolic LV dysfunction, HF with preserved or decresed LVEF and finally the acute ischemic injury and LV overload of STEMI. The impact of neurohormonal activation after STEMI on cardiac remodeling increases as the reparative and proliferative phases begin. The post STEMI left ventricular overload leads to increased proBNP production by left ventricular cardiomyocytes [23]. Neprilysin clears BNP from circulation, resulting in a limitation of its adaptative natriuretic action [22]. There are controversial data about the ability of natriuretic peptides levels at admission to predict LVR following STEMI [24–26]. Our study, in concordance with prior studies, showed that soluble neprilysin levels were not correlated to natriuretic peptide levels [15] at the time of measurement, early after STEMI. Accordingly, we observed no correlation between initial assessment of neprilysin levels and adverse remodeling

Table 4 LVEF improvement at follow-up: univariate and multivariate analysis

	Correlation coefficient, [95%CI]	Univariate *p*.value	Multivariate beta coefficient, [95%CI]	Multivariate *p*.value
Age	−0.04 [−0.20, 0.12]	0.63		
Gender, male	0.97 [−4.30, 6.24]	0.71		
Hypertension	− 0.16 [−4.34, 4.01]	0.94		
Diabetes mellitus	2.50 [−2.58, 7.59]	0.33		
Hypercholesterolemia	2.77 [−1.20, 6.74]	0.17		
Current smoking	−3.90 [−7.95, 0.17]	0.06	−3.41 [−7.35, 0.53]	0.09
Body Mass Index,	0.14 [−0.30, 0.58]	0.52		
Heart rate	0.13 [0.02, 0.24]	0.03	0.09 [−0.03, 0.20]	0.13
Systolic BP	0.04 [−0.04, 0.12]	0.30		
Diastolic BP	−0.03 [− 0.14, 0.08]	0.57		
Anterior STEMI	1.79 [−2.30, 5.88]	0.38		
Symptoms to balloon	−0.17 [−0.55, 0.20]	0.36		
GFR	0.06 [−0.07, 0.19]	0.36		
log neprilysin	1.85 [0.31, 3.40]	0.02	1.62 [0.13, 3.11]	0.03
log NT-proBNP	−0.98 [−2.17, 0.22]	0.11	−0.99 [− 2.12, 0.13]	0.08
log hs-cTnI	−0.43 [−1.26, 0.40]	0.30		

during follow-up. These results, in concordance with a prior study [14] suggest that neprilysin may not be an early biomarker of adverse remodeling after STEMI. Unlike the prior study, we assessed dynamic changes of LV volumes and function. The lower LVEF observed in STEMI patients with the highest levels of neprilysin in our study was driven by a non-significant lower EDV at baseline. Interestingly, these patients showed significant improvement of LVEF at follow-up when compared to other groups. These findings arise the hypothesis of a relationship between high levels of neprilysin and the extent of stunned myocardium, with low contractility at baseline and recovery at follow-up following successful myocardial reperfusion. One speculative explanation to our findings may be that in patients with extended stunned myocardium, levels of BNP may be high very early after STEMI, leading to an up-regulation of neprilysin, leading itself to a reduction of BNP levels at the time of measurement. In such patients without LV enlargement and heart failure higher levels of neprilysin may only be a marker of stunned myocardium, recovering at follow-up. Other hypotheses with a beneficial action of high levels of neprilysin, as a direct or indirect consequence of post-STEMI neurohormonal activation, acting more effectively on vasoconstrictive/pro-proliferative peptides may be considered. Bernelin et al. showed a non-significant decrease of neprilysin levels following STEMI, from baseline, to 1 month [14]. This non-significant trend ($p = 0.70$) may possibly be related to the small sample size ($n = 21$) in the latter study. The latter study evaluated LV volumes and function only once at 1 month, hence not allowing the analysis of changes in such parameters. In our study neprilysin level measurements were performed only once, on admission, hence not allowing any analysis of the impact of neprilysin level kinetics on the studied parameters. It may be interesting to assess the evolution of neprilysin concentrations and the evolution of cardiac imaging parameters in a larger STEMI population at different timpoints.

The present study has several limitations. The analysis includes a small number of patients. The population is highly selected including only patients with successful myocardial reperfusion, without heart failure and who had complete 3D-transthoracic echocardiogram at 2 timepoints and a collection of blood samples. Because of a high drop-out rate a selection bias could not be excluded. Our results could not be generalized to all settings of STEMI. Neprilysin has complex pleiotropic effects and is involved in different pathways and our study may not assess the pathophysiological bases of our findings. Moreover, the absence of correlation between circulating neprilysin concentration and activity has been previously reported [27].

Conclusions

Our study shows that after admission for STEMI, in a selected population with successful myocardial reperfusion and no clinical sign of HF, highest levels of plasma neprilysin are associated with lower LVEF at baseline, a trend towards lower EDV and higher magnitude of improvement of LVEF at follow-up when compared to other groups. These findings suggest that high neprilysin levels may identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up. If confirmed by other large sized studies, neprilysin level measurements may contribute to identifying patients with decreased LVEF at baseline but who are more likely to recover at follow-up. Further studies are also warranted to assess the impact of neprilysin in the general setting of STEMI and its potential blockade.

Abbreviations

ACE: Angiotensin-converting enzyme; AT1: Angiotensin-II receptor type 1; BNP: Brain natriuretic peptide; EDV: End-diastolic volume; ESV: End-systolic volume; HF: Heart failure; hs-cTnI: High-sensitivity cardiac troponin I; LV: Left ventricular; LVEF: Left ventricular ejection fraction; LVR: Left ventricular remodeling; NTpro-BNP: N-terminal pro-B-type natriuretic peptide; pPCI: Primary percutaneous coronary intervention; RAAS: Renin-angiotensin-aldosterone system; STEMI : ST-elevation myocardial infarction

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Authors' contributions

DL extracted and analyzed the data and drafted the manuscript. CM extracted the data and drafted the manuscript. AH and ES carried out echocardiography imaging and revised the manuscript. SA performed the assays and revised the manuscript. IEK extracted the data. AM revised the manuscript. PM participated in data analysis and revised the manuscript. FB designed the study, analysed the data and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent was obtained from the patients. This non-interventional study complied with the Declaration of Helsinki and was approved by the local ethics committee (Comité de Protection des Personnes Nord-Ouest 3, Centre Hospitalier Universitaire de Caen, France). The protocol registration number is A14-D17-VOL.20.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Relation entre taux de coenzyme Q10 et remodelage ventriculaire gauche

Lors de la revascularisation coronaire, il existe paradoxalement des lésions myocardiques secondaires à la restauration du flux sanguin [110]. Il a été précédemment montré que ces lésions d'ischémie-reperfusion sont responsables d'une partie significative de la taille finale de l'infarctus [111, 112]. Par ailleurs, l'ischémie-reperfusion induit un dysfonctionnement de la fonction mitochondriale conduisant à la production d'ERO avec pour conséquence la survenue de dégâts cellulaires par peroxidation des lipides, déséquilibre de la balance entre les agents antioxydants et oxydants et finalement, diminution globale de la capacité à produire de l'énergie à l'étage mitochondrial [113]. Nous nous sommes donc intéressés au rôle du coenzyme Q10 (CoQ10) (ou ubiquinone/ubiquinol), vitamine liposoluble majoritairement localisée dans la paroi interne des mitochondries [114] et dont les effets biologiques sont multiples: transport d'électrons entre les complexes de la chaîne respiratoire mitochondriale [115], antioxydant [116], phosphorylation de diverses structures extra-mitochondriales, régulation de la perméabilité du pore de transition mitochondrial ou encore amélioration de la dysfonction endothéliale, probablement par stimulation de la synthèse de NO [117].

Nous avons dosé le CoQ10 chez 68 patients de notre registre RESIST pour lesquels nous disposions de données échocardiographiques complètes, à la phase initiale et au cours du suivi, mais aussi de prélèvements sanguins prélevés sur tubes EDTA, au moment de la procédure de revascularisation coronaire. Les patients ont été séparés en deux groupes selon l'existence ou non d'un RVG défini comme une augmentation d'au moins 20% du volume télédiastolique entre les deux sessions d'imagerie. Dans ce travail, nous n'avons pas trouvé

d'association entre les taux sériques de CoQ10 à la phase aiguë du STEMI et le RVG au cours du suivi (1,20 μmol/L $\pm$ 0,42 μmol/L dans le groupe remodelage vs. 1,23 μmol/L $\pm$ 0,32 μmol/L dans le groupe sans remodelage ; p=0.78).

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Is plasma level of Coenzyme Q10 a predictive marker for left ventricular remodeling after revascularization for ST-segment elevation myocardial infarction ?

Soumis à Annals of Clinical Biochemistry.

Is plasma level of Coenzyme Q10 a predictive marker for left ventricular remodeling after revascularization for ST-segment elevation myocardial infarction ?

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ABSTRACT

Background. Left ventricular remodeling (LVR) that frequently occurs after acute myocardial infarction (AMI) is associated with an increased risk of heart failure and cardiovascular death. Although several risk factors have been identified, there is still no marker in clinical use to predict LVR. Plasma level of Coenzyme Q10 (CoQ10), that plays a key role in mitochondrial energy production and as an antioxidant, was shown to be negatively correlated with mortality after AMI.

Objective. The goal of our study was to determine whether the plasma CoQ10 baseline concentration at time of the ST-elevation myocardial infarction (STEMI) could predict the LVR at 6 months of follow-up.

Methods. 68 patients who were admitted to hospital for STEMI and successfully revascularized with primary percutaneous coronary intervention (PPCI) were recruited. All patients underwent a 3D-echocardiography examination within the first 4 days after PPCI and 6 months later and were divided into a favorable and an unfavorable LVR groups. Plasma CoQ10 level at the time of PPCI was determined using high performance liquid chromatography-tandem mass spectrometry (HPLC/ MSMS).

Results. While we found similar plasma CoQ10 concentrations compared to other studies, no statistical difference was evidenced between unfavorable or favorable remodeling groups (RR=0.99 ; 95%CI[0.90 ; 1.09] ; p=0.89).

Conclusion. We found no evidence for using plasma CoQ10 concentration as an early prediction marker for LVR after STEMI.

ABBREVIATIONS

AMI	Acute myocardial infarction
BMI	Body Mass Index
CoQ10	Coenzyme Q10
ECG	Electrocardiogram
EDV	End-diastolic volume
ESV	End-systolic volume
HF	Heart failure
HPLC/MSMS	High performance liquid chromatography-tandem mass spectrometry
hs-TnI	High-sensibility cardiac troponin I
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVR	Left ventricular remodeling
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
PPCI	Primary percutaneous coronary intervention
ROS	Reactive oxygen species
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction

INTRODUCTION

Acute myocardial infarction (AMI) is a common and severe disease, and constitutes a great socioeconomic burden for society, with high mortality and morbidity.[1] Over the past few decades, reperfusion therapies and secondary prevention medications have considerably reduced short-term mortality after AMI. Paradoxically, patients who survive are more likely to develop left ventricular remodeling (LVR), a progressive alteration in ventricular function and architecture that ultimately results in an increased risk of heart failure (HF) and cardiovascular death.[2,3] Morphological changes include cardiomyocyte loss, cardiac hypertrophy and fibrosis.[4] Several molecules have been investigated for LVR prediction, including natriuretic peptides, markers of fibrosis (collagen peptides, matrix metalloproteinases) and markers of inflammation (Soluble suppression of tumorigenicity 2 or SST2, Galectin-3).[5] However, there is still no reliable biomarker that could be used in clinical practice for early diagnosis and management of patients undergoing LVR.[6] This is probably due to the complexity of the pathophysiological mechanisms involved in LVR which is a dynamic, time-dependent and multifactorial process triggered by mechanical stretch, neurohormonal activation, inflammation, metabolic abnormalities and oxidative stress.[7] It is well admitted that mitochondrial dysfunction which results from ischemia/reperfusion injury leads to reactive oxygen species (ROS)-induced cellular damages, including lipid peroxidation, antioxidant deficiency and decrease in energy production.[8,9]

Coenzyme Q10 (CoQ10), or ubiquinone/ubiquinol, is a liposoluble vitamin-like molecule mainly located within the inner mitochondrial membrane.[10] CoQ10 plays a key role in oxidative phosphorylation, acting as an electron transporter from mitochondrial complexes I and II to complex III.[11] It also acts as a powerful endogenous antioxidant and free radical scavenger due to its ability to switch from a reduced to an oxidized state (ubiquinol <=> semiquinone <=> ubiquinone).[12] Other biological functions of CoQ10 include extramitochondrial oxidative phosphorylation (platelets, myelin sheath, retina…), regulation of the mitochondrial permeability transition pore, activation of mitochondrial uncoupling proteins and improvement of endothelial dysfunction (probably by increasing nitrogen oxide).[13]

In rat models of AMI, pretreatment with exogenous administration of CoQ10 has been shown to reduce infarct size and preserve ventricular function by reducing oxidative stress, pro-inflammatory cytokines and pro-apoptotic factors.[14,15,16] A recent clinical study suggests that early CoQ10 supplementation in patients with left ventricular ejection fraction < 50% after AMI may reduce LVR.[17] In another study, plasma CoQ10 concentrations at 1 month after PPCI in patients with STEMI are positively correlated with favorable LVR.[18] These studies suggest that CoQ10 could play a key role in LVR, by reducing ROS production and optimizing mitochondrial function, but data are scarce and the clinical interest of CoQ10 level in AMI has to be established.[19,20]

Therefore, we hypothesized that a low plasma CoQ10 level at the time of myocardial infarction may be associated with an increased risk of developing adverse LVR at 6 months of follow-up.

MATERIALS AND METHODS

Patients and study protocol

A total of 68 adult patients admitted for STEMI and treated with PPCI between 2017 January 1st and 2018 October 30 at Caen University Hospital (France) were retrospectively enrolled. This study is an ancillary study to that designed by Legallois *et al.* and inclusion and exclusion criteria were as previously described.[21] The study complied with the Declaration of Helsinki and was approved by the local ethics committee (protocol number A14-D17-VOL.20).

A second and totally distinct cohort of patients was designed to compared plasma and muscle CoQ10 levels. We prospectively enrolled 12 patients who simultaneously underwent a muscle biopsie and a blood test in the course of the investigation of a putative mitochondrial disorder. Informed consent was obtained from all patients.

Measurement of biochemical parameters

Plasma CoQ10 measurement

Peripheral venous blood samples for baseline plasma CoQ10 measurement were collected at the time of PPCI in Vacutainer tubes (Becton-Dickinson) with EDTA as anticoagulant. Samples were centrifuged at room temperature for 12 min at 2000g and plasma were stored at -80°C until analysis. The plasma CoQ10 concentration was determined using high performance liquid chromatography-tandem mass spectrometry (HPLC/MSMS) following a slightly modified procedure described by Ruiz-Jimenez *et al.*[22] A mixture of 100 µL of thawed plasma and 50 µL CoQ10-d^9 internal standard at 2 µg/mL was deproteinized with 500 µL methanol and extracted three times with 1000 µL *n*-hexane. The organic phases were pooled and evaporated to dryness using a vacuum concentrator. The dry residue was suspended within 100 µL of ethanol, vortexed for 2 min and put into vial. Three µL were injected on a NexeraXR® system (Shimadzu, Marne-la-Vallée, France) with a 3 µm (2,0 x 150mm) Pursuit PFP® column (Agilent, Santa Clara, USA). The mobile phase was methanol-formic acid 0.1% from 80:20 (v/v) to 100% methanol. The flow rate was fixed at 0.35 mL/min for 7.5 min and the temperature of the analytical column was 40°C. Detection and quantification were done by mass spectrometry using an API 5500 QTRAP® (ABSciex, Les Ulis, France) tandem mass spectrometer equipped with an APCI source in positive mode. CoQ10 was analyzed in the MRM mode with the following transitions: CoQ10 *m/z* 863.4±197.1 and CoQ10-d^9 *m/z* 872.9±206.3. Linearity was achieved over the following range:

0.02 to 2.30 µmol/L. The intra- and inter-assay precision were respectively 3.3% and 6.6% for a CoQ10 concentration of 0.96 µmol/L and 3.0% and 8.5% for a concentration of 1.97 µmol/L. The recoveries of CoQ10 were comprised between 90 and 110%. Measurement of the patients' plasma CoQ10 level was performed in duplicate. Plasma CoQ10 concentration was expressed in µmol/L or indexed to LDL or total cholesterol (µmol/mmol).

Muscle CoQ10 measurement

Muscle biopsies were stored at -80°C until their preparation. Pieces of frozen tissue (m=30-50mg) were homogenized twice in 10 volumes of grinding buffer (mannitol 225mM; sucrose 70mM; TRIS 10mM; EDTA 0,1mM; pH 7.2) using a tight-fit Potter-Elvehjem tissue grinder. Samples were centrifuged for 20 min at 650g at +4°C. Supernatants were pooled and stored at -80°C until CoQ10 quantification. CoQ10 concentration was determined as previously described using 40µL of the muscle homogenate diluted by a 2- or a 4-fold in grinding buffer (according to protein content), and 40µL of internal standard. Linearity was achieved over the following range: 0.015 to 2.30 µmol/L. The intra-assay precision were respectively 3.92% for a CoQ10 concentration of 0.40 µmol/L and 2.21% for a concentration of 0.74 µmol/L. Protein content of muscle homogenate was determined with the bicinchoninic acid assay and muscle CoQ10 content was finally expressed as molar concentration per gram of protein (nmol/g of protein).[23]

Other biochemical parameters

Total cholesterol, high-density lipoprotein cholesterol and triglyceride concentrations were determined using an AU680 chemistry analyzer (Beckman Coulter). Plasma low-density lipoprotein cholesterol concentration was calculated using Friedwald equation when triglyceride level was over 3.75 mmol/L or determined using a Konelab 20 analyzer (Thermo Scientific). High sensitivity cardiac troponin I (hs-TnI) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) concentrations were respectively measured on a Unicel DxI system (Beckman Coulter) and a Cobas e411 system (Roche). Glomerular Flow Rate (GFR) was calculated using the Chronic Kidney Disease - Epidemiology Collaboration (CKD-EPI) equation.

Echocardiographic assessments

All subjects had two transthoracic echocardiograms, within 48 hours and after a median follow-up of 7 months (6 to 10 months). Echocardiograms were performed as described by Legallois *et al.* and obtained by experienced ultrasonographers who were blinded to the patients' plasma CoQ10 concentrations.[21] Adverse LVR was defined as a 20% increase in EDV between baseline and follow-up imaging sessions.[24,25]

Statistical analysis

Qualitative variables are shown as count and frequency (%). Quantitative variables are presented as mean±SD or median and interquartile ranges when they had a skewed distribution. Continuous variables were compared using either the t-test or Wilcoxon rank sum test and categorical variables were compared by the $\chi 2$ test or Fisher's exact test, depending on whether the data followed anormal distribution. Logistic regression models were carried out to assess the relationship between LVR and baseline parameters. All statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were 2-sided and used a significance threshold of $p<0.05$.

RESULTS

A total of 68 patients fulfilling complete biological data and echocardiography was included in the analysis. Demographic and clinical characteristics are summarized in Table 1. Median age was 58.6 ± 12.7 years and 57 (83.8%) were men. Using the definition of adverse LVR as a 20% increase in EDV between baseline and follow-up echocardiography, we could discriminate an adverse LVR group (n=19, 28%) and a no adverse LVR group (n=49). As shown in Table 1, baseline characteristics were comparable between the 2 groups. Moreover, logistic regression models did not find any relationship between baseline parameters and LVR (Table 2). At baseline, LV end-diastolic and end-systolic volumes, as well as the LV ejection fraction, were similar between the two groups (Table 3) without significant association between LVR and LV volumes (Table 4). At 6-month follow-up, as expected, both LV end-diastolic and end-systolic volumes were significantly higher in the adverse LVR group compared to the no adverse LVR group. Biological data of interest for the study are depicted in Table 4 and Table 5. No significant differences were found between the adverse and no adverse LVR groups in regard to hs-cTnI and NT-proBNP levels. No difference in the lipid profile was observed either.

While investigating plasma CoQ10 concentration, values ranged from 0.46 to 2.21 µmol/L but with no statistical difference between groups with and without LVR (mean 1.21 ± 0.41 µmol/L in the non-remodeling group, 1.20 ± 0.34 µmol/L in the remodeling group, p=0.89) (Table 5 and Figure 1A). No significant relationship was found using logistic regression model between CoQ10 levels and LVR (Table 4). We found a similar positive correlation between CoQ10 and total cholesterol concentrations ($r=0.605$; $p<0.001$), as well as between CoQ10 and LDL-cholesterol concentrations ($r=0.586$; $p<0.001$) (Figure 2). In contrast, HDL-cholesterol level was not significantly related to CoQ10 concentrations ($r=0.125$; $p=0.360$, data not shown). Thus, CoQ10 levels were indexed to LDL and total cholesterol. No statistical difference between both groups was observed either (Figure 1B and 1C).

Finally, skeletal muscle and plasma CoQ10 status was investigated in an independent series of 12 patients undergoing a muscle biopsy in our laboratory. Plasma CoQ10 values ranged from 0.42 to 2.04 µmol/L and muscle values ranged from 50.00 to 1431.43 pmol/mg of protein. We found no correlation between skeletal muscle and plasma CoQ10 concentrations (data not shown).

Table 1. Demographic and clinical characteristics of the study population. Data are presented as mean (± standard deviation) , median (quartiles) or as number (percentage).

	Overall Population	**Left Ventricular Remodeling**		**p**
	(n=68)	**No (n=49)**	**Yes (n=19)**	**Value**
Age (years)	58.65 (12.73)	58.62 (12.95)	58.74 (12.48)	0.97
Male gender	57 (83.8)	40 (81.6)	17 (89.5)	0.72
GFR (mL/min/1.73m²)	92.87 (16.89)	94.28 (15.67)	89.50 (19.56)	0.32
BMI (kg/m²)	27.37 (4.69)	27.75 (5.04)	26.39 (3.60)	0.29
Smoking habit	44 (64.7)	33 (67.3)	11 (57.9)	0.57
Hypertension	25 (36.8)	19 (38.8)	6 (31.6)	0.58
Family history of cardiovascular disease	12 (17.6)	9 (18.4)	3 (15.8)	1
Diabetes mellitus	13 (19.1)	10 (20.4)	3 (15.8)	1
Hypercholesterolemia	32 (47.1)	22 (44.9)	10 (52.6)	0.57
Heart rate (beats/min)	77 (18)	77 (18)	76 (18)	0.77
Systolic blood pressure (mmHg)	142 (25)	142 (28)	145 (19)	0.48
Diastolic blood pressure (mmHg)	85 (19)	86 (20)	82 (15)	0.50
Symptoms to balloon (hours)	4.7 [3.2 ; 8.85]	4.7 [2.9 ; 9.7]	5.0 [3.6 ; 8.1]	0.59
Site of acute myocardial infarction				
Anterior	28 (41.2)	19 (38.8)	9 (47.4)	0.52
Inferior	36 (52.9)	26 (53.1)	10 (52.6)	0.97
Lateral	19 (27.9)	14 (28.6)	5 (26.3)	0.85
Basal	4 (5.9)	3 (6.1)	1 (5.3)	1
Right ventricle	5 (7.4)	4 (8.2)	1 (5.3)	1

GFR=Glomerular Filtration Rate. BMI=Body Mass Index.

GFR: 7 data missing ; BMI: 1 data missing

Table 2. Association between Left Ventricular Remodeling and baseline demographic/clinical factors

		n	Left Ventricular Remodeling		Crude RR*	95% CI	p
			n	%			
Age (years)		68			1.01	(0.75 ; 1.35)	0.97
Gender	Male	57	17	29.8%	1.64	(0.44 ; 6.11)	0.46
	Female	11	2	18.2%	1		
GFR (mL/min/1.73m²)		61			0.87	(0.69 ; 1.11)	0.27
BMI (kg/m²)		67			0.95	(0.87 ; 1.04)	0.31
Smoking habit	No	43	13	30.2%	1		
	Yes	25	6	24.0%	0.80	(0.37 ; 1.72)	0.57
Hypertension	No	25	8	32.0%	1		
	Yes	43	11	25.6%	0.79	(0.35 ; 1.82)	0.59
Family history of cardiovascular disease	No	56	16	28.6%	1		
	Yes	12	3	25.0%	0.88	(0.30 ; 2.54)	0.81
Diabetes mellitus	No	55	16	29.1%	1		
	Yes	13	3	23.1%	0.79	(0.27 ; 2.32)	0.67
Hypercholesterolemia	No	36	9	25.0%	1		
	Yes	32	10	31.3%	1.25	(0.58 ; 2.68)	0.57
Heart rate (beats/min)		68			0.97	(0.77 ; 1.21)	0.77
Systolic blood pressure (mmHg)		68			1.049	(0.91 ; 1.21)	0.51
Diastolic blood pressure (mmHg)		68			0.99	(0.81 ; 1.20)	0.88
Symptoms to ballon (hours)		68			1.00	(0.94 ; 1.07)	0.96
Antiplatelet agent	Ticagrelor	49	15	30.6%	1.53	(0.25 ; 9.29)	0.75
	Prasugrel	14	3	21.4%	1.07	(0.14 ; 8.07)	
	Clopidogrel	5	1	20.0%	1		

** Age, GFR, Heart Rate, Systolic and Diastolic blood pressure: for a 10-unit increase BMI, Symptoms to ballon: for a 1-unit increase*

Table 3. Changes in left ventricular characteristics on 3D-echocardiography. Data are presented as mean ± standard deviation.

	Overall Population	**Left Ventricular Remodeling**		**p Value***
	(n=68)	**No (n=49)**	**Yes (n=19)**	
At baseline				
End diastolic volume (mL/m²)	54.38 (13.29)	55.39 (12.65)	51.75 (14.85)	0.31
End systolic volume (mL/m²)	30.45 (10.02)	30.65 (10.44)	29.93 (9.11)	0.79
Ejection fraction (%)	44.32 (9.09)	45.12 (9.95)	42.26 (6.11)	0.25
At follow-up				
End diastolic volume (mL/m²)	57.31 (15.89)	52.63 (11.85)	69.38 (18.77)	0.0014
End systolic volume (mL/m²)	28.58 (11.90)	25.27 (8.94)	37.10 (14.40)	0.0028
Ejection fraction (%)	51.12 (9.65)	52.57 (9.34)	47.37 (9.66)	0.045

Table 4. Association between Left Ventricular Remodeling and baseline echocardiographic/biological factors

	n	Crude RR*	95% CI	p
End diastolic volume (mL/m²)	68	0.85	(0.62 ; 1.15)	0.28
End systolic volume (mL/m²)	68	0.95	(0.65 ; 1.40)	0.79
Ejection fraction (%)	68	0.83	(0.60 ; 1.16)	0.28
Cardiac output (L/min)	47	0.91	(0.62 ; 1.33)	0.63
hs-cTnI (pg/mL)	67	1.01	(0.98 ; 1.04)	0.45
NT-proBNP (pg/mL)	68	1.14	(0.94 ; 1.38)	0.17
Total cholesterol (mmol/L)	63	1.24	(0.83 ; 1.86)	0.30
LDL cholesterol (mmol/L)	58	1.27	(0.74 ; 2.18)	0.38
HDL cholesterol (mmol/L)	56	3.73	(0.65 ; 21.44)	0.14
Triglycerides (mmol/L)	63	0.85	(0.53 ; 1.37)	0.51
CoQ10 (µmol/L)	**68**	**0.99**	**(0.90 ; 1.09)**	**0.89**
CoQ10/T-CHL (µmol/mmol)	63	0.76	(0.41 ; 1.40)	0.38
CoQ10/LDL-CHL (µmol/mmol)	58	0.79	(0.52 ; 1.20)	0.27

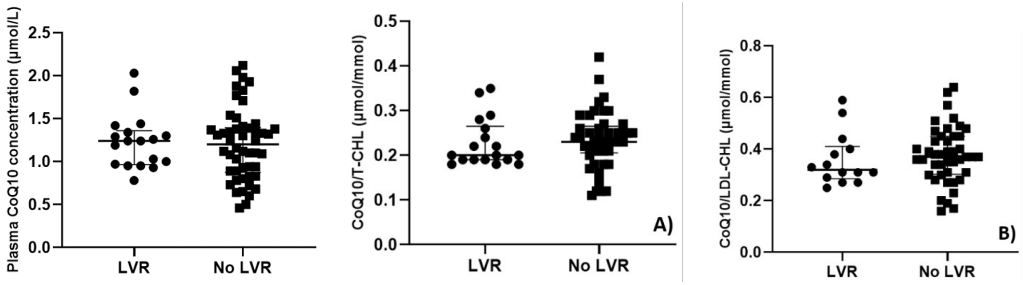
** End diastolic and systolic volumes, Ejection fraction: for a 10-unit increase. Cardiac output, Total, LDL and HDL cholesterol, Triglycerides: for a 1-unit increase. hs-cTnI, NTproBNP: for a 1000-unit increase. CoQ10, CoQ10 / T-CHL, CoQ10 / LDL-CHL: for a 0.1-unit increase*

Table 5. Biological data at baseline according to LVR groups. Data are presented as mean ± standard deviation.

	Overall Population (n=68)	**Left Ventricular Remodeling**		**p Value**
		No (n=49)	**Yes (n=19)**	
hs-cTnI (pg/mL)	1947 (164 ; 9991)	2080 (164 ; 9906)	1556 (242 ; 10421)	0.72
NT-proBNP (pg/mL)	204 (66 ; 1040)	221 (74 ; 927)	177 (55 ; 1181)	0.68
Total cholesterol (mmol/L)	5.25 (0.98)	5.16 (0.98)	5.44 (0.97)	0.30
LDL cholesterol (mmol/L)	3.38 (0.82)	3.32 (0.87)	3.55 (0.69)	0.37
HDL cholesterol (mmol/L)	1,15 (0.26)	1.13 (0.22)	1.23 (0.36)	0.22
Triglycerides (mmol/L)	1.52 (1.02 ; 2.11)	1.53 (1.06 ; 2.19)	1.36 (0.77 ; 1.80)	0.40
CoQ10 (µmol/L)	1.21 (0.39)	1.21 (0.41)	1.20 (0.34)	0.89
CoQ10/T-CHL (µmol/mmol)	0.23 (0.061)	0.24 (0.063)	0.22 (0.058)	0.39
CoQ10/LDL-CHL (µmol/mmol)	0.37 (0.11)	0.38 (0.11)	0.35 (0.11)	0.29

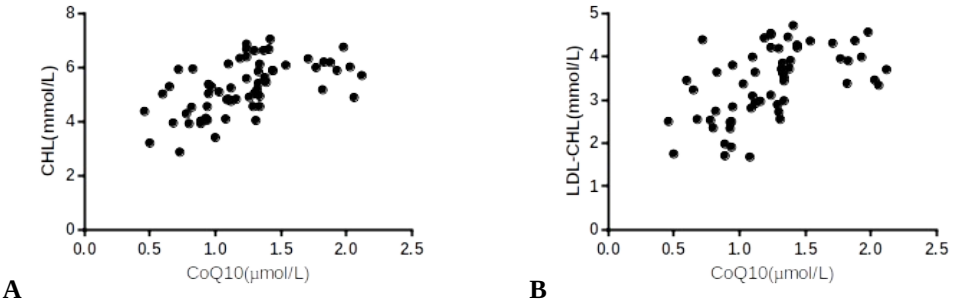
hs-cTnI: 1 data missing ; total cholesterol: 5 data missing ; LDL cholesterol: 10 data missing ; HDL cholesterol: 12 data missing ; triglycerides: 5 data missing.

Figure 1. Plasma CoQ10 concentration (A) and plasma CoQ10 concentration indexed to total cholesterol (T-CHL, B) or LDL cholesterol (LDL-CHL, C) according to adverse LVR and no adverse LVR groups. Bottom and top bands represent the 1st and 3rd quartile and middle band represent the median.



A B C

Figure 2. Correlation between plasma CoQ10 concentrations and total cholesterol (A) or LDL cholesterol (B).



A **B**

DISCUSSION

This study aimed to measure the plasma CoQ10 concentration in a cohort of patients who were admitted to hospital for STEMI in order to determine whether baseline CoQ10 level could be an early biomarker to predict adverse LVR at 6 months of follow-up. Among the 68 patients included in the study, 19 patients (28%) developed adverse LVR. This is in accordance with data from literature where postinfarct ventricular remodeling was found to develop in about 30% patients.[26,27] We found plasma CoQ10 concentrations ranging from 0.46 to 2.21 µmol/L which are similar to those described in the literature.[28] For example, concentrations of total CoQ10 in plasma of healthy subjects have been reported (means ± SD) with different methods: 0.675 ± 0.315 µmol/L (HPLC/MSMS),[38] 0.75 ± 0.22 µmol/L (HPLC with UV detection)[29] and 1.11 ± 0.24 µmol/L (HPLC with electrochemical detection).[30] As circulating CoQ10 is mainly transported by lipoproteins (about 58% with LDL and 26% with HDL), we studied their relationships and found a positive correlation between CoQ10 and total cholesterol concentrations ($r=0.605$; $p<0.001$), as well as between CoQ10 and LDL-cholesterol concentrations ($r=0.586$; $p<0.001$). This is also in accordance with results from Tomasetti *et al.* and Niklowitz *et al.* who found similar correlations with total cholesterol ($r=0,63$, $p<0,001$) and LDL-cholesterol levels ($r=0,57$, $p<0,001$).[31,32] However, we found no evidence that plasma CoQ10 concentrations at baseline were lowered in the remodeling group *vs.* non-remodeling patients.

The most probable hypothesis is that plasma CoQ10 concentrations may not accurately reflect tissue concentrations, particularly in cardiomyocytes where mitochondria account for about 25% of cell volume.[33] As with many biomarkers, CoQ10 status in humans is determined from plasma concentrations primarily because of easy sample collection. However, plasma and tissue CoQ10 contents exhibit several differences. In heart, CoQ10 is mainly intracellular and located within the mitochondrial inner membrane where it constitutes a 50/50 ubiquinone/ubiquinol pool that both participates in the respiratory chain and as antioxidant.[34] In plasma, CoQ10 is known to be carried by lipoproteins and is present almost entirely - about 95% - in its reduced form to protect lipoproteins from oxidative stress and lipid peroxidation.[35]

Furthermore, the correlation between tissue and plasma CoQ10 status is not obvious. For example, Duncan *et al.* found a close association between skeletal muscle and mononuclear cells CoQ10 concentration, but no correlation between skeletal muscle and plasma CoQ10 concentrations.[36] In this study we did not any correlation between skeletal muscle and plasma CoQ10 concentrations either. A similar conclusion was drawn by Folkers *et al.* who showed no correlation between blood and heart CoQ10 concentrations. However, they observed low blood CoQ10 levels in patients suffering from cardiomyopathy but not as markedly as for the heart biopsies. Thus, they hypothesized that a correlation between plasma and organ levels may exist only

for the most severe deficiency state.[37] In our study, we found similar values of plasma CoQ10 concentrations to those described in the literature. So, based on the reference values obtained from controls in previous studies, we can ruled out severe CoQ10 deficiency in our patients. Thus, this may explain the lack of correlation between plasma and cardiac CoQ10 concentrations and the absence of significant difference in CoQ10 levels between patients with and without adverse LVR.

The reason why the plasma and tissues CoQ10 levels are not correlated is probably due to the endogenous biosynthesis of this compound. In physiological conditions, tissue CoQ10 levels mainly depend on *de novo* synthesis. In contrast, plasma CoQ10 concentrations are significantly influenced by dietary uptake after incorporation within lipoproteins in the liver and release into the blood.[38] However, we could not ensure that the patients were on an empty stomach before PPCI and blood sample. Supplementation studies with labeled CoQ10 revealed that tissue uptake was limited mainly to the liver and plasma, indicating that heart CoQ10 content mainly relies on the endogenous synthesis.[39] This is also illustrated by the fact that exogenous CoQ10 does not down-regulate its endogenous synthesis.[40] The situation is however completely different when there is a severe deficiency in CoQ10 tissue level, for example in patients with a genetic deficiency of CoQ10 synthesis or in patients with heart failure who exhibit low levels of CoQ10 in cardiomyocytes. In those cases, the plasma uptake of exogenous CoQ10 is necessary to maintain adequate tissue levels, suggesting that tissue deficiency precedes plasma deficiency.

In a murine model of CoQ10 deficiency ($ApoA1^{-/-}$), Dadabayev *et al.* observed significantly larger infarct size in ApoA1 null ($ApoA1^{-/-}$) and ApoA1 heterozygous ($ApoA1^{+/-}$) mice compared to wild-type (WT) mice.[41] They found a reduced cardiac CoQ10 pool in $ApoA1^{-/-}$ mice with impaired electron transfer from Complex II to Complex III. Administration of CoQ10 to $ApoA1^{-/-}$ mice normalized the myocardial CoQ10 level but had no effect in WT mice, showing that mitochondrial dysfunction directly arises from a pre-existing depleted pool of CoQ10 in cardiomyocytes. On the other hand, higher values than “normal” plasma CoQ10 concentrations seem to be necessary for an efficient uptake by peripheral tissues. For instance, in cardiovascular diseases, the achievement of a plasma threshold of at least 2.78 µmol/mL is necessary to observe a therapeutic benefit.[37] Thus, it would be interesting to investigate whether patients who exhibit a real plasma CoQ10 deficiency/overload would be more/less likely to develop LVR compared to patients with CoQ10 in the normal range.

Another point to consider is that we decided to investigate the plasma CoQ10 concentration at the onset of STEMI. In a similar study, Huang *et al.* examined the potential correlation between plasma CoQ10 level at baseline and 3 days, 7 days, and 1 month after STEMI and the LV performance. They found that CoQ10 levels gradually decreased with time and that lower CoQ10 concentrations in plasma at 1 month was predictive of adverse LVR 6 months after STEMI (adverse

LVR was defined as a 10% increase in ESV between baseline and follow-up).[17] However, they did not interpret the prognostic value of CoQ10 at the other measured times, suggesting that earlier measurements – particularly at baseline – were not predictive of LV performance as found in our study. It is thus likely that we did not found any evidence that circulating levels of CoQ10 were lowered before cardiac remodeling because the CoQ10 decrease might happen as a result from compensatory mechanisms that gradually fall into place after the onset of STEMI. This is consistent with all findings in patients with chronic heart failure where myocardial remodeling is already present and who exhibit low circulating and tissue levels of CoQ10.[42]

When we initially designed the study, we have not considered to take a blood sample at 6 months of follow-up and it would have been interesting determine the CoQ10 concentration at that time. Another limitation is that we determined the amount of CoQ10 in its oxidized form but not the Ubiquinol ($CoQ10H_2$)/Ubiquinone (CoQ10) ratio. However, measurement of both reduced and oxidized forms implies great technical considerations regarding sample processing and analytical stability.[38] Ubiquinol is readily oxidized to Ubiquinone during sample preparation or long-term storage, even at -80°C, which is the case in our study where the first samples were collected on January 2017 and analyzed two years later. A prospective study with immediate determination of CoQ10 redox state would be interesting as altered plasma ratios reflect oxidative stress and could be involved in the LV remodeling.[38]

In conclusion, we found no evidence for a role of circulating CoQ10 as an early biomarker for prediction of unfavorable LVR in patients with STEMI. As shown by a comparison between plasma and skeletal muscle, the plasma CoQ10 levels presumably do not accurately reflect CoQ10 content in cardiomyocytes.

Authors' contributions

FF performed the CoQ10 assays, analyzed the data and drafted the manuscript. DL extracted and analyzed the data and revised the manuscript. CC performed the statistical analysis. MC et LC participated to the CoQ10 assays. AH and ES carried out echocardiography imaging. PM revised the manuscript. FB and SA designed the study and revised the manuscript. All authors read and approved the final manuscript.

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Discussion

L'objectif de ce travail de thèse était donc d'apporter de nouveaux éléments dans la compréhension des mécanismes physiopathologiques conduisant à la survenue d'un RVG chez les patients ayant présenté un STEMI. Le RVG est un phénomène complexe, multifactoriel, faisant intervenir des mécanismes tels que l'inflammation, l'activation neuro-hormonale ou encore la bioénergétique cellulaire et en particulier du cardiomyocyte. Il est également communément admis que l'ensemble du myocarde – aussi bien la zone infarcie que la zone controlatérale, non directement concernée par l'occlusion coronaire – subit des modifications cellulaires et histologiques qui vont conduire au RVG.

Remodelage ventriculaire gauche post-infarctus: état des lieux des connaissances

De très nombreux travaux, aussi bien précliniques que cliniques, ont cherché à expliquer la physiopathologie de survenue du RVG et à en chercher des facteurs prédictifs. La première partie de ce travail de thèse a donc consisté à un examen de l'état des lieux des connaissances sur ce sujet. Nous avons donc commencé par réaliser deux revues de la littérature, la première portant sur les critères de définition du RVG en IRM (page 12, [118]) et la seconde sur l'association entre les biomarqueurs dosés à la phase aiguë de l'infarctus et la survenue d'un RVG au cours du suivi (page 71).

Lors de la mise en place du registre RESIST, nous avions décidé d'étudier le RVG en ayant recours à l'échocardiographie. Ce choix a été porté par des raisons pratiques, la réalisation d'une échocardiographie à la phase aiguë d'un STEMI et au décours étant une pratique recommandée [1] et qui correspondait à nos habitudes sur le centre. Nous avons alors commencé ce travail de revue en incluant tous les articles qui avaient étudié le RVG après STEMI et ceci, quelle que soit la modalité d'imagerie utilisée. Nous avons ainsi retrouvé un total de 282 études et avons décidé de nous limiter alors aux 77 études utilisant l'IRM comme modalités d'imagerie, considérant sa meilleure reproductibilité pour la mesure des volumes VG [54] et la possibilité d'analyser des critères tels que la fibrose ou encore la taille de l'infarctus. La revue de la littérature portant sur la définition du RVG dans les études cliniques utilisant l'IRM a permis de montrer que la prévalence du RVG varie entre 11,3% et 48,4% dans les études ayant utilisé une valeur de seuil d'augmentation des volumes ventriculaires au cours du suivi (prévalence groupée de 22,8% ; $IC_{95\%}$[19,4% – 26,7%]) [118]. Ce travail a aussi permis de mettre en évidence la grande hétérogénéité de la littérature sur le sujet. En effet, il n'existe aucun consensus dans la quantification du RVG après un infarctus. Malgré une littérature très abondante sur le sujet, il n'existe pas d'études ayant une méthodologie reproductible concernant les points suivants : modalité d'imagerie utilisée, définition du remodelage (simple valeur du volume ventriculaire gauche et donc variable quantitative ou alors valeur seuil de remodelage permettant de séparer les patients présentant un RVG de ceux qui ne remodèlent pas), mais aussi délai entre la survenue de l'infarctus et la première imagerie et délai entre l'examen initial et l'examen de suivi. L'examen des études d'IRM montre par ailleurs que la mesure des volumes ventriculaires n'est pas la seule à donner lieu à une hétérogénéité de sa quantification. Nous avons initialement envisagé stratifier les résultats obtenus dans les études en fonction de la taille de l'infarctus en IRM mais la méthodologie diffère aussi d'une étude à l'autre notamment sur le délai de réalisation de la première IRM [119, 120]. Or, il est probablement préférable que l'imagerie initiale

n'ait pas lieu durant la première semaine post-infarctus, avant la fin de la période de stunning et le début de la régression des processus inflammatoires et œdémateux [119].

Les patients inclus dans les études de remodelage sont également particulièrement sélectionnés et ne représentent pas un échantillon représentatif des patients se présentant en salle de cathétérisme pour une angioplastie primaire. Dans notre revue de la littérature portant sur la définition en IRM du RVG, l'âge médian ou moyen des patients inclus dans les études est de 59 ans, avec une FEVG moyenne ou médiane de 48,6% et un taux plus élevé de recours à l'angioplastie primaire que des registres publiés *a posteriori* de certaines de ces études [121]. Plus du quart des patients inclus dans notre travail étaient initialement inclus dans des études randomisées. Ces patients étaient donc sélectionnés et l'objectif initial de l'étude à laquelle ils étaient initialement inclus n'avait pas toujours un lien avec l'étude du RVG, l'analyse post-hoc étant faite rétrospectivement sur des données prospectivement acquises. Notre seconde revue portant sur le lien entre biomarqueurs et RVG permet elle aussi d'affirmer que les patients inclus dans les études de remodelage sont très sélectionnés. Nous avons retrouvé 25 études qui renseignent les valeurs de créatininémie ou d'estimation du débit de filtration glomérulaire dans leur population. La créatininémie moyenne de ces patients varie entre 68 et 96 μmol/L (après éventuelle conversion de l'unité de mesure). Le débit de filtration glomérulaire estimé est entre 71 et 113 mL/min/1,73m^2. Ces chiffres sont manifestement éloignés des patients pris en charge en angioplastie primaire, montrant bien la grande sélection des patients inclus dans ces études.

D'autres éléments objectifs d'ordre méthodologique doivent être soulignés comme limites à ces nombreuses études. Le premier est bien évidemment la taille des effectifs, certains travaux incluant parfois à peine une quarantaine de patients. Nous avons par ailleurs étudié la qualité des études observationnelles incluses dans notre travail, aussi bien concernant les

études observationnelles (pages 168 et 179, en annexe) que les études post-hoc d'essais randomisés (page 180). Une grande partie de ces travaux présentent des risques de biais, que ce soit sur la sélection des patients, le manque d'information concernant le suivi (notamment les évènements cardiovasculaires majeurs) ou sur la méthodologie des mesures effectuées (par exemple l'absence de core lab d'échocardiographie). Enfin, certaines cohortes de patients ont été publiées à plusieurs reprises, utilisant des critères de définition du RVG qui pouvaient varier d'une étude à l'autre.

Cette problématique de reproductibilité des résultats a été retrouvée dans notre second travail de revue portant sur le lien entre biomarqueurs et RVG. En dehors des problématiques de définition du RVG que nous avons déjà évoqué, nous avons mis en évidence que la capacité d'un biomarqueur à prédire la survenue du RVG était grandement variable d'une étude à l'autre, surtout lorsqu'il s'agit de dosages qui ne sont pas réalisés en pratique clinique courante (page 73). Cette absence de reproductibilité liée à l'absence de standardisation des dosages est multifactorielle. Elle repose tout d'abord sur des limites intrinsèques aux kits utilisés: (i) les anticorps utilisés sont différents d'une trousse à l'autre, (ii) il n'existe pas de contrôle qualité comme pour les dosages en routine, (iii) il existe également une grande variabilité interexpérience et (iv) une absence de valeurs usuelles qui peuvent compliquer l'interprétation des résultats. L'autre point fondamental est la chronologie du prélèvement, qui doit être en adéquation avec la place du biomarqueur dans la physiopathologie du processus de remodelage. A titre d'exemple, nous avons ainsi identifié dans notre revue plusieurs études où les peptides natriurétiques ont été dosés plusieurs fois au cours du suivi [122–124, 102, 125]. Dans toutes ces études le dosage précoce des peptides natriurétiques – avant que l'activation neuro-hormonale n'ait pu vraiment débuter – n'est pas prédictif de la

survenue du RVG au cours du suivi alors que le dosage réalisé à la sortie d'hospitalisation du patient y est significativement associé, dans les mêmes publications.

Il est fondamental d'aborder la problématique de la valeur pronostique du RVG. En effet, tout le travail réalisé jusqu'alors de définition du RVG puis de recherche de facteurs prédictifs de survenue n'a de sens que si le fait de mettre en évidence un remodelage délétère chez un patient donné nous apporte une information sur son pronostic, dans le but ensuite d'impacter sur sa prise en charge. Ces données sont absentes de la plupart des études que nous avons incluses dans nos travaux de revue. Les études qui ont initialement décrit le RVG comme un facteur de mauvais pronostic après STEMI ont maintenant 20 ans [54, 126]. Depuis, la prise en charge de ces patients a radicalement évolué avec une réduction des délais de prise en charge, une meilleure anti-agrégation plaquettaire à la phase aiguë, un développement des techniques de revascularisation myocardique et une meilleure prise en charge au décours de l'infarctus [127]. Plusieurs études publiées très récemment, postérieurement au début de ce travail de thèse, remettent en question le caractère pronostique du RVG après un STEMI. Ainsi, une équipe autrichienne a récemment proposé de rechercher quel paramètre de remodelage est associé à la survenue d'évènements cardio-vasculaires majeurs au décours d'un STEMI [128]. L'augmentation du volume télédiastolique d'au moins 10% à 4 mois est associé à un risque relatif de 8,68 ; $IC_{95\%}$[2,39 – 31,56] dans cette cohorte de 224 patients où seulement 13 (6%) ont eu un évènement cardio-vasculaire majeur à 24 mois. Deux études publiées en 2019 vont à l'encontre d'un intérêt de l'évaluation du RVG dans un but pronostique. L'étude de Rodriguez-Palomares a inclus 374 patients ayant eu une IRM à la phase initiale et 6 mois après un STEMI et ne retrouve pas d'apport pronostique d'un critère de remodelage défini par une augmentation de plus de 15% du volume télédiastolique associé à une diminution de plus de 3% de la FEVG sur la prédiction des évènements cardio-vasculaires majeurs par rapport aux données de l'IRM initiale seulement [129]. L'équipe de Masci a inclus

492 patients ayant eu une IRM à la phase initiale et 4,8 mois après le STEMI. Le critère de jugement principal composite – comprenant décès toutes causes et hospitalisation pour IC – est survenu chez 84 patients après un délai moyen de 8,3 ans [130]. Aucun des deux critères les plus communément retrouvés pour définir un RVG (augmentation du volume télédiastolique $>$20% et augmentation du volume télésystolique $>$15%) n'a permis de prédire indépendamment la survenue d'un évènement. Ces études ont tout de même des limites. La population est ici aussi sélectionnée, et est l'agrégat de plusieurs cohortes plus petites dont certaines ont été incluses il y a plus de 15 ans comme en témoigne les caractéristiques des patients à l'inclusion (par exemple, seulement $\frac{2}{3}$ des patients ont bénéficié d'une angioplastie primaire dans les 12 heures suivant le début de la symptomatologie [129]). L'utilisation d'une variation de 3% de la FEVG dans la définition du remodelage pose problème vis-à-vis de la reproductibilité de la mesure [131]. Une dernière étude, elle aussi publiée en 2019 a inclus 1995 patients depuis 2004 [132]. Les patients ont été classés en quatre groupes : remodelage précoce en cas d'augmentation d'au moins 20% du volume télédiastolique dans les 3 mois suivant le STEMI (613 patients, 30,7%), remodelage à moyen terme si cette augmentation de volume survient entre le 3^e et le 6^e mois (216 patients, 10,8%), remodelage tardif si l'augmentation de volume est observée entre le 6^e et le 12^e mois (124 patients, 6,2%). Enfin, les patients n'ayant jamais eu une augmentation de volume télédiastolique du VG de plus de 20% sont classés dans un groupe sans remodelage (1042 patients, 52,2%). Il n'existe pas de différence en terme de mortalité au terme d'un suivi médian de 94 mois. En revanche, les patients ayant un RVG au cours du suivi sont plus fréquemment hospitalisés pour IC (risque relatif: 2,81 ; $IC_{95\%}$[1,78 – 4,42], p<0,001 en analyse univariée et 2,66 ; $IC_{95\%}$[1,69 – 4,19], p<0,001 en analyse multivariée). Ce sur-risque est retrouvé dans les sous-groupes FEVG<40% et FEVG entre 40 et 49% mais pas dans le groupe FEVG$\geq$50% et après analyse de sensibilité basée sur la valeur initiale du volume télédiastolique VG.

L'ensemble de ces travaux et de ces résultats nous conduisent donc à plaider pour une homogénéisation des pratiques concernant les études portant sur le RVG. La position de Bulluck et al. consistant à prendre en compte l'évolution des volumes ventriculaires télédiastolique et télésystolique [133] est intéressante car elle permet de séparer les patients selon différents modèles de remodelage ventriculaire. En effet, le volume télédiastolique est plutôt en rapport avec le remodelage "macroscopique" du VG et la précharge alors que le volume télésystolique est plutôt dépendant des conditions de charge et de la capacité des fibres à se contracter [51]. Ces deux aspects sont importants, et, à augmentation de volume télédiastolique équivalente, il existe des arguments pour penser que le profil évolutif n'est pas le même chez un patient ayant augmenté significativement son volume télésystolique et altéré sa FEVG par rapport à un patient ayant compensé son remodelage ventriculaire par une augmentation de son volume télésystolique avec pour conséquence, un maintien de sa FEVG [132]. Cette approche devra à l'avenir être validée dans des cohortes de grandes tailles afin de pouvoir aussi évaluer l'impact pronostique de la survenue d'un RVG, chez des patients non sélectionnés et ayant bénéficié à la phase aiguë des stratégies modernes de reperfusion myocardique. Il est probablement préférable que l'évaluation du RVG se fasse précocement, environ 3 mois après la survenue du STEMI. En effet, les études d'imagerie sériées montrent que l'essentiel de l'évolution des volumes VG est observable dès le $3^{ème}$ mois [134, 135] chez les patients qui évoluent vers un RVG. Le dépistage précoce de ces patients pourrait à terme peut être faire envisager une optimisation de leur traitement, en utilisant les classes thérapeutiques recommandées dans l'IC post-infarctus, et notamment les bloqueurs du SRAA [1, 30]. Ainsi, il a été montré que les patients qui ont un RVG et une FEVG inférieure à 50% au cours du suivi sont plus souvent ré-hospitalisés pour IC [132], ce qui pourrait être alors l'occasion de modifier leur traitement au profit d'un ARNI en remplacement de leur inhibiteur de l'enzyme de conversion de l'angiotensine (IEC) ou de leur antagoniste du récepteur AT_1 de l'angiotensine-II (ARA2) [107]. Dans une étude

préclinique, le traitement par ARNI a montré une supériorité par rapport au valsartan pour prévenir la dégradation de la FEVG [136]. Quant à la création de modèles prédictifs de survenue du RVG, la complexité de sa physiopathologie impose probablement une approche multiparamétrique associant données cliniques, d'imagerie et biologiques.

Nouveaux paramètres échocardiographiques et remodelage ventriculaire gauche en post-infarctus

De nombreux paramètres d'imagerie sont décrits comme étant prédictifs de la survenue d'un RVG au cours du suivi, comme par exemple l'obstruction micro-vasculaire en IRM [61, 62], la taille de la zone infarcie [58–60] ou encore le strain longitudinal global du VG en échocardiographie [55, 56]. Ces paramètres ont en commun une évaluation – directe ou indirecte – de l'impact de l'infarctus sur la fonction systolique du VG. Le processus de remodelage post-infarctus n'étant pas exclusivement lié à l'atteinte de la fonction contractile de la zone infarcie, nous avons donc souhaité étudier l'implication d'autres paramètres: la zone *remote* non directement concernée par l'occlusion coronaire, la fonction atriale gauche et la fonction diastolique du VG par l'étude du GPIVD.

L'étude REMOD-TEP avait pour but de quantifier la fonction endothéliale coronaire et la fibrose dans le territoire de l'infarctus mais également dans le territoire non directement atteint par l'occlusion coronaire, chez 30 patients admis pour STEMI et ayant une atteinte mono-tronculaire à la coronarographie, en utilisant une imagerie TEP, un radiopharmaceutique librement diffusible (l'eau marquée à l'oxygène-15) et un test au froid (cf. page 28). L'étude n'ayant pu actuellement être menée à son terme pour des raisons matérielles, nous ne discuterons pas davantage ce point ici. Simplement, depuis l'écriture de

ce protocole en 2015, il existe désormais des données dans la littérature sur le rôle de la zone *remote* dans la survenue du RVG post-infarctus, chez l'homme [64–66].

Dans le travail portant sur la fonction OG dans une sous-population de 121 patients de notre registre RESIST, nous avons analysé le lien entre la survenue du RVG et les 3 composantes du strain atrial, évaluées 24 à 48 heures après la survenue de l'infarctus: (i) la fonction réservoir, dépendante de la relaxation et de la compliance atriale et de la descente du plancher basal du ventricule gauche durant la systole ventriculaire [137, 138], (ii) la fonction conduit, dépendante de la fonction diastolique du ventricule gauche et notamment de la succion du ventricule gauche, lorsque la valve mitrale est ouverte en début de diastole [139], et (iii) la fonction contractile, fonction de la contractilité atriale gauche, de la compliance du VG et des PRVG [140].

Il a été montré que la fonction réservoir de l'OG permet de limiter l'augmentation de la pression atriale secondaire à l'altération de la FEVG, et ainsi de maintenir des PRVG adaptées [141]. Dans notre étude, nous n'avons pas retrouvé de corrélation entre la composante réservoir du strain de l'OG ou le volume de l'OG d'une part et le RVG d'autre part. Il est possible que cette absence de corrélation soit en rapport avec des PRVG plutôt basses dans notre population de patients sans signe clinique d'IC, comme en atteste les différents indicateurs de fonction diastolique (rapport $\frac{E}{A}$ = 0,96 [0,84 – 1,20] ; temps de décélération de l'onde E mitrale = 200 ms [170 – 235] et rapport $\frac{E}{e'}$ = 8,1 [7,1 – 9,9]). D'après les recommandations 2016 concernant l'évaluation de la fonction diastolique [72], deux tiers de nos patients ont une pression atriale normale et une dysfonction diastolique de grade 1, trois patients ont une élévation de la pression OG et une dysfonction diastolique de grade 2 et trois patients ont une élévation de la pression OG et une dysfonction diastolique de grade 3. En raison d'une discordance entre le ratio $\frac{E}{e'}$ et le volume indexé de l'OG chez les patients ayant un

rapport $\frac{E}{A}$ entre 0,8 et 2 ou $\leq$0,8 avec une onde E$\geq$50 cm/s, il n'est pas possible de statuer sur le niveau de pression OG et le grade de dysfonction diastolique dans 31% de notre population.

Dans notre étude, seule la composante contractile du strain OG est corrélée à la survenue d'un RVG au décours du STEMI. Les liens qui existent entre fonction pompe atriale gauche et fonction systolique VG sont étroits. L'altération de la fonction systolique VG est un facteur indépendant d'altération de la fonction pompe atriale [142], via une élévation des PRVG. Inversement, l'altération de la fonction pompe de l'oreillette va altérer le remplissage du VG, diminuer le volume télédiastolique VG et ainsi altérer la FEVG et le débit cardiaque. Il est possible d'expliquer l'association entre une altération de la composante contractile du strain atrial à la phase sub-aiguë de l'infarctus et la survenue d'un RVG au cours du suivi. En effet, l'altération de la fonction pompe peut être un marqueur indirect d'une diminution de la compliance VG secondaire à l'infarctus [143]. Cette anomalie de la compliance va induire une élévation des PRVG, puis une activation des mécanismes neuro-hormonaux, dont les effets délétères au long cours vont conduire au RVG [144]. Dans le cercle vicieux qui lie fonction contractile atriale, fonction systolique ventriculaire gauche puis RVG, il existe des arguments dans notre étude pour dire que c'est l'anomalie de la fonction contractile atriale qui est l'élément déclencheur. Premièrement, les valeurs de la composante contractile du strain atrial restent associées au RVG indépendamment des volumes ventriculaires initiaux. Ensuite, l'altération du strain contractile atrial précède l'existence du RVG. Enfin, il est probable que les PRVG soient basses dans notre cohorte de patients sans signe clinique d'IC, comme précisé précédemment.

Dans notre étude, nous n'avons pas retrouvé de corrélation entre les valeurs de la composante conduit du strain OG et l'existence d'un RVG au cours du suivi. Il est possible ici aussi que l'inclusion de patients sans signe clinique d'IC explique en partie ce résultat, en

sélectionnant des patients ayant une compliance VG relativement conservée et des PRVG non élevées. Il a été également montré que dans le contexte de SCA, la composante contractile atriale peut être transitoirement améliorée afin de partiellement compenser une altération de la composante conduit [145]. Dans notre seconde étude d'imagerie, la valeur du GPIVD, secondaire à la détorsion du VG, contribuant ainsi à un phénomène de succion en début de diastole [146], n'est pas prédictrice de la survenue du RVG dans cette même population de patients admis pour un STEMI sans signe clinique d'IC. En dehors du temps de décélération de l'onde E (groupe RVG$\oplus$: 200 ms [170 – 240] vs. groupe RVG$\ominus$: 180 ms [153 – 230] ; p=0.046), les autres paramètres recommandés pour l'évaluation de la fonction diastolique ne sont pas prédictifs de RVG (rapport $\frac{E}{A}$, rapport $\frac{E}{e'}$ et taille de l'OG indexée). La valeur prédictrice d'un RVG de ces mêmes paramètres de fonction diastolique est controversée, que ce soit concernant le volume OG indexé [76, 55], le rapport $\frac{E}{A}$ [75, 55, 77], le temps de décélération de l'onde E [77, 76] ou encore le rapport $\frac{E}{e'}$ [76, 75]. La dysfonction diastolique est un processus complexe, associant une anomalie de la relaxation (notamment de la succion en début de diastole) et une diminution de la compliance ventriculaire. En pratique quotidienne, la dysfonction diastolique ne peut être affirmée sur un paramètre, mais sur un faisceau d'arguments [72]. Dès lors, il est possible que la valeur prédictrice d'un paramètre de fonction diastolique pris isolément – comme le GPIVD – ne soit pas suffisante pour être discriminante.

Ces deux études ont par ailleurs des limites communes, notamment méthodologiques. Le nombre de patients inclus est modeste, principalement limité par le fait que les patients ne sont pas reconvoqués dans le centre à titre systématique mais uniquement s'ils habitent dans l'aire urbaine caennaise et par les problématiques liées au serveur ayant conduit à la perte d'examens. La population incluse est sélectionnée, avec notamment exclusion des patients non revascularisés en phase aiguë, ayant des signes cliniques d'IC ou présentant une mauvaise échogénicité sur la session d'imagerie initiale. Enfin, il existe une importante

variabilité entre les logiciels existants pour la quantification du strain de l'OG [73] et du GPIVD [82]. Ce dernier point est un frein à la reproductibilité des résultats puis, dans un second temps, à la diffusion de la technique de quantification.

Nouveaux paramètres biologiques et remodelage ventriculaire gauche en post-infarctus

Lors de la phase initiale de ce travail, nous avions envisagé mesurer les taux sériques de matrix metalloproteinase (MMP)s, CRP ultra-sensible, fibrinogène, interleukines et cytokines chez les patients du registre RESIST pour lesquels nous allions disposer des données échocardiographiques et de prélèvements biologiques réalisés à la phase aiguë du SCA. Nous avons ensuite conduit notre revue de la littérature, mettant en évidence qu'il existe déjà des données en faveur d'une association entre les taux sériques des marqueurs de nécrose myocardique, des peptides natriurétiques, des protéines de l'inflammation et du remodelage matriciel, notamment les MMPs. Ce sont donc principalement et logiquement des biomarqueurs qui ont un rapport – direct ou indirect – avec l'étendue de la nécrose qui sont associés à un risque de survenue du RVG. Plus les lésions de nécrose sont importantes, plus il y a une activation de l'inflammation, une élévation des pressions de remplissage et une activation des systèmes neuro-hormonaux, mais aussi une plus grande dégradation de la matrice extracellulaire et plus de fibrose. Devant ces résultats, nous avons choisi d'explorer d'autres axes, nous conduisant ainsi à étudier successivement la néprilysine et le coenzyme Q10.

Nous nous sommes donc intéressés à la néprilysine, endopeptidase neutre qui hydrolyse et inactive divers peptides, dont les peptides natriurétiques, la bradykinine ou encore l'adrénomédulline [105, 106]. La néprilysine a ainsi une position centrale dans les systèmes neuro-hormonaux, et son inhibition – associé à un ARA2 – a montré une supériorité par

rapport au traitement par IEC sur la réduction de la mortalité et des hospitalisations pour IC chez des patients ayant une FEVG$\leq$40% [107]. L'utilisation d'un ARNI dans cette même population a permis d'obtenir une réduction des volumes ventriculaires à 4 mois [147]. Dans notre étude, nous avons dosé la néprilysine sur un prélèvement sanguin réalisé au moment de la procédure de revascularisation coronaire chez 68 patients du registre RESIST [148]. Le taux de néprilysine n'est pas associé à la survenue d'un RVG mais est corrélé au stunning, les patients ayant les plus hauts niveaux de néprilysine ont une FEVG plus basse lors de l'échocardiographie initiale et ont la meilleure augmentation de FEVG au terme du suivi. Par ailleurs, nous n'avons pas retrouvé de corrélation entre les niveaux sériques de néprilysine et de NT-proBNP, comme cela avait déjà été mis en évidence antérieurement dans une large cohorte [149]. Les taux de néprilysine que nous avons mesurés sont comparables à ceux obtenus dans une étude lyonnaise récente dans une population de 203 patients hospitalisés pour STEMI [150]. Dans cette dernière étude, il n'existe pas de variation significative du dosage de néprilysine au cours du premier mois. Aussi, les taux de néprilysine ne sont pas corrélés ni à la taille de l'infarctus, ni à la FEVG, évaluées une seule fois en IRM à 1 mois de l'épisode. D'autres données, acquises dans une large population sans pathologie cardiovasculaire connue a montré que les patients ayant les taux les plus bas de néprilysine sont plus fréquemment fumeurs, hypertendus ou ayant une dysfonction diastolique [149], des situations où la fonction endothéliale est fréquemment altérée. La méthodologie de notre étude ne nous permet pas de lier le taux de néprilysine et le stunning d'une part et la régulation des peptides agissant sur la fonction endothéliale par la néprilysine d'autre part. Il sera peut-être possible d'avancer davantage sur point avec les données de fonction endothéliale coronaire qui seront acquises dans le cadre de l'étude REMOD-TEP.

Dans notre autre étude, nous avons étudié la relation entre le taux de CoQ10 et la survenue d'un RVG au cours du suivi. Dans une étude préclinique, le prétraitement par CoQ10 a permis une diminution de la taille de l'infarctus et également de préserver la fonction ventriculaire en diminuant le stress oxydatif par diminution de la production de facteurs pro-inflammatoires et pro-apoptotiques [151]. Il existe quelques données chez l'homme également, la supplémentation en CoQ10 pourrait permettre de limiter le RVG chez des patients ayant une FEVG inférieure à 50% en post-infarctus [152]. Aussi, il a été montré que la concentration plasmatique en CoQ10 à 1 mois du STEMI est corrélée avec la survenue d'un remodelage [153]. Toutes ces données suggèrent une possible implication du CoQ10 dans la survenue du RVG après STEMI, en particulier via la préservation des fonctions mitochondriales et la diminution de la production d'ERO [154, 155]. En effet, une partie des lésions d'ischémie-reperfusion sont secondaires à un dysfonctionnement de la fonction mitochondriale conduisant notamment à une production d'ERO [113]. Dans notre étude, nous avons donc dosé le CoQ10 chez 68 patients de notre registre RESIST pour lesquels nous disposions de données échocardiographiques complètes, à la phase initiale et au cours du suivi, mais aussi de prélèvements sanguins prélevés sur tubes EDTA, au moment de la procédure de revascularisation coronaire. Nous avons retrouvé des valeurs de CoQ10 entre 0,46 et 2,21 μmol/L, valeurs similaires à celles retrouvées dans la littérature [156]. De plus, le CoQ10 étant principalement transporté par des lipoprotéines, les corrélations que nous avons trouvées avec les taux de cholestérol total et LDL-cholestérol sont également similaires à celles décrites dans la littérature [157, 158]. En revanche, nous n'avons pas trouvé d'association entre les taux sériques de CoQ10 à la phase aiguë du STEMI et le RVG au cours du suivi. Plusieurs explications peuvent être avancées pour expliquer ces résultats. Tout d'abord, la concentration plasmatique de CoQ10 n'est pas un reflet de la concentration tissulaire, en particulier dans les cardiomyocytes dont la composition en mitochondrie est importante [159]. Par ailleurs, dans la circulation sanguine, le CoQ10 est lié à des lipopro-

téines sous sa forme réduite afin de les protéger de l'oxidation [160]. Nous avons observé des résultats comparables en ne retrouvant aucune corrélation entre les taux plasmatiques de CoQ10 et le taux retrouvé dans les biopsies musculaires de 12 patients explorés dans le cadre d'une suspicion de maladie mitochondriale. Il existe d'autres arguments indiquant que le taux plasmatique de CoQ10 n'est pas un bon marqueur de son activité au sein des mitochondries des cardiomyocytes. La supplémentation par CoQ10 marqué ne retrouve pas ou peu de fixation au niveau cardiaque, soulignant l'importance de sa synthèse endogène [161]. Nous avons abordé précédemment l'importance du délai entre le début du STEMI et la réalisation du prélèvement. Dans notre étude, nous n'avons pas mis en évidence de lien entre la concentration plasmatique de CoQ10 à la phase aiguë de l'infarctus et le RVG. Dans une étude similaire, le taux plasmatique de CoQ10 avait été évalué 3 jours, 7 jours et 1 mois après le STEMI [153]. Le taux de CoQ10 diminuait progressivement au cours du temps et les patients avec les taux les plus bas de CoQ10 à 1 mois de l'épisode évoluaient plus souvent vers un RVG.

Nos deux études ont donc cherché à évaluer si la néprilysine d'une part et le CoQ10 d'autre part peuvent être des marqueurs pronostiques de l'évolution vers un RVG au décours d'un STEMI. Ces deux études sont donc négatives sur ce point et présentent des limites similaires. Il s'agit dans les deux cas d'une petite cohorte incluant des patients sélectionnés, où le biomarqueur d'intérêt n'a été dosé qu'une seule fois, à la phase aiguë du STEMI. Il existe probablement un intérêt à conduire d'autres études sur le sujet, sur une population de plus grande taille et moins sélectionnée, et en prenant en compte les limitations des études de ce manuscrit afin d'axer les recherches sur les éventuels mécanismes impliquant l'activation neuro-hormonale et la bioénergétique cellulaire des cardiomyocytes dans la survenue d'un RVG post-infarctus.

Perspectives

Ce travail de thèse ouvre des perspectives pour les recherches futures. Il existe un besoin d'une clarification de la notion de RVG en post-infarctus, notamment en ce qui concerne sa définition et la méthodologie à utiliser pour le mesurer. La standardisation des pratiques est un point important car elle permet d'augmenter la puissance des analyses à l'heure du développement des procédures de data mining. Il est important d'évaluer le caractère pronostique du RVG, dans une population de patients non sélectionnés. Les paramètres – cliniques, biologiques et d'imagerie – qui ont jusqu'ici été montrés comme étant prédictifs de la survenue d'un RVG doivent être validés prospectivement dans de telles cohortes. Ce pré-requis est indispensable à une approche multiparamétrique dans le but d'identifier puis de traiter le plus précocement possible les patients à plus haut risque de RVG durant le suivi.

Conclusion

Nos travaux ont donc essayé de mieux comprendre les mécanismes impliqués dans la survenue du remodelage ventriculaire gauche au décours d'un syndrome coronarien aigu avec sus-décalage du segment ST en utilisant une approche multiple. Les résultats que nous avons obtenus et les données de la littérature que nous avons colligées montrent bien la complexité de ce phénomène. Si nous avons retrouvé que la composante contractile du strain atrial est bien corrélée à l'existence d'un remodelage ventriculaire au cours du suivi, ce n'est pas le cas pour deux paramètres évaluant la fonction diastolique ventriculaire gauche, la fonction conduit de l'oreillette gauche et le gradient de pression intraventriculaire diastolique. Le taux de néprilysine, endopeptidase clef dans la régulation de plusieurs systèmes neuro-hormonaux est significativement associé au stunning et à la récupération d'une fraction d'éjection ventriculaire gauche au décours de l'infarctus. En revanche, sa quantification – tout comme celle du coenzyme Q10 – n'est pas corrélée à l'existence d'un remodelage ventriculaire gauche. Plus généralement, il existe encore de nombreux points à étudier afin de mieux comprendre le pronostic et les mécanismes physiopathologiques complexes mis en jeu dans la survenue d'un remodelage ventriculaire gauche après un infarctus du myocarde. Il est notamment fondamental que les travaux futurs puissent être menés selon une méthodologie standardisée et dans des populations larges de patients moins sélectionnés.

Annexes

Définition du remodelage ventriculaire gauche en IRM : revue de la littérature

Ces annexes concernent l'article suivant: **Legallois D**, Hodzic A, Alexandre J, Dolladille C, Saloux E, Manrique A, Roule V, Labombarda F, Milliez P, Beygui F. Definition of left ventricular remodelling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade. Heart Failure Reviews. 2020 ; In press. doi:10.1007/s10741-020-09975-3.

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- Poster ESC 2020 : page 186

Definition of left ventricular remodeling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies in the past decade

Heart Failure Reviews - Online resource

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SUPPLEMENTAL MATERIAL

Supplementary Methods 1. Search terms used for MEDLINE

Supplementary Methods 2. Modified Newcastle-Ottawa risk of bias scoring guide

Supplementary Table S1. PRISMA checklist for the meta-analysis

Supplementary Table S2. Characteristics of the studies included in this systematic review

Supplementary Table S3. Magnetic resonance imaging data of the studies included in this systematic review

Supplementary Table S4. Newcastle-Ottawa risk of bias scores for the non-interventional studies included in this systematic review

Supplementary Table S5. Assessment of risk of bias in the randomized controlled trials included in this review, using the Cochrane Collaboration's tool

Supplementary Table S6. Sensitivity analysis of the prevalence of left ventricular remodeling among patients with ST-elevation myocardial infarction

Supplementary Methods 1. Search terms used for MEDLINE

Acute coronary syndrome

1. Acute Coronary Syndrome [Mesh]

2. Myocardial infarction

3. OR / 1 – 2

Time frame

4. ("2010/01/01"[PDat] : "2019/08/31"[PDat])

Left ventricular remodeling

5. remodeling [Title/Abstract]

6. remodelling [Title/Abstract]

7. OR / 5 – 6

Combined search : #3 AND #4 AND #7

Legend : MeSH indicates Medical Subject Heading in MEDLINE, PDat indicates publication date.

Supplementary Methods 2. Modified Newcastle-Ottawa risk of bias scoring guide.

(1) Sample representativeness:

1 point: the study population contained consecutive STEMI patients

0 points: the study population contained only specific STEMI patients (e.g., occlusion of the left anterior descending artery or patients with altered left ventricular ejection fraction) or this point is not clearly stated in the manuscript.

(2) Sample size:

1 point: sample size was greater than or equal to 100 participants.

0 points: sample size was less than 100 participants.

(3) Lost to follow-up:

1 point: more than 70% of included patients were evaluated at the second CMR imaging session

0 points: there was no description of the proportion of patients with two CMR imaging session or less than 70% of patients were evaluated twice

(4) Ascertainment of left ventricular remodeling:

1 point: the study employed a commonly used measurement criteria for left ventricular remodeling (e.g., increase of ≥20% of enddiastolic volume between the two CMR imaging sessions)

0 points: the study employed an infrequently used measurement criteria for left ventricular remodeling

(5) Quality of descriptive statistics reporting:

1 point: The study reported descriptive statistics to describe the population (e.g., age, left ventricular ejection, culprit vessel) with proper measures of dispersion (e.g., mean, standard deviation or interquartile range for quantitative data).

0 points: The study did not report descriptive statistics, incompletely reported descriptive statistics, or did not report measures of dispersion.

Legend: The individual components listed above are summed to generate a total modified Newcastle-Ottawa risk of bias score for each study. Total scores range from 0 to 5. For the total score grouping, studies were judged to be of low risk of bias (≥3 points) or high risk of bias (<3 points).

Supplementary Table S1. PRISMA checklist for the meta-analysis

Section/topic	#	Checklist item	Reported section # (top-level heading)
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**Title**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**Abstract**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**Background**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**Background**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**Methods, Study Selection**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**Methods, Data sources and searches, Study Selection**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**Methods, Data sources and searches**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Methods, Data sources and searches**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**Methods, Study Selection**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**Methods, Data extraction and quality assessment**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**Methods, Data extraction and quality assessment**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**Methods, Data extraction and quality assessment**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**Methods, Data synthesis and analysis**

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**Methods, Data synthesis and analysis**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**Methods, Data extraction and quality assessment**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**Methods, Data synthesis and analysis**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Results, Literature search**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**Table 1, Online Resource**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Online Resource**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**Results, Definition of left ventricular remodeling**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**Results, Definition of left ventricular remodeling**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**Results, Online Resource**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**Results, Online Resource**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**Results**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**Discussion, Limitations**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**Discussion**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**Source of Funding**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplementary Table S2. Characteristics of the studies included in this systematic review

First author, year	Sample size	Population	Design	Timing of the second CMR	Definition of LVR	Patients with LVR	Age	Sex, male	Anterior AMI and/or LAD occlusion	Revascularization	Pain to balloon, min	Outcomes
Achilli, 2014	35	Anterior STEMI LVEF ≤ 45%	RCT (G-CSF)	6 months	ΔEDV > 20mL or ΔLVEF > 5%	NA	61 ± 8 (G-CSF) 62 ± 10 (placebo)	100% (G-CSF) 92% (placebo)	anterior MI : Inclusion criteria	PPCI: inclusion criteria	277 ± 166 (G-CSF) 238 ± 129 (placebo)	Follow-up at 3 years. Relationship with LVR not available
Biesbroek, 2017	42	STEMI	Post-hoc analysis of a prospective study	3 months	ΔEDV ≥ 15%	8 (19%)	60 ± 9	81%	57%	PPCI: inclusion criteria	147 ± 67	No further follow-up
Bulluck, 2016	40	STEMI	Prospective	5 months	ΔEDV ≥ 20%	8 (20%)	59 ± 13	88%	60%	PPCI: inclusion criteria	267 [122-330]	No further follow-up
Caldentey, 2017	227	STEMI	Prospective	6 months	ΔEDV ≥ 20%	29 (16%)	58 ± 12 (LVR) 59 ± 11 (No LVR)	93% (LVR) 83% (No LVR)	43%	PCI: inclusion criteria Complete revascularization: 79% (LVR) and 70% (No LVR)	217 ± 168 (LVR) 288 ± 315 (No LVR)	Follow-up: 79 ± 49 months. Relationship with LVR not available
Carberry, 2017	283	STEMI	Prospective	6 months	ΔEDV ≥ 20%	32 (11.3%)	59 ± 11	75%	37%	PPCI: 94% Rescue PCI: 4% Successful fibrinolysis: 2%	248 ± 207	Median follow-up 1330 days. Relationship with LVR not available
Cha, 2019	82	STEMI	Retrospective	6.5 months	ΔEDV ≥ 20%	20 (24.4%)	59.2 ± 11.1	89%	not precisely described >53.6%	not available	322 ± 336 (LVR) 566 ± 1844 (no LVR)	No further follow-up
Eitel, 2011	112	STEMI	RCT (intracoronary vs. intravenous abciximab)	6 months	ΔESVI > 0%	51 (45.5%)	64 [54-70] (IC abciximab) 66 [54-73] (IV abciximab)	82% (IC abciximab) 77% (IV abciximab)	57% (IC abciximab) 52% (IV abciximab)	PPCI: inclusion criteria	244 [163-433] (IC abcix.) 218 [159-323] (IV abcix.)	No further follow-up
Fabregat-Andrés, 2015	31	Anterior STEMI	Prospective (PGC-1 α induction)	6 months	ΔEDV > 10%	15 (48%)	57.2 ± 10.6 (induction) 60.1 ± 13.9 (no induction)	62.5% (induction) 91.3% (no induction)	anterior MI : Inclusion criteria	PPCI/Rescue PCI: 37.5%/62.5% (PGC-1 α induction) 60.9%/39.1% (No PGC-1 α induction)	283 ± 192 (induction) 202 ± 154 (no induction)	No further follow-up
Garcia, 2019	192	STEMI	Prospective	3 months 12 months	ΔESV ≥ 10%	32 (16.7%)	58 ± 9	81%	53%	PPCI: inclusion criteria	293 ± 130	No further follow-up
Garg, 2017	50	STEMI	Prospective (increase in average normal myocardial extra-cellular volume at follow-up or not)	3 months	ΔESV > 15%	10 (20%)	58 ± 11 (increase) 60 ± 11 (no increase)	84%	60%	PPCI: inclusion criteria	222 [149-344] (increase) 261 [158-454] (no increase)	No further follow-up
Gerbaud, 2014	124	STEMI	Prospective	3 months	ΔESV ≥ 15%	34 (27.4%)	56.7 ± 11.7 (ivabradine) 58.2 ± 10.5 (control)	90.3% (ivabradine) 88.7% (control)	46.8% (ivabradine) 43.5% (control)	PPCI: inclusion criteria	294 ± 182 (ivabradine) 291 ± 169 (control)	No further follow-up
Gohbara, 2015	69	STEMI	Prospective	7 months	ΔEDVI ≥ 20%	18 (26%)	63 ± 13	86%	51%	not available	210 ± 144	No further follow-up
Grabmaier, 2017	44	STEMI	Post-hoc analysis of a RCT (sitagliptin and G-CSF)	6 months	ΔEDV (continuous)	NA	56 [48-66]	84.1%	non available	PCI: inclusion criteria	366 ± 300	Long-term follow-up available but relationship with LVR is not described
Hallen, 2010	132	STEMI	Post-hoc analysis of a RCT (FX06)	4 months	ΔESVI and ΔEDVI (continuous)	NA	58.9 ± 11.2	76%	47%	PPCI: inclusion criteria	195 ± 85	No further follow-up
Husser, 2013	234	STEMI	Prospective	6 months	dilated ESVI according to reference values	94 (40%)	57 ± 12 (LVR) 58 ± 11 (no LVR)	83% (LVR) 82% (no LVR)	66% (LVR) 48% (no LVR)	PPCI: 35% Thombolysis: 53% Rescue PCI: 13%	265 ± 176 (LVR) 226 ± 164 (no LVR)	Median follow-up 140 weeks. Relationship with LVR not available

First author, year	Sample size	Population	Design	Timing of the second CMR	Definition of LVR	Patients with LVR	Age	Sex, male	Anterior AMI and/or LAD occlusion	Revascularization	Pain to balloon, min	Outcomes
Huttin, 2017	121	STEMI	Prospective	6 months	ΔEDV > 17,3mL	36 (29.8)	56 ± 10	85%	54%	PPCI: inclusion criteria	258 ± 138	No further follow-up
Janssens, 2018	197	STEMI	RCT (inhaled nitric oxide)	4 months	ΔESV and ΔEDV (continuous) and sphericity index	NA	63 ± 13 (inhaled nitric oxide) 60 ± 11 (control)	64% (inhaled nitric oxide) 74% (control)	43% (inhaled nitric oxide) 43% (control)	PPCI: inclusion criteria	222 [162-336] (inhaled nitric oxide) 210 [156-360] (control)	One year follow-up but relationship with LVR is not described
Mangion, 2016	72	STEMI	Post-hoc analysis of a RCT (culprit-artery PCI only vs. preventive PCI)	7 months	ΔESVI ≥ 20% and ΔEDVI ≥ 20%	11 (13%)	60 [39-83] (culprit only) 61 [38-89] (preventive)	81% (culprit only) 74% (preventive)	55% (culprit only) 24% (preventive)	PPCI: inclusion criteria	174 [129-413] (culprit only) 177 [123-326] (preventive)	No further follow-up
Mele, 2017	41	STEMI	Retrospective	6 months	ΔEDV ≥ 15%	10 (24%)	55.4 ± 9.1 (LVR) 61.2 ± 11.2 (No LVR)	90% (LVR) 87% (no LVR)	60% (LVR) 61% (No LVR)	myocardial revascularization within 90 min from the onset of symptoms	< 90 min (inclusion criteria)	No further follow-up
Najjar, 2011	124	STEMI	RCT (erythropoietin (EPO))	3 months	EDVI, ESVI and LV mass index (continuous)	NA	55.6 ± 12.6 (EPO) 57.4 ± 11.9 (placebo)	89.7% (EPO) 80% (placebo)	29.4% (EPO) 27.1% placebo)	PPCI/Rescue PCI: 94.1%/5.9% (EPO) 78.6%/21.4% (placebo)	210.9 ± 98.3 (EPO) 201.9 ±111.2 (placebo)	No further follow-up
O'Regan, 2012	46	STEMI	Prospective	12 months	ΔEDV ≥ 20%	16 (35%)	55 ± 10	96%	54%	PPCI: inclusion criteria	210 ± 156	No further follow-up
Pokorney, 2012	66	STEMI	Prospective	4 months 14 months	ΔEDVI > 20%	12 (18%)	58 ± 11	91%	56%	PPCI: inclusion criteria	not available	No further follow-up
Reindl, 2018	102	STEMI	Prospective	4 months	ΔEDV ≥ 20%	15 (14.7%)	56 [49-65]	89%	42%	PPCI: inclusion criteria	194 [137-337]	LVR showed a significant association with lower event-free survival (events: 3%, median follow-up: 367 days)
Reinstadler, 2013	47	STEMI	Prospective	4 months	ΔEDV ≥ 20%	6 (13%)	57 ± 10	85.2%	40.7%	PPCI: inclusion criteria	not available	No further follow-up
Rodriguez-Palomares, 2019	374	STEMI	Variable	6 months	ΔEDV > 15%	105 (28.1%)	59.2 ± 12	83.4%	56.4%	67.1% (acute phase)	not available	The primary endpoint (cardiovascular mortality, hospitalization for heart failure or ventricular arrhythmia) occurred in 49 patients (13.1%)
Shetelig, 2018	240	STEMI	Post-hoc analysis of a RCT (ischemic postconditioning)	4 months	increase EDVI ≥ 10mL/m2	not available	60 [53-77]	82.2%	48.8%	PPCI: inclusion criteria	187 [125-265]	Adverse clinical event at 12 months and vital status at 70 months. Relationship with LVR not available
Shetye, 2017	65	STEMI	Prospective	4 months	ΔESVI ≥ 15% or ΔEDVI ≥ 20%	11 (16.9%)	59.5 ± 11.0	92%	46%	PPCI: 60% Thrombolysis: 20% Rescue PCI: 12% Late PCI: 8%	not available	No further follow-up
Sörensson, 2013	68	STEMI	Post-hoc analysis of a RCT (Postconditioning)	3 months 12 months	ΔESV ≥ 15%	9 (13%)	63 [37-85] (postconditioning) 62 [42-85] (control)	85% (postconditioning) 89% (control)	33% (postconditioning) 37% (control)	PPCI: inclusion criteria	165 [133-202] (postconditioning) 180 [141-255] (control)	No further follow-up
Sugano, 2017	68	STEMI	Prospective	6 months	ΔEDV > 5%	22 (32%)	62.2 ± 14.3 (LVR) 63.8 ± 12.5 (No LVR)	84% (LVR) 69% (No LVR)	57% (LVR) 49% (No LVR)	PPCI: inclusion criteria	360 [180-540] (LVR) 180 [120-288] (No LVR)	No further follow-up

First author, year	Sample size	Population	Design	Timing of the second CMR	Definition of LVR	Patients with LVR	Age	Sex, male	Anterior AMI and/or LAD occlusion	Revascularization	Pain to balloon, min	Outcomes
Sürder, 2016	150	STEMI LVEF < 45%	Post-hoc analysis of a RCT (Intracoronary delivery of BM-MNC)	12 months	EDV, ESV (continuous)	NA	56 ± 14.5 (control) 55 ± 15 (early BM-MNC) 62 ± 15 (late BM-MNC)	83.6% (control) 86.2% (early BM-MNC) 82.5% (late BM-MNC)	89% (control) 95% (early BM-MNC) 92% (late BM-MNC)	PPCI 94% (control) 98.5% (early BM-MNC) 100% (late BM-MNC)	270 ± 300 (control) 288 ± 324 (early BM-MNC) 240 ± 288 (late BM-MNC)	Median follow-up: 38 months. Relationship between events and LVR is not described
Symons, 2016	383	STEMI	Prospective	4 months	ΔEDV > 20%	78 (20.4%)	60.0 ± 11.6	83%	50%	PPCI: inclusion criteria	196 [140-295]	No further follow-up
Tanimoto, 2010	104	STEMI	Prospective	8 months	ΔEDV > 15%	21 (20%)	64 ± 13 (papillary muscle infarction) 65 ± 12 (no papillary muscle infarction)	83% (papillary muscle infarction) 68% (no papillary muscle infarction)	13% (papillary muscle infarction) 55% (no papillary muscle infarction)	PPCI: inclusion criteria	318 ± 210 (papillary muscle infarction) 300 ± 216 (no papillary muscle infarction)	No further follow-up
Traverse, 2010	40	Anterior STEMI	RCT (stem cells)	6 months	ΔESV and ΔEDV (continuous)	NA	52.5 [43-64] (BMC) 57.5 [54-59] (placebo)	83.3% (BMC) 60% (placebo)	anterior MI : Inclusion criteria	PPCI: inclusion criteria	276 [120-720] (BMC) 174 [168-636] (placebo)	No further follow-up
Van Melle, 2010	50	STEMI	Prospective	4 months	ΔESV ≥ 15%	9 (18%)	55.1 ± 9.2	86%	52%	PPCI: inclusion criteria	not available	No further follow-up
Watabe, 2016	92	STEMI	Prospective (heterogeneous enhancement (HE))	6 months	ΔESV > 0%	29 (32%)	66 ± 12 (HE (-)) 58 ± 12 (HE (+))	81% (HE(-)) 88% (HE(+))	49% (HE (-)) 64% (HE (+))	not available	384 ± 384 (HE (-)) 444 ± 390 (HE (+))	No further follow-up
Wong, 2013	64	STEMI	Prospective	3 months	EDV (continuous)	NA	61 ± 10	83%	41%	PPCI: inclusion criteria	192 [147-279]	No further follow-up
Yoon, 2013	84	STEMI	RCT (PCI with distal protection)	6 months	ΔEDV > 20%	17 (20%)	58 ± 12 (distal protection) 58 ± 11 (control)	80% (distal protection) 78.7% (control)	54% (distal protection) 56% (control)	PPCI: inclusion criteria	291 ± 133 (distal protection) 309 ± 157 (control)	No further follow-up

AMI, acute myocardial infarction; BMC, bone marrow-derived cells; BM-MNC, bone marrow–derived mononuclear cells; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EPO, erythropoietin; ESV, end-systolic volume; ESVI, end-systolic volume index; G-CSF, granulocyte-colony-stimulating factor; HE, heterogeneous enhancement; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; LVR, left ventricular remodeling; PCI; percutaneous coronary intervention; PGC-1 α, Peroxisome proliferator-activated receptor gamma coactivator 1 α; PPCI, primary percutaneous coronary intervention; RCT, randomized clinical trial; STEMI, ST-elevation myocardial infarction; Values are expressed as mean ± standard deviation or median [interquartile range].

Supplementary Table 3. Magnetic resonance imaging data of the studies included in this systematic review

First author, year	Sample size	Infarct size	Initial LV volumes	Initial LVEF, %	LV volumes at follow-up	LVEF at follow-up
Achilli, 2014	35	4.2 ± 3.0 transmural LGE segments (G-CSF) 4.1 ± 2.8 transmural LGE segments (placebo)	EDV: 144.3 ± 33 (G-CSF) ESV: 76.1 ± 27.1 (G-CSF) EDV: 147.1 ± 42.8 (placebo) ESV: 79.0 ± 33.3 (placebo)	47.8 ± 10.9 (G-CSF) 47.3 ± 8.5 (placebo)	EDV: 145.1 ± 33.9 (G-CSF) ESV: 76.3 ± 25.4 (G-CSF) EDV: 166.7 ± 43.7 (placebo) ESV: 86.5 ± 35.7 (placebo)	48.0 ± 10.0 (G-CSF) 49.3 ± 9.2 (placebo)
Biesbroek, 2017	42	16% [8-26]	EDV: 183 ± 35 ESV: 91 ± 28	51 ± 8	EDV: 189 ± 45 ESV: 95 ± 39	52 ± 10
Bulluck, 2016	40	27.4% ± 14.6%	EDV: 172 ± 38 ESV: 90 ± 30	49 ± 8	EDV: 182 ± 49 ESV: 88 ± 38	53 ± 10
Caldentey, 2017	227	23.4% ± 15.9% (LVR) 16.2% ± 11.1% (No LVR)	EDVI: 77.5 ± 21.3 (LVR) ESVI: 45.2 ± 20.3 (LVR) EDVI: 83.6 ± 15.2 (No LVR) ESVI: 43.1 ± 12.5 (No LVR)	44 ± 13 (LVR) 49 ± 8 (No LVR)	EDVI: 105.0 ± 29.6 (LVR) ESVI: 60.3 ± 31.4 (LVR) EDVI: 80.9 ± 15.4 (No LVR) ESVI: 37.7 ± 11.7 (No LVR)	46 ± 14 (LVR) 54 ± 7 (No LVR)
Carberry, 2017	283	18% ± 13%	EDV: 161 ± 31 (men) ESV: 74 ± 26 (men) EDV: 124 ± 25 (women) ESV: 54 ± 18 (women)	55.3	EDV: 169 ± 42 (men) ESV: 68 ± 35 (men) EDV: 127 ± 30 (women) ESV: 46 ± 18 (women)	62 ± 9
Cha, 2019	82	27.3% ± 15.1% (LVR) 19.2% ± 10.6% (no LVR)	125.8 ± 35.0 (LVR) 141.6 ± 29.9 (no LVR)	50.9 ± 12.0 (LVR) 55.3 ± 9.3 (no LVR)	not available	not available
Eitel, 2011	112	18.2% ± 14.8% (IC abciximab) 25.0% ± 13.9% (IV abciximab)	EDVI: 80.0 ± 16.8 (IC abciximab) ESVI: 45.8 ± 17.1 (IC abciximab) EDVI: 78.4 ± 16.9 (IV abciximab) ESVI: 44.1 ± 15.2 (IV abciximab)	44.0 ± 10.6 (IC abciximab) 45.4 ± 10.2 (IV abciximab)	EDVI: 80.8 ± 21.8 (IC abciximab) ESVI: 42.7 ± 21.3 (IC abciximab) EDVI: 78.9 ± 22.7 (IV abciximab) ESVI: 44.3 ± 20.8 (IV abciximab)	48.1 ± 12.1 (IC abciximab) 46.8 ± 11.6 (IV abciximab)
Fabregat-Andrés, 2015	31	20.9% ± 7.9% PGC-1 α induction) 16.9% ± 11.8% (No PGC-1 α induction)	EDVI: 92.3 ± 6.2 (PGC-1 α induction and/or microvascular obstruction) EDVI: 91.0 ± 11.3 (No PGC-1 α induction, no microvascular obstruction)	50.1 ± 2.1 (PGC-1 α induction and/or MVO) 49.1 ± 2.9 (No PGC-1 α induction, no MVO)	EDVI: 102.0 ± 7.7 (PGC-1 α induction and/or microvascular obstruction) EDVI: 81.0 ± 6.2 (No PGC-1 α induction, no microvascular obstruction)	49.1 ± 2.1 (PGC-1 α induction and/or microvascular obstruction) 57.0 ± 3.2 (No PGC-1 α induction, no microvascular obstruction)
Garcia, 2019	192	20% ± 14.4% (LVR) 15.8% ± 10.0% (No LVR)	EDVI: 91.3 ± 22.4 (LVR) ESVI: 46.8 ± 17.5 (LVR) EDVI: 94.7 ± 14.8 (No LVR) ESVI: 49.6 ± 12.2 (No LVR)	48.6 ± 10.1 (LVR) 47.7 ± 9.0 (No LVR)	EDVI: 99.3 ± 25.2 (LVR – 3 months) ESVI: 53.1 ± 22.1 (LVR – 3 months) EDVI: 88.8 ± 16.2 (No LVR – 3 months) ESVI: 42.1 ± 13.5 (No LVR – 3 months) EDVI: 106.2 ± 27.6 (LVR – 12 months) ESVI: 57.2 ± 25.0 (LVR – 12 months) EDVI: 86.6 ± 17.9 (No LVR – 12 months) ESVI: 40.9 ± 14.5 (No LVR – 12 months)	48.6 ± 10.4 (LVR – 3 months) 53.1 ± 8.6 (No LVR – 3 months) 47.3 ± 9.9 (LVR – 12 months) 53.5 ± 8.9 (No LVR – 12 months)
Garg, 2017	50	23.9% [17-38]	EDVI: 79.1 [71-87] ESVI: 42 [36-50]	45.65 [36-51]	EDVI: 80.45 [70-89] ESVI: 38.7 [31-47]	52.35 [43-59]

Gerbaud, 2014	124	16.3% ± 7.5% (ivabradine) 15.6% ± 6.8% (control)	EDVI: 72.5 ± 14.6 (ivabradine) ESVI: 31.0 ± 11.1 (ivabradine) EDVI: 72.3 ± 16.1 (control) ESVI: 32.0 ± 10.4 (control)	57.9 ± 9.8 (ivabradine) 56.4 ± 9.1 (control)	EDVI: 75.0 ± 18.5 (ivabradine) ESVI: 31.0 ± 14.4 (ivabradine) EDVI: 78.5 ± 18.0 (control) ESVI: 35.3 ± 14.3 (control)	60.0 ± 10.4 (ivabradine) 56.5 ± 10.6 (control)
Gohbara, 2015	69	not available	EDVI: 78 ± 20	46 ± 11	EDVI : 80 ± 20	47 ± 9
Grabmaier, 2017	44	non available	non available	non available	non available	non available
Hallen, 2010	132	not available	mean EDVI: 76.1 mean ESVI: 41	mean LVEF: 46.6%	mean EDVI: 80.2 mean ESVI: 42.4	mean LVEF: 48.5%
Husser, 2013	234	22% ± 16%	EDVI: 94 ± 26 (LVR) ESVI: 54 ± 22 (LVR) EDVI: 70 ± 16 (no LVR) ESVI: 29 ± 10 (no LVR)	43 ± 10 (LVR) 58 ± 10 (no LVR)	not available	not available
Huttin, 2017	121	16% ± 13%	EDVI: 92 ± 15	42 ± 8	EDVI: 96 ± 18	49 ± 9
Janssens, 2018	197	18% ± 13% (inhaled nitric oxide) 19% ± 15% (control)	EDV: 79 ± 16 (inhaled nitric oxide) ESV: 41 ± 14 (inhaled nitric oxide) EDV: 82 ± 19 (control) ESV: 44 ± 18 (control)	49 ± 11 (inhaled nitric oxide) 47 ± 10 (control)	EDV: 84 ± 18 (inhaled nitric oxide) ESV: 41 ± 16 (inhaled nitric oxide) EDV: 90 ± 22 (control) ESV: 46 ± 21 (control)	53 ± 10 (inhaled nitric oxide) 51 ± 10 (control)
Mangion, 2016	72	18.12% ± 13.85% (culprit only PCI) 14.83% ± 11.75% (preventive PCI)	EDVI: 64.8 [57.1-77.4] (culprit only) ESVI: 33.5 [27.3-47.8] (culprit only) EDVI: 68.5 [54.7-79.0] (preventive) ESVI: 34.1 [25.5-49.1] (preventive)	47.9 [40.3-47.9] (culprit only PCI) 48.5 [38.6-55.8] (preventive PCI)	EDVI: 69.3 [59.4-79.9] (culprit only) ESVI: 31.8 [24.4-43.0] (culprit only) EDVI: 66.1 [54.7-73.7] (preventive) ESVI: 30.7 [23.0-36.3] (preventive)	51.7 [42.9-60.2] (culprit only) 54.4 [49.3-62.8] (preventive)
Mele, 2017	41	non available	EDV: 145.1 ± 29.3 (LVR) ESV: 90.6 ± 26.4 (LVR) EDV: 154.9 ± 36.2 (No LVR) ESV: 81.2 ± 28.5 (No LVR)	38.4 ± 6.9 (LVR) 48.6 ± 8.0 (No LVR)	EDV: 185.9 ± 49.8 (LVR) ESV: 114.7 ± 44.3 (LVR) EDV: 151.8 ± 39.9 (No LVR) ESV: 74.0 ± 31.3 (No LVR)	39.9 ± 7.5 (LVR) 52.5 ± 8.2 (No LVR)
Najjar, 2011	124	10.6% ± 8.6% (EPO) 10.4% ± 7.6% (placebo)	EDVI: 65.6 ± 18.2 (EPO) ESVI: 34.7 ± 14.7 (EPO) EDVI: 63.4 ± 15.4 (placebo) ESVI: 32.6 ± 10.6 (placebo)	48.2 ± 9.1 (EPO) 48.9 ± 8.7 (placebo)	EDVI: 70.0 ± 17.1 (EPO) ESVI: 34.1 ± 14.0 (EPO) EDVI: 66.6 ± 19.1 (placebo) ESVI: 32.0 ± 11.7 (placebo)	52.2 ± 9.3 (EPO) 52.0 ± 8.8 (placebo)
O'Regan, 2012	46	13.3% (range 1.2 – 34.0%)	EDV: 146 ± 38 ESV: 67 ± 26	56 ± 9	EDV: 160 ± 46 ESV: 71 ± 31	57 ± 12
Pokorney, 2012	66	21% ± 13%	EDVI: 79 ± 17	42 ± 10	EDVI: 82 ± 18 (4 months) EDVI: 82 ± 20 (14 months)	46 ± 10 (4 months) 46 ± 11 (14 months)
Reindl, 2018	102	16% [8-25]	EDV: 150 [127-167] ESV: 64 [51-82]	55 [48-61]	EDV: 154 [131-172] ESV: 58 [49-77]	60 [53-66]
Reinstadler, 2013	47	18% ± 10%	EDV: 144 ± 27 ESV: 66 ± 22	55 ± 10	EDV: 148 ± 29 ESV: 60 ± 25	61 ± 10
Rodriguez-Palomares, 2019	374	21.9% ± 14.3%	EDVI: 79.7 ± 21.9 ESVI: 39.6 ± 18.8	51.6 ± 12.0	EDV: 82 ± 26 ESV: 39 ± 23	55 ± 12

Shetelig, 2018	240	15.1% [9.7-22.5] (IL-8 ≤ median) 23.8% [12.7-34.6] (IL-8 > median)	not available	52 [47-59] IL-8 ≤ median 48 [38-56] IL-8 > median	not available	58% [52-63] IL-8 ≤ median 52% [42-61] IL-8 > median
Shetye, 2017	65	22.3% [14.5-35.5]	EDVI: 91.1 [84.5-102.2] ESVI: 53.5 [47.6-65.9]	41.0 ± 8.4	EDVI: 93.5 [85-106] ESVI: 47.7 [39.8-61.6]	47.2 ± 8.46
Sörensson, 2013	68	9.9% [5.5-14.9] (postconditioning) 8.0% [5.5-14.1] (control)	EDVI: 79 [73-84] (postconditioning) ESVI: 43 [36-55] (postconditioning) EDVI: 89 [80-99] (control) ESVI: 49 [37-56] (control)	not available	EDVI: 79 [73-91] (postconditioning) ESVI: 40 [32-48] (postconditioning) EDVI: 86 [70-104] (control) ESVI: 39 [33-57] (control)	not available
Sugano, 2017	68	3.6 ± 2.8 transmural infarct segments (LVR) 2.7 ± 2.5 transmural infarct segments (No LVR)	EDV: 109.2 ± 37.0 (LVR) ESV: 63.1 ± 32.4 (LVR) EDV: 121.7 ± 35.1 (No LVR) ESV: 67.7 ± 28.9 (No LVR)	43.6 ± 10.4 (LVR) 45.7 ± 9.6 (No LVR)	EDV: 134.9 ± 41.9 (LVR) ESV: 71.6 ± 33.4 (LVR) EDV: 105.4 ± 34.1 (No LVR) ESV: 51.9 ± 24.0 (No LVR)	47.9 ± 9.7 (LVR) 52.9 ± 10.4 (No LVR)
Sürder, 2016	150	28.3% ± 16.3% (control) 28.1% ± 16.2% (early BM-MNC) 26.6% ± 15.9% (late BM-MNC)	EDV: 153 ± 38 (control) ESV: 94 ± 33 (control) EDV: 156 ± 41 (early BM-MNC) ESV: 100 ± 36 (early BM-MNC) EDV: 157 ± 37 (late BM-MNC) ESV: 100 ± 29 (late BM-MNC)	40.0 ± 9.9 (control) 36.5 ± 9.9 (early BM-MNC) 36.3 ± 8.2 (late BM-MNC)	EDV: 170 ± 56 (control) ESV: 110 ± 53 (control) EDV: 179 ± 61 (early BM-MNC) ESV: 118 ± 56 (early BM-MNC) EDV: 164 ± 47 (late BM-MNC) ESV: 107 ± 44 (late BM-MNC)	38.1 ± 13.6 (control) 36.2 ± 11.4 (early BM-MNC) 36.6 ± 12.2 (late BM-MNC)
Symons, 2016	383	16.7 ± 12.8	EDVI: 78.3 ± 18.5 ESVI: 40.1 ± 14.5	49.5 ± 9.9	EDVI: 82.5 ± 21.4 ESVI: 40.7 ± 16.8	51.8 ± 10.3
Tanimoto, 2010	104	21% ± 8% (mitral regurgitation) 16% ± 11% (no mitral regurgitation)	EDV: 130 ± 33 (mitral regurgitation) ESV: 71 ± 28 (mitral regurgitation) EDV: 116 ± 29 (no mitral regurgitation) ESV: 60 ± 25 (no mitral regurgitation)	47 ± 10 (mitral regurgitation) 50 ± 10 (no mitral regurgitation)	non available	non available
Traverse, 2010	40	not available	EDV: 88 ± 31 (BMC) ESV: 46 ± 26 (BMC) EDV: 77 ± 12 (placebo) ESV: 40 ± 11 (placebo)	49.0 ± 9.5 (BMC) 48.6 ± 8.5 (placebo)	ΔEDV: -4 ± 22 (BMC) ΔESV: -7 ± 3.3 (BMC) ΔEDV: 17 ± 11 (placebo) ΔESV: -2 ± 8.4 (placebo)	55.1 ± 9.6 (BMC) 56.7 ± 13.9 (placebo)
Van Melle, 2010	50	not available	not available	42 ± 9	not available	47 ± 10
Watabe, 2016	92	not available	EDV: 119 ± 31 (HE (-)) ESV: 67 ± 25 (HE (-)) EDV: 143 ± 38 (HE (+)) ESV: 90 ± 33 (HE (+))	45 ± 9 (HE (-)) 38 ± 8 (HE (+))	EDV: 110 ± 32 (HE (-)) ESV: 56 ± 25 (HE (-)) EDV: 149 ± 40 (HE (+)) ESV: 93 ± 34 (HE (+))	49 ± 10 (HE (-)) 39 ± 8 (HE (+))
Wong, 2013	64	30g [21-40]	ESV: 63 [50-75]	58 {49-62]	EDV: 152 [133-192] ESV: 55 [39-84]	61 [56-67]
Yoon, 2013	84	34.7% ± 13.6% (distal protection) 35.7% ± 14.6% (control)	EDV: 127 ± 30 (distal protection) ESV: 55 ± 25 (distal protection) EDV: 133 ± 29 (control) ESV: 59 ± 28 (control)	57.7 ± 12.8 (distal protection) 57.2 ± 13.0 (control)	EDV: 140 ± 39 (distal protection) ESV: 59 ± 32 (distal protection) EDV: 133 ± 37 (control) ESV: 54 ± 28 (control)	59.5 ± 12.9 (distal protection) 60.7 ± 14.7 (control)

BMC, bone marrow-derived cells; BM-MNC, bone marrow–derived mononuclear cells; EDV, end-diastolic volume; EDVI, end-diastolic volume index; EPO, erythropoietin; ESV, end-systolic volume; ESVI, end-systolic volume index; G-CSF, granulocyte-colony-stimulating factor; HE, heterogeneous enhancement; IC, intracoronary; IL-8, interleukin-8; IV, intravenous; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVR, left ventricular remodeling; MVO, microvascular obstruction; PCI; percutaneous coronary intervention; PGC-1 α, Peroxisome proliferator-activated receptor gamma coactivator 1 α; STEMI, ST-elevation myocardial infarction. Values are expressed as mean ± standard deviation or median [interquartile range].

Supplementary Table S4. Modified Newcastle-Ottawa risk of bias scores for the non-interventional studies included in this systematic review. See Supplementary Methods 2 for explanation.

First author, year	Representativeness	Sample size	Lost to follow-up	Definition of LVR	Descriptive statistics	Total score
Biesbroek, 2017	0	0	1	1	1	3
Bulluck, 2016	0	0	1	1	1	3
Caldentey, 2017	0	1	1	1	1	4
Carberry, 2017	0	1	1	1	1	4
Cha, 2019	0	0	0	1	1	2
Fabregat-Andrés, 2015	0	0	0	1	1	2
Garcia, 2019	1	1	0	1	1	4
Garg, 2017	0	0	1	1	1	3
Gerbaud, 2014	0	1	1	1	1	4
Gohbara, 2015	0	0	0	1	1	2
Husser, 2013	0	1	1	1	1	4
Huttin, 2017	0	1	1	0	1	3
Mele, 2017	0	0	0	1	1	2
O'Regan, 2012	0	0	0	1	1	2
Pokorney, 2012	0	0	0	0	1	1
Reindl, 2018	1	1	1	1	1	5
Reinstadler, 2013	0	0	1	1	1	3
Rodriguez-Palomares, 2019	0	1	0	1	1	3
Shetye, 2017	0	0	0	1	1	2
Sugano, 2017	0	0	1	1	1	3
Symons, 2016	0	1	1	1	1	4
Tanimoto, 2010	1	1	1	1	0	4
Van Melle, 2010	0	0	0	1	0	1
Watabe, 2016	1	0	1	1	1	4
Wong, 2013	1	0	1	0	1	3

Supplementary Table S5. Assessment of risk of bias in the randomized controlled trials included in this review, using the Cochrane Collaboration's tool (Higgins et al. 2011).

	Achilli, 2014	Eitel, 2011	Grabmaier, 2017	Hallen, 2010	Janssens, 2018	Mangion, 2016	Najjar 2011	Shetelig, 2018	Sörensson, 2013	Sürder, 2016	Traverse, 2010	Yoon, 2013
Random sequence generation	+	+	+	+	+	+	+	+	+	+	?	?
Allocation concealment	+	+	+	+	+	+	+	+	+	?	?	?
Blinding of participants and personnel	−	−	+	+	+	−	+	−	−	−	+	−
Blinding of outcome assessment	+	+	+	+	?	+	+	+	+	?	+	+
Incomplete outcome data	+	+	+	−	+	+	−	+	+	−	+	−
Selective reporting	?	+	+	+	+	?	+	+	?	+	?	?
Other bias	−	−	−	−	−	−	+	−	−	+	−	−

Key: + low risk of bias; − high risk of bias; ? unclear risk of bias

Supplementary Table 6. Sensitivity analysis of the prevalence of left ventricular remodeling among patients with ST-elevation myocardial infarction. 95%-CI: 95% confidence interval.

Influential analysis (Random effects model)

	proportion	95%-CI	p-value	tau^2	I^2
Omitting Fabregat-Andrés Ó 2015	0.2221	[0.1884-0.2598]		0.2259	81.6%
Omitting Bulluck H 2016	0.2290	[0.1938-0.2686]		0.2419	82.6%
Omitting Mele D 2017	0.2277	[0.1925-0.2672]		0.2433	82.7%
Omitting Biesbroek PS 2017	0.2294	[0.1941-0.2689]		0.2415	82.6%
Omitting O'Regan DP 2012	0.2246	[0.1899-0.2636]		0.2394	82.4%
Omitting Reinstadler SJ 2013	0.2316	[0.1964-0.2709]		0.2357	82.3%
Omitting van Melle JP 2010	0.2298	[0.1945-0.2694]		0.2411	82.6%
Omitting Garg P 2017	0.2291	[0.1938-0.2687]		0.2425	82.6%
Omitting Shetye AM 2017	0.2304	[0.1950-0.2700]		0.2402	82.5%
Omitting Pokorney SD 2012	0.2299	[0.1945-0.2696]		0.2417	82.5%
Omitting Sörensson P 2013	0.2319	[0.1967-0.2714]		0.2347	82.2%
Omitting Sugano A 2017	0.2250	[0.1900-0.2642]		0.2422	82.4%
Omitting Gohbara M 2015	0.2270	[0.1916-0.2667]		0.2459	82.7%
Omitting Mangion K 2016	0.2312	[0.1958-0.2707]		0.2379	82.3%
Omitting Cha MJ 2019	0.2275	[0.1920-0.2674]		0.2471	82.7%
Omitting Yoon CH 2013	0.2292	[0.1936-0.2690]		0.2447	82.6%
Omitting Watabe H 2016	0.2250	[0.1899-0.2645]		0.2442	82.4%
Omitting Reindl M 2018	0.2318	[0.1964-0.2713]		0.2357	82.1%
Omitting Tanimoto T 2010	0.2292	[0.1936-0.2692]		0.2458	82.6%
Omitting Eitel I 2011	0.2208	[0.1886-0.2568]		0.1992	79.0%
Omitting Huttin O 2017	0.2255	[0.1901-0.2653]		0.2481	82.5%
Omitting Gerbaud E 2014	0.2263	[0.1907-0.2663]		0.2505	82.6%
Omitting Garcia G 2019	0.2311	[0.1955-0.2710]		0.2398	81.9%
Omitting Caldentey G 2017	0.2337	[0.1990-0.2724]		0.2186	80.6%
Omitting Husser O 2013	0.2220	[0.1898-0.2578]		0.1949	77.7%
Omitting Carberry J 2017	0.2352	[0.2013-0.2728]		0.2011	79.1%
Omitting Rodriguez-Palomares JF 2019	0.2257	[0.1891-0.2669]		0.2693	82.3%
Omitting Symons R 2016	0.2291	[0.1926-0.2703]		0.2620	82.3%
Pooled estimate	0.2282	[0.1938-0.2668]		0.2377	82.0%

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Definition of left ventricular remodeling following ST-elevation myocardial infarction: a systematic review of cardiac magnetic resonance studies

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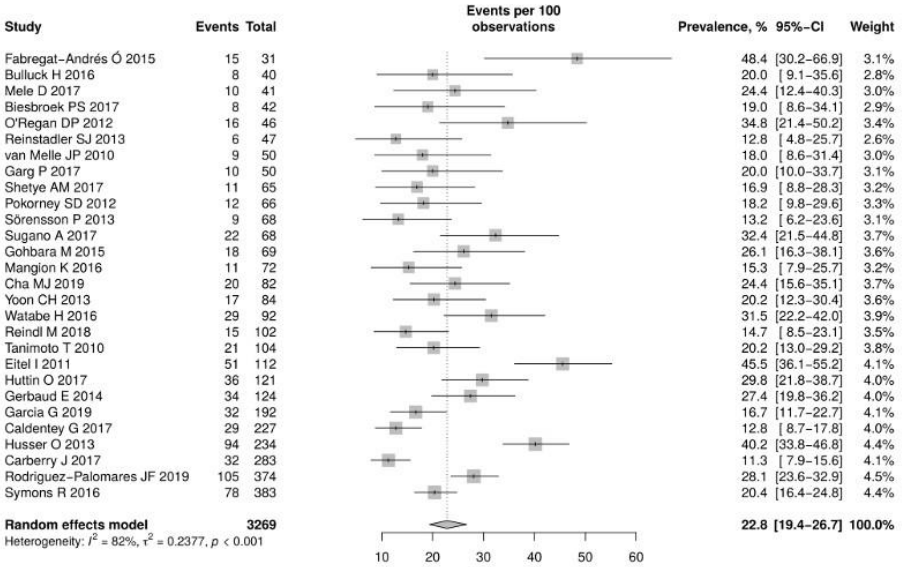
Purpose. An increase in left ventricular volumes between baseline and follow-up imaging is the main criteria for the quantification of left ventricular remodeling (LVR) after ST-elevation myocardial infarction, but without consensual definition. We aimed to review the criterion used for the definition of left ventricular remodeling based on cardiac magnetic resonance imaging in studies including patients with ST-elevation myocardial infarction.

Methods. A systematic literature search was conducted using MEDLINE and the Cochrane Library from January 2010 to August 2019. Thirty-seven studies involving a total of 4209 patients were included.



Meta-analysis of the prevalence of left ventricular remodeling among patients presenting with STEMI using CMR imaging. The square area is proportional to the inverse variance of the estimate

Results. The median age of the patients was 59 years, 82 % were male, and 93 % underwent primary percutaneous coronary intervention. The median follow-up duration was 6 months (range, 3–12), and the second cardiac magnetic resonance session was performed at 6 months in 14 (38%) studies. Among these studies, 30 (81%) used a cut-off value for defining LVR, with a pooled LVR prevalence estimate of 22.8%, 95%-CI[19.4%-26.7%], and a major between-study heterogeneity (I^2=82%). The seven remaining studies (19%) defined LVR as a continuous variable. A 20% increase in end-diastolic volumes or a 15% increase in end-systolic volumes between a baseline and a follow-up cardiac magnetic resonance imaging were the two most common criterion (13 [35%] and 9 [24%] studies, respectively). Seven studies used both end-diastolic and end-systolic left ventricular volumes.

Conclusions. The definition of LVR using cardiac magnetic resonance following ST-elevation myocardial infarction is highly variable, among studies including highly selected patients. The most frequent LVR criterion were a 20% increase in end-diastolic volumes or a 15% increase in end-systolic volumes. A composite cut-off value of a 12% to 15% increase in end-systolic volume and a 12% to 20% increase in end-diastolic volume using a follow-up cardiac magnetic resonance imaging 1 to 3 months after myocardial infarction might be proposed as a consensual cut-off for defining LVR for future large-sized, prospective studies with serial cardiac magnetic resonance imaging and long-term follow-up in unselected patients.

Étude REMOD-TEP, poster présenté aux JESFC 2016

Poster présenté aux JESFC 2016, dans les suites de l'obtention en décembre 2015 de la bourse SFC "Les syndromes coronariens aigus", de 20000 €.

Relationship between left ventricular remodeling, coronary endothelial function and myocardial fibrosis using positron emission tomography in patients with ST-elevation myocardial infarction (REMOD-TEP)

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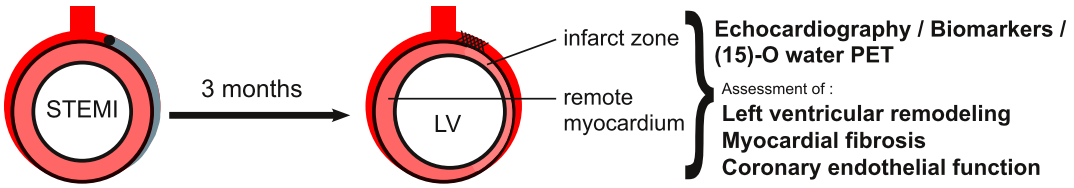
5 - FHU REMOD-VHF

Background. Left ventricular remodeling is a common complication in patients with ST-elevation myocardial infarction (STEMI) and may lead to heart failure. Hemodynamic, metabolic and inflammatory mechanisms are involved in this pathophysiological process. Recent data demonstrated that remote, noninfarct-related region of the myocardium is also implicated. There is no data about the assessment of coronary endothelial function or myocardial fibrosis in the remote zone in patients with STEMI. The correlation between these parameters and left ventricular remodeling is not known.



Primary objective. Assessment of coronary endothelial function and myocardial fibrosis 3 months after onset of STEMI (infarct-related and remote myocardium).

Secondary objectives. Correlation between global and regional coronary endothelial function, myocardial fibrosis and echocardiographic parameters of left ventricular remodeling (3 months).

Methods. A total of 30 patients with STEMI successfully treated with primary coronary intervention (TIMI 3) and single-vessel coronary artery disease will be included. Transthoracic echocardiography and measurements of biomarkers of endothelial function, fibrosis and inflammation (MMP-2, hsCRP, fibrinogen, IL-1, and TNF-alpha) will be performed during the initial hospitalization and after 3 months. Coronary endothelial function will be assessed using (15)-O water positron emission tomography (PET) at rest and after cold pressor test at 3 months. Fibrosis will be quantified using the amount of perfusable tissue fraction assessed by (15)-O water PET. These quantitative parameters will be compared between remote and infact myocardium and correlated with left ventricular remodeling and biomarkers.

Conclusion. This study will provide valuable information on the mechanisms involved in left ventricular remodeling following STEMI, with a special focus on the role of remote myocardium.

Relation entre le strain atrial gauche et le remodelage ventriculaire gauche

Cette annexe concerne le manuscrit suivant: **Legallois D**, Hodzic A, Milliez P, Manrique A, Saloux E, Beygui F. Left atrial strain quantified after myocardial infarction is associated with ventricular remodeling. Soumis à American Journal of Cardiology.

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Left atrial strain is associated with left ventricular remodeling in patients with ST-elevation myocardial infarction

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Purpose. Left ventricular remodeling (LVR) is associated with outcomes in patients with ST-elevation myocardial infarction (STEMI). Left atrial (LA) volume has been described as a predictor of outcomes in the latter population. We investigated the association between LA mechanical function using speckle tracking imaging and LVR at follow-up after STEMI.

Methods. Baseline and 6-month 3D transthoracic echocardiograms were performed in 121 STEMI patients. LA global longitudinal strain was reported for the reservoir (LASr), conduit (LAScd), and contraction (LASct) phases.

Results. Mean age was 58.3±12.5 years and 98 (81%) were men. Baseline left ventricular ejection fraction (LVEF) was 46.8% [41.0, 52.9] and improved to 52.1% [45.8, 57.0] at follow-up, (p<0.001). A lower LASct was associated with a dilation of left ventricle at follow-up (%end-diastolic volume increase : -1.9% [-11.0, 15.2] in the two higher LASct tertiles group vs. 19.2% [5.0, 34.3] in the lower LASct tertile group, p=0.001). A higher %end-systolic volume increase at follow-up was associated with lower LASct: 12.6% [-16.2, 39.8] in the lower LASct group vs. -6.8% [-23.6, 14.4] in the two higher LASct tertiles group (p=0.004). Regarding LVEF, a low LVEF at follow-up was associated with the worst tertile of all LA strains.

Conclusions. The three components of baseline LA strain were associated with LVEF at follow-up in patients with STEMI. Some of these components were also significantly associated with lower LVEF at baseline or predictive of a significant increase in left ventricular volumes during follow-up, indicating LVR.

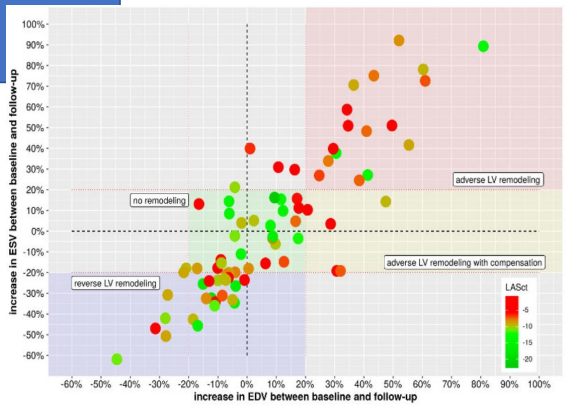

Figure. Relationship between LASct and remodeling pattern after STEMI

	Overall (n=121)	Lowest LASr tertile (abs. values) (n=40)	Other tertiles (abs. values) (n=81)	p.value	Lowest LAScd tertile (abs. values) (n=40)	Other tertiles (abs. values) (n=81)	p.value	Lowest LASct tertile (abs. values) (n=40)	Other tertiles (abs. values) (n=81)	p.value
Echocardiography, at baseline										
EDV, mL/m2	56 [48, 67]	60 [52, 66]	55 [47, 68]	0.38	60 [53, 67]	55 [47, 66]	0.32	54 [46, 65]	58 [49, 67]	0.25
ESV, mL/m2	30 [24, 36]	32 [27, 38]	28 [23, 35]	0.18	33 [27, 39]	29 [24, 35]	0.12	30 [25, 38]	31 [24, 36]	0.91
LVEF, %	46.8 [41.0, 52.9]	44.8 [40.0, 49.3]	48.4 [42.3, 54.0]	0.042	44.9 [39.1, 49.3]	48.2 [42.5, 54.0]	0.026	44.9 [39.8, 50.3]	48.4 [42.4, 53.3]	0.067
Echocardiography, at follow-up										
EDV, mL/m2	59 [49, 72]**	60 [49, 78]*	59 [49, 70]*	0.67	62 [53, 76]**	57 [48, 70]*	0.20	64 [52, 80]***	58 [48, 70]	0.20
% increase in EDV, %	7.7 [-8.4, 24.9]	9.2 [-7.7, 19.6]	3.3 [-8.3, 27.5]	0.99	9.3 [-6.2, 17.6]	2.8 [-10.1, 27.5]	0.48	19.2 [5.0, 34.3]	-1.9 [-11.0, 15.2]	<0.001
ESV, mL/m2	27 [21, 40]	30 [22, 45]	27 [20, 36]	0.13	31 [25, 43]	26 [20, 37]	0.047	31 [22, 46]*	27 [20, 37]	0.06
% increase in ESV, %	-2.6 [-21.0, 21.3]	2.2 [-20.6, 31.7]	-3.5 [-20.9, 21.2]	0.42	2.2 [-20.6, 23.5]	-3.7 [-20.9, 21.6]	0.52	12.6 [-16.2, 39.8]	-6.8 [-23.6, 14.4]	0.004
LVEF, %	52.1 [45.8, 57.0]***	48.2 [41.9, 54.7]	54.0 [48.1, 59.5]***	0.002	49.2 [42.9, 54.4]*	54.4 [48.1, 59.4]***	0.01	48.2 [39.9, 54.9]	53.2 [47.4, 59.2]***	0.01

*Table. Echocardiographic data according to left atrial strain status. *p<0.05, **p<0.01 and ***p<0.001 vs. baseline.*

Biomarqueurs et remodelage ventriculaire gauche : revue de la littérature

Ces annexes concernent le manuscrit suivant: **Legallois D**, Hodzic A, Allouche S, Milliez P, Beygui F. The relationship between circulating biomarkers and left ventricular remodeling after my-ocardial infarction: an updated review. Soumis à Disease Markers.

The relationship between circulating biomarkers and left ventricular remodeling after myocardial infarction: an updated review

Heart Failure Reviews - Online resource

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SUPPLEMENTAL MATERIAL

Supplementary Table S1. Association between infarct size-related biomarkers levels and LVR at follow-up in STEMI patients. AMI, acute myocardial infarction; CMR, cardiac magnetic resonance; LVEDD, left ventricular end-diastolic diameter; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV(i), (indexed) left ventricular end-systolic volume ; IQR, interquartile range; LVR, left ventricular remodeling; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; SPECT, single photon emission computed tomography; STEMI, ST-elevation myocardial infarction; TTE, transthoracic echocardiography.

Supplementary Table S2. Association between natriuretic peptides, biomarkers of inflammation or involved in the turnover of matrix and collagen synthesis levels and LVR at follow-up in STEMI patients. Only data not available in the main manuscript are provided in this supplementary table. AMI, acute myocardial infarction; ANP, atrial natriuretic peptide; CMR, cardiac magnetic resonance; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV, left ventricular end-systolic volume ; LVR, left ventricular remodeling; MMP, matrix metalloproteinase; PCI, percutaneous coronary intervention; RCT, randomized clinical trial; STEMI, ST-elevation myocardial infarction; TIMP, tissue inhibitor of metalloproteinase ; TNF, tumor necrosis factor; TTE, transthoracic echocardiography.

Supplementary Table S3. Association between routine biomarkers levels and LVR at follow-up in STEMI patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMR, cardiac magnetic resonance; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV, left ventricular end-systolic volume ; HbA1c, glycated hemoglobin; IQR, interquartile range; LVR, left ventricular remodeling; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TSH, thyroid-stimulating hormon; TTE, transthoracic echocardiography.

Supplementary Table S4. Association between lipid profile and LVR at follow-up in STEMI patients. CMR, cardiac magnetic resonance; LVEDV(i), (indexed) left ventricular end-diastolic

volume ; LVESV, left ventricular end-systolic volume ; LVR, left ventricular remodeling; PCI, percutaneous coronary intervention; TTE, transthoracic echocardiography.

Supplementary Table S5. Association between remaining biomarkers levels, not described in other tables, and LVR in STEMI patients. ACE-2, angiotensin-converting enzyme 2; ADAMTS-7, A disintegrin and metalloproteinase with thrombospondin motifs 7; AMI, acute myocardial infarction; CMR, cardiac magnetic resonance; FGF, Fibroblast growth factor; LVEDV(i), (indexed) left ventricular end-diastolic volume ; LVESV(i), (indexed) left ventricular end-systolic volume ; LVR, left ventricular remodeling; MBL, Mannose-binding lectin; miR, micro RNA; PCI, percutaneous coronary intervention; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SPECT, single photon emission computed tomography; STEMI, ST-elevation myocardial infarction; TTE, transthoracic echocardiography.

Table 1

Table 1	sample size	design	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	reference
Troponin I	62	Prospective	within 24 hours	TTE, 1 month	≥20% increase in LVEDV	16 (26%)	none	Abdel Hamid 2016
	227	Prospective	every 6 hours during the first 12 hours and every 12 hours thereafter	CMR, 6 months	≥20% increase in LVEDV	29 (16%)	none	Caldentey 2019
	290 (84% STEMI)	Prospective	before discharge (average day 4)	TTE, 6 months	increase in LVEDV	146 (50%)	none	Devaux 2012
	60 (derivation cohort) 30 (validation cohort)	Prospective	day 3-4 (before discharge)	TTE, 176 days (derivation cohort, n=60) CMR, 121 days (validation cohort, n=30)	increase in LVEDV	30 (50%)	none	Devaux 2013
	92	Prospective	baseline	TTE, 6 months	≥15% increase in LVESV	26 (28.2%)	none	Di Tano 2017
	226 (Q-wave MI)	Prospective	at discharge (day 3 to day 7)	TTE, 12 months	>20% increase in LVEDV	87 (38%)	positive	Fertin 2010
	132	RCT substudy	24 hours, 48 hours	CMR, 4 months	unavailable	NA	positive	Hallen 2010
	198	Not available	day 5	TTE, 12 months	≥20% increase in LVEDV	56 (28.3%)	none	Liu 2015
	48	Prospective	day 2, day 7	CMR, 1 month and 3 months	none	NA	positive (day 2)	Mather 2013
	141	Not available	unavailable	TTE, 4 months	≥20% increase in LVEDV	49 (34.8%)	none	Zaliaduonyte-Peksiene 2014
	75	Prospective	every 6 h after admission until peak values	TTE, 6 months	≥15% increase in LVEDV	22 (29.3%)	positive	Karuzas 2019
Peak troponin I	74	Not available	baseline	TTE, 3 months	decrease in LVEF	NA	positive	Acar 2016
	109	Retrospective	repeated measurements within the first 96 hours	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	positive	Buono 2011
	131	Not available	every four hours after hospital admission for three days	TTE, 6 months	>20% increase in LVEDV	42 (32%)	positive, multivariate	Choi 2013
	161 (AMI)	Prospective	at admission	TTE, 12 months	>20% increase in LVEDV	24 (14.9%)	none	Dominguez-Rodriguez 2012
	97	Prospective	at admission	TTE, 12 months	>20% increase in LVEDV	21 (21.6%)	none	Dominguez-Rodriguez 2011
	80	Prospective	at admission	TTE, 6 months	≥20% increase in LVEDV	29 (36.3%)	positive, multivariate	Erkol 2012
	58	Prospective	unavailable	CMR, 4 and 12 months	unavailable	18 (31%), at 12 months	positive	Ganame 2011
	78	Prospective	within the first 24 to 96 hours after the onset of symptoms	TTE and CMR, 6 months	>20% increase in LVEDV	26 (31.7%)	none	Garcia-Alvarez 2009
	97 (61 % STEMI)	Prospective	at first 3 days	TTE, 6 months	>20% increase in LVEDV	24 (32.9%)	none	Hsu 2017
	35	prospective	at admission	TTE, 2 months, 12 months	≥20% increase in LVEDV (2 months)	14 (40%)	none	Khurelsukh 2016
	97	Prospective	unavailable	TTE, 6 months	≥20% increase in LVEDV	38 (39.2%)	positive, multivariate	Lacalzada 2015
	208	Not available	unavailable	TTE, 6 months	>20% increase in LVEDV	53 (25.5%)	none	Na 2016
	46	Not available	unavailable	CMR, 12 months	≥20% increase in LVEDV	16 (35%)	none	O'Regan 2012
	88	Prospective	every 6 hours during the first 12 hours and every 12 hours thereafter, during 48 hours	CMR, 6.4 months	≥20% increase in LVEDVi	15 (16.9%)	none	Ortiz-Perez 2013
	75	Not available	unavailable	TTE, 6 months	≥10% decrease in LVESV (reverse remodeling)	25 (33.3%)	positive	Spinelli 2013
	198	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	55 (27.8%)	none	Swiatkiewicz 2012
	383	Prospective	unavailable	CMR, 4 months	>20% increase in LVEDV	unavailable	positive	Symons 2016
	110	Prospective	unavailable	TTE, 3 months	≥20% increase in LVEDV	26 (23.6%)	positive	Xu 2017
	87	Prospective	on admission and every 12 hours for at least 72 hours after PCI	TTE, 6 months	≥15% increase in LVESV	44 (50.6%)	positive	Spinelli 2018
	104	Prospective	every 4 hours until the values started to decrease	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%), reverse	none	Wu 2018
	82	Retrospective	unavailable	CMR, 7 months	≥20% increase in LVEDV	20 (24.4%)	positive	Cha 2019
hs Troponin I	64	Matched cohorts	48h [IQR 24;72]	CMR, 3 months, 12 months	>10% increase in LVESV	NA	none	Garcia 2019
Troponin T	359 (AMI)	Not available	at admission	TTE, 6 months	>10% increase in LVEDV	116 (32.3%)	positive	Lv 2014
	42	Not available	prior to PCI, day 2, week 1	CMR, 2 months and 12 months	none	NA	variable	Manhenke 2014
	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019
	39	Prospective	during PCI, 3 hours, 6 hours, 12 hours and/or 24 hours	TTE, 6 months	≥20% increase in LVEDV With LVEF<50 %	14 (35.9%)	none	Galeano-Otero 2020
Peak troponin T	213	Retrospective	baseline	TTE, 6 months	≥15% increase in LVESV	44 (21%)	positive	Abate 2014
	39	RCT	unavailable	TTE, 3 months	>20% increase in LVEDV	13 (33.3%)	none	Elżbieciak 2013
	89	Prospective	serially	CMR, 4 months	≥20% increase in LVEDV	14 (15.7%)	positive, multivariate	Feistritzer 2015
	159	Prospective	unavailable	TTE, 6 months	≥20% increase in LVEDV	31 (19.5%)	positive	Haldon 2010
	964	Prospective	unavailable	TTE, 6 months	≥20% increase in LVEDV	296 (30.7%)	positive	Joyce 2013

Table 1

	35	prospective	at admission	TTE, 2 months, 12 months	≥20% increase in LVEDV (2 months)	14 (40%)	positive	Khurelsukh 2016
	112	Not available	unavailable	TTE, 6 months	≥15% increase in LVESV	19 (17.0%)	positive	Nucifora 2010
	47	Prospective	before PCI, every 6 hours during 24 hours then daily until discharge	CMR, 4 months	≥20% increase in LVEDV	6 (12.8%)	positive	Reinstadler 2013
	111	Prospective	baseline, 6 hours, 24 hours	TTE, 6 months	≥20% increase in LVEDV and/or LVESV	33 (29.7%)	none	Tiryakioglu 2016
	112	Prospective	at admission, 0-3 hours, 6 hours, 12 hours, 24 hours and daily until discharge	TTE, 6 months	≥20% increase in LVEDV	24 (21.4%)	positive, multivariate	Urbano-Moral 2012
	1995	Retrospective	unavailable	TTE, 3 months, 6 months, 12 months	≥20% increase in LVEDV	953 (47.8%)	positive	van der Bijl 2020
	600	Retrospective	Within 48 hours of admission	TTE, 3 months	≥20% increase in LVEDV	150 (25.0%)	positive	Lustosa 2020
hs Troponin T	88	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	11 (12.5%)	positive, multivariate	Reindl 2017
	123	Prospective	at admission, 6 hours, 12 hours, daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	none (admission)	Reinstadler 2016
Peak hs troponin T	143	Prospective	unavailable	CMR, 4 months	≥15% increase in LVEDV	29 (20%)	positive, multivariate	Reindl 2016
	102	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	15 (14.7%)	positive, multivariate	Reindl 2019
	123	Prospective	at admission and daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	positive	Reinstadler 2016
	40	Prospective	unavailable	CMR, 3 months	≥10% decrease in LVESV (reverse remodeling)	15 (37.5%)	positive	Grabka 2018
Peak troponin	66	Prospective	upon admission and after 6, 12, and 24 hours	TTE, 3 months	>20% increase in LVEDV	22 (33%)	ɔsitive, none (mutlivariat	Bochenek 2011
	83	RCT substudy	unavailable	TTE, 3 months, 12 months	≥20% increase in LVESVi	43 (51.8%)	borderline (p=0.05)	Manrique 2016
	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	positive	Türkoğlu 2016
	60	Not available	unavailable	TTE, 6 months	≥20% increase in LVEDV	14 (23.3%)	none	Wita 2011
	1237	Registry	unavailable	TTE, 6 months	>10% decrease in LVESV (reverse remodeling)	466 (37,7%) reverse	positive, multivariate	Choe 2018
Troponin	55	Not available	baseline	TTE, 2 months	≥15% increase in LVESV	13 (24%)	positive	Barberato 2013
Peak Creatin Kinase total	137	Not available	at admission	TTE, 12 months	>20% increase in LVEDV	44 (32%)	positive	Bauters 2007
Creatin Kinase	100	Not available	baseline	TTE, 6 months	≥20% increase in LVEDV and/or LVESV	39 (39%)	positive	Awadalla 2007
	290 (84% STEMI)	Prospective	before discharge (average day 4)	TTE, 6 months	increase in LVEDV	146 (50%)	none	Devaux 2012
	60 (derivation cohort) 30 (validation cohort)	Prospective	day 3-4 (before discharge)	TTE, 176 days (derivation cohort, n=60) CMR, 121 days (validation cohort, n=30)	increase in LVEDV	30 (50%)	none	Devaux 2013
	216	Prospective	day 2	TTE, 6 months	change in LVEDVi	NA	positive, multivariate	Lin 2014
	48	Not available	every 6 hours until peak levels	TTE, 6 months	≥15% increase in LVESVi	11 (22.9%)	positive	Turan 2012
	81	Not available	on admission then every 8 hours for the first 24 hours then daily until peak	TTE, 6 months	≥20% increase in LVEDV	33 (40.7%)	positive	Bastawy 2018
	64	Matched cohorts	48h [IQR 24;72]	CMR, 3 months, 12 months	>10% increase in LVESV	NA	none	Garcia 2019
	39	Prospective	during PCI, 3 hours, 6 hours, 12 hours and/or 24 hours	TTE, 6 months	≥20% increase in LVEDV with LVEF<50 %	14 (35.9%)	positive	Galeano-Otero 2020
Log Creatin Kinase	264	Not available	day 2	TTE, 6 months	>20 ml/m² increase in LVEDVI	unavailable	positive, multivariate	Lin 2015
	331	Prospective	unavailable	TTE, 6 months	increase in LVEDVi	NA	positive, multivariate	Liu 2019
Peak Creatin Kinase	226 (Q-wave MI)	Prospective	at discharge (day 3 to day 7)	TTE, 12 months	percent change in LVEDV	NA	positive, multivariate	Bauters 2013
	131	Not available	at presentation and every 24 h for at least 5 days	Left ventriculography, 6 months	≥10% increase in LVEDVI	48 (37%)	none	Aoki 2011
	109	Retrospective	repeated measurements within the first 96 hours	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	none	Buono 2011
	512	Not available	baseline	TTE, 6 months	>10% decrease in LVESV (reverse remodeling)	252 (49%) reverse	positive, multivariate	Carrabba 2012
	89	Prospective	serially	CMR, 4 months	≥20% increase in LVEDV	14 (15.7%)	positive	Feistritzer 2015
	36	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	13 (36.1%)	positive	Lombardo 2012
	359 (AMI)	Not available	at admission	TTE, 6 months	>10% increase in LVEDV	116 (32.3%)	none	Lv 2014
	208	Not available	unavailable	TTE, 6 months	>20% increase in LVEDV	53 (25.5%)	none	Na 2016
	46	Not available	unavailable	CMR, 12 months	≥20% increase in LVEDV	16 (35%)	none	O'Regan 2012
	75	Prospective	unavailable	CMR, 6 months	>5% increase in LVEDV	22 (32%)	positive	Sugano 2017
	75	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	15 (20%)	negative	Sumiyoshi 2017

Table 1

	92	Not available	unavailable	CMR, 6 months	any increase in LVESV	29 (32%)	positive	Watabe 2016
	104	Prospective	every 4 hours until the values started to decrease	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
	64	Matched cohorts	48h [IQR 24;72]	CMR, 3 months, 12 months	>10% increase in LVESV	NA	positive	Garcia 2019
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
Creatin Kinase-MB	100	Not available	baseline	TTE, 6 months	≥20% increase in LVEDV and/or LVESV	39 (39%)	positive	Awadalla 2007
	55	Not available	baseline	TTE, 2 months	≥15% increase in LVESV	13 (24%)	none	Barberato 2013
	39	RCT	4 hours after PCI	TTE, 3 months	>20% increase in LVEDV	13 (33.3%)	none	Elżbieciak 2013
	198	Not available	day 5	TTE, 12 months	≥20% increase in LVEDV	56 (28.3%)	positive	Liu 2015
	30	Not available	at admission, 8 hours, 16 hours, 24 hours	TTE, 1 month, 6 months	none	NA	none	Radovan 2006
	198	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	55 (27.8%)	positive	Swiatkiewicz 2012
	48	Not available	every 6 hours until peak levels	TTE, 6 months	≥15% increase in LVESVi	11 (22.9%)	positive, multivariate	Turan 2012
	81	Not available	on admission then every 8 hours for the first 24 hours then daily until peak	TTE, 6 months	≥20% increase in LVEDV	33 (40.7%)	positive	Bastawy 2018
	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019
	199	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	49 (24.6%)	positive	Chu 2020
Peak Creatin Kinase-MB	109	Retrospective	repeated measurements within the first 96 hours	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	none	Buono 2011
	131	Not available	every four hours after hospital admission for three days	TTE, 6 months	>20% increase in LVEDV	42 (32%)	positive, multivariate	Choi 2013
	478	Not available	overnight after admission	TTE, 12 months	≥15% increase in LVEDV	226 (47.3%)	positive, multivariate	Fan 2017
	54	Not available	immadiately, 8 hours, 16 hours	TTE, 3 months, 6 months	>15% increase in LVESV (6 months)	19 (35.2%)	none	Hsiao 2016
	97 (61 % STEMI)	Prospective	at first 3 days	TTE, 6 months	>20% increase in LVEDV	24 (32.9%)	positive	Hsu 2017
	234	Prospective	unavailable	CMR, 6 months	dilated LVESV according to accepted reference values according to gender, age and body surface area	94 (40.2%)	positive	Husser 2013
	35	Prospective	at admission	TTE, 2 months, 12 months	≥20% increase in LVEDV (2 months)	14 (40%)	none	Khurelsukh 2016
	262	Not available	unavailable	TTE, 6 months	≥20% increase in LVEDV	66 (25.2%)	positive	Kim 2017
	105	Prospective	unavailable	SPECT, 44 months	≥20% increase in LVEDV	25 (23.8%)	positive	Sato 2006
	75	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	15 (20%)	negative	Sumiyoshi 2017
	111	Prospective	baseline, 6 hours, 24 hours	TTE, 6 months	≥20% increase in LVEDV and/or LVESV	33 (29.7%)	none	Tiryakioglu 2016
	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	positive	Türkoğlu 2016
	1237	Registry	unavailable	TTE, 6 months	>10% decrease in LVESV (reverse remodeling)	466 (37,7%) reverse	positive	Choe 2018
	87	Prospective	on admission and every 12 hours for at least 72 hours after PCI	TTE, 6 months	≥15% increase in LVESV	44 (50.6%)	positive	Spinelli 2018
	104	Prospective	every 4 hours until the values started to decrease	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
	40	Prospective	unavailable	CMR, 3 months	≥10% decrease in LVESV (reverse remodeling)	15 (37.5%)	none	Grabka 2018
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
	82	Retrospective	unavailable	CMR, 7 months	≥20% increase in LVEDV	20 (24.4%)	positive	Cha 2019
	199	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	49 (24.6%)	positive	Chu 2020
Creatin phospho kinase	83	Prospective	baseline	TTE, 6 months	≥10% increase in LVEDD or LVESD	26 (31%)	positive	Cogni 2013
	35	Prospective	at admission	TTE, 2 months, 12 months	≥20% increase in LVEDV (2 months)	14 (40%)	none	Khurelsukh 2016
Peak Creatin phospho kinase	213	Retrospective	baseline	TTE, 6 months	≥15% increase in LVESV	44 (21%)	positive	Abate 2014
	218	Not available	at admission	TTE, 6 months	≥20% increase in LVEDV	52 (24%)	positive, multivariate	Araszkiewicz 2014
	42	Not available	baseline	TTE, 3 months	>15% increase in LVESV	13 (31%)	positive	Bonios 2014
	80	Prospective	at baseline and every six hours until their levels started to decrease	TTE, 6 months	≥15% increase in LVEDV and/or LVESV	41 (51.3%)	positive, multivariate	Farah 2013
	964	Prospective	unavailable	TTE, 6 months	≥20% increase in LVEDV	296 (30.7%)	positive	Joyce 2013
	78	Not available	unavailable	Left ventriculography, 6 months	>10% increase in LVEDV	35 (44.9%)	positive	Obata 2020
	600	Retrospective	within 48 hours of admission	TTE, 3 months	≥20% increase in LVEDV	150 (25.0%)	positive	Lustosa 2020

Table 1

Creatin phospho kinase-MB	83	Prospective	baseline	TTE, 6 months	≥10% increase in LVEDD or LVESD	26 (31%)	positive	Cogni 2013
Peak Creatin phospho kinase-MB	135	Not available	baseline	TTE, 6 months	≥20% increase in LVEDVI	28 (21%)	positive	Ahn 2013
	80	Prospective	at baseline and every six hours until their levels started to decrease	TTE, 6 months	≥15% increase in LVEDV and/or LVESV	41 (51.3%)	positive	Farah 2013
	208	Not available	unavailable	TTE, 6 months	>20% increase in LVEDV	53 (25.5%)	positive	Na 2016
Peak lactate dehydrogenase	109	Retrospective	repeated measurements within the first 96 hours	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	positive	Buono 2011
	123	Prospective	at admission and daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	positive	Reinstadler 2016
Lactate dehydrogenase	123	Prospective	at admission and daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	none (admission)	Reinstadler 2016
Peak myoglobin	109	Retrospective	repeated measurements within the first 96 hours	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	none	Buono 2011

Table 2

Table 2	sample size	design	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	reference
NT-pro ANP	71	Prospective	Baseline, 3 months	TTE, 3 months, 12 months, 24 months	LVEDVI increase >20 ml/m²	12 (17%)	positive, multivariate (baseline)	Hole 2004
Atrial natriuretic peptide	33	Not available	at admission, 1 month, 3 months	Left ventriculography, 3 months	≥8% increase in LVEDVi	14 (42.4%)	none	Yoshitomi 1998
Hematocrit	104	Prospective	day 1, day 3, day 5 and day 7	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%,) reverse	none	Wu 2018
Platelets	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	negative	Türkoğlu 2016
Mean platelet volume	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	positive	Türkoğlu 2016
Peak peripheral blood mononuclear cell	131	Not available	at presentation and every 24 h for at least 5 days	Left ventriculography, 6 months	≥10% increase in LVEDVI	48 (37%)	positive, multivariate	Aoki 2011
Fibrinogen	131	Not available	at presentation	Left ventriculography, 6 months	≥10% increase in LVEDVI	48 (37%)	positive	Aoki 2011
TNF-alpha	33 (AMI)	Not available	day 1, day 7 and day 14	Left ventriculography, 6 months	unavailable	NA	none	Kondo 2009
interleukin-8	258	RCT substudy	before and immediately after PCI, day 1	CMR, 4 months	an increase in LVEDVi >10 ml/m²	unavailable	none	Shetelig 2018
MMP-1	226 (Q-wave MI)	Prospective	at discharge (day 3 to day 7)	TTE, 12 months	>20% increase in LVEDV	87 (38%)	none	Fertin 2013
MMP-7	106	RCT substudy	early after PCI and at days 1, 7	TTE, 6 months	unavailable	NA	none	Cerisano 2015
	32 (84 % STEMI)	Prospective	at enrollment, , days 2 to 5	TTE, 3 months, 6 months	none	NA	none	Webb 2006
TIMP-3	106	RCT substudy	early after PCI and at days 1, 7	TTE, 6 months	unavailable	NA	none	Cerisano 2015
TIMP-4	106	RCT substudy	early after PCI and at days 1, 7	TTE, 6 months	unavailable	NA	none	Cerisano 2015
	226 (Q-wave MI)	Prospective	at discharge (day 3 to day 7)	TTE, 12 months	>20% increase in LVEDV	87 (38%)	none	Fertin 2013
	42	Not available	prior to PCI, day 2, week 1	CMR, 2 months and 12 months	none	NA	none	Manhenke 2014

Table 3

Table 3	sample size	design	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	reference
Creatinin	131	Not available	at presentation	Left ventriculography, 6 months	≥10% increase in LVEDVI	48 (37%)	none	Aoki 2011
	62	Prospective	within 24 hours	TTE, 1 month	≥20% increase in LVEDV	16 (26%)	none	Abdel Hamid 2016
	55	Not available	baseline	TTE, 2 months	≥15% increase in LVESV	13 (24%)	none	Barberato 2013
	42	Not available	baseline	TTE, 3 months	>15% increase in LVESV	13 (31%)	none	Bonios 2014
	109	Retrospective	once daily during hospitalization	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	positive	Buono 2011
	92	Prospective	baseline	TTE, 6 months	≥15% increase in LVESV	26 (28.2%)	none	Di Tano 2017
	97	Prospective	at admission	TTE, 12 months	>20% increase in LVEDV	21 (21.6%)	none	Dominguez-Rodriguez 2011
	89	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	14 (15.7%)	none	Feistritzer 2015
	208	Not available	unavailable	TTE, 6 months	>20% increase in LVEDV	53 (25.5%)	none	Na 2016
	88	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	11 (12.5%)	none	Reindl 2017
	198	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	55 (27.8%)	none	Swiatkiewicz 2012
	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	none	Türkoğlu 2016
	60	Not available	unavailable	TTE, 6 months	≥20% increase in LVEDV	14 (23.3%)	none	Wita 2011
	104	Prospective	before and after PCI	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
	40	Prospective	unavailable	CMR, 3 months	≥10% decrease in LVESV (reverse remodeling)	15 (37.5%)	none	Grabka 2018
	64	Matched cohorts	48h [IQR 24;72]	CMR, 3 months, 12 months	>10% increase in LVESV	NA	none	Garcia 2019
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019
	199	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	49 (24.6%)	none	Chu 2020
estimated glomerular filtration	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019
	109	Retrospective	once daily during hospitalization	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	negative	Buono 2011
	89	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	14 (15.7%)	none	Feistritzer 2015
	54	Not available	immadiately, 8 hours, 16 hours	TTE, 3 months, 6 months	>15% increase in LVESV (6 months)	19 (35.2%)	none	Hsiao 2016
	964	Prospective	unavailable	TTE, 6 months	≥20% increase in LVEDV	296 (30.7%)	none	Joyce 2013
	198	Not available	day 5	TTE, 12 months	≥20% increase in LVEDV	56 (28.3%)	negative, multivariate	Liu 2015
	143	Prospective	unavailable	CMR, 4 months	≥15% increase in LVEDV	29 (20%)	none	Reindl 2016
	110	Prospective	unavailable	TTE, 3 months	≥20% increase in LVEDV	26 (23.6%)	none	Xu 2017
	1237	Registry	unavailable	TTE, 6 months	>10% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Choe 2018
	1995	Retrospective	unavailable	TTE, 3 months, 6 months, 12 months	≥20% increase in LVEDV	953 (47.8%)	positive	van der Bijl 2020
	199	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	49 (24.6%)	none	Chu 2020
Uric acid	97 (61 % STEMI)	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	24 (32.9%)	none	Hsu 2017
Fasting plasma glucose	131	Not available	at presentation	Left ventriculography, 6 months	≥10% increase in LVEDVI	48 (37%)	positive, multivariate	Aoki 2011
	109	Retrospective	once daily during hospitalization	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	none	Buono 2011
	104	Prospective	in the morning of the first day after admission	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
HbA1c	69	Prospective	at admission	CMR, 7 months	≥20% increase in LVEDVI	18 (26.1%)	none	Gohbara 2015
	143	Prospective	unavailable	CMR, 4 months	≥15% increase in LVEDV	29 (20%)	none	Reindl 2016
	104	Prospective	in the morning of the first day after admission	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
mean amplitude of glycemic excursions	69	Prospective	24-h period of 11±6 days	CMR, 7 months	≥20% increase in LVEDVI	18 (26.1%)	positive, multivariate	Gohbara 2015
homeostasis model assessment-estimated insulin resistance (HOMA-IR)	485	Retrospective	at discharge	TTE, 12 months	none	NA	positive	Yang 2019
Bilirubin	145	Prospective	the morning after admission	CMR, 6 months	≥20% increase in LVEDV	42 (29.2%)	none	Miranda 2016
ALT	123	Prospective	at admission and daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	none	Reinstadler 2016
AST	123	Prospective	at admission and daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	none	Reinstadler 2016
Peak ALT	123	Prospective	at admission and daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	positive	Reinstadler 2016

Table 3

Peak AST	123	Prospective	at admission and daily between day 1 and day 4	CMR, 4 months	≥20% increase in LVEDV	16 (13.0%)	positive	Reinstadler 2016
Calcium	88	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	11 (12.5%)	none	Reindl 2017
Phosphate	88	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	11 (12.5%)	none	Reindl 2017
TSH	102	Prospective	day 1	CMR, 4 months	≥20% increase in LVEDV	15 (14.7%)	negative, multivariate	Reindl 2019

Table 4

Table 4	sample size	design	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	reference
Total cholesterol	131	Not available	at presentation	Left ventriculography, 6 months	≥10% increase in LVEDVI	48 (37%)	none	Aoki 2011
	109	Retrospective	the day after admission, after a 12-hour overnight fast	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	none	Buono 2011
	97	Prospective	at admission	TTE, 12 months	>20% increase in LVEDV	21 (21.6%)	none	Dominguez-Rodriguez 2011
	89	Prospective	unavailable	CMR, 4 months	≥20% increase in LVEDV	14 (15.7%)	none	Feistritzer 2015
	208	Not available	unavailable	TTE, 6 months	>20% increase in LVEDV	53 (25.5%)	none	Na 2016
	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	none	Türkoğlu 2016
	104	Prospective	in the morning of the first day after admission	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019
High-density lipoprotein cholesterol	109	Retrospective	the day after admission, after a 12-hour overnight fast	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	positive	Buono 2011
	198	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	55 (27.8%)	none	Swiatkiewicz 2012
	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	none	Türkoğlu 2016
	104	Prospective	in the morning of the first day after admission	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019
Low-density lipoprotein cholesterol	109	Retrospective	the day after admission, after a 12-hour overnight fast	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	none	Buono 2011
	198	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	55 (27.8%)	none	Swiatkiewicz 2012
	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	none	Türkoğlu 2016
	1237	Registry	unavailable	TTE, 6 months	>10% decrease in LVESV (reverse remodeling)	466 (37,7%) reverse	none	Choe 2018
	104	Prospective	in the morning of the first day after admission	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	none	Wu 2018
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019
Triglycerides	131	Not available	at presentation	Left ventriculography, 6 months	≥10% increase in LVEDVI	48 (37%)	none	Aoki 2011
	109	Retrospective	the day after admission, after a 12-hour overnight fast	TTE, 17 months	≥20% increase in LVEDVI	30 (28%)	none	Buono 2011
	208	Not available	unavailable	TTE, 6 months	>20% increase in LVEDV	53 (25.5%)	none	Na 2016
	198	Prospective	unavailable	TTE, 6 months	>20% increase in LVEDV	55 (27.8%)	none	Swiatkiewicz 2012
	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	none	Türkoğlu 2016
	58	Not available	unavailable	TTE, 6 months	change in LVEDV	NA	none	Hatasa 2019
	57	Not available	during PCI	TTE, 6 months	≥20% increase in LVESV	22 (38.6%)	none	Andrejic 2019

Table 5

Table 5	sample size	design	biomarker assessment	follow-up imaging	definition of LVR	LVR	correlation	reference
microRNAs								
miR-133a	226 (Q-wave MI)	Prospective	at discharge (day 3 to day 7)	TTE, 12 months	percent change in LVEDV	NA	positive, multivariate	Bauters 2013
miR-423-5p	226 (Q-wave MI)	Prospective	at discharge (day 3 to day 7)	TTE, 12 months	percent change in LVEDV	NA	positive, multivariate	Bauters 2013
miR-150	60 (derivation cohort) 30 (validation cohort)	Prospective	day 3-4 (before discharge)	TTE, 176 days (derivation cohort, n=60) CMR, 121 days (validation cohort, n=30)	increase in LVEDV	30 (50%)	negative	Devaux 2013
miR-1	44	RCT substudy	day 4, day 9	CMR, 6 months	absolute change of LVEDV	NA	none	Grabmaier 2017
miR-21	44	RCT substudy	day 4, day 9	CMR, 6 months	absolute change of LVEDV	NA	none	Grabmaier 2017
miR-29b	44	RCT substudy	day 4, day 9	CMR, 6 months	absolute change of LVEDV	NA	negative (day 9)	Grabmaier 2017
miR-92a	44	RCT substudy	day 4, day 9	CMR, 6 months	absolute change of LVEDV	NA	negative (day 9)	Grabmaier 2017
MiR-21	198	Not available	day 5	TTE, 12 months	≥20% increase in LVEDV	56 (28.3%)	positive, multivariate	Liu 2015
miR-146a	198	Not available	day 5	TTE, 12 months	≥20% increase in LVEDV	56 (28.3%)	positive, multivariate	Liu 2015
miR-208b	359 (AMI)	Not available	at admission	TTE, 6 months	>10% increase in LVEDV	116 (32.3%)	negative	Lv 2014
miR-34a	359 (AMI)	Not available	at admission	TTE, 6 months	>10% increase in LVEDV	116 (32.3%)	negative	Lv 2014
miR-1254	70	Prospective	at admission	CMR, 6 months	none	NA	variable (negative regarding changes in LVESVi, none otherwise)	de Gonzalo-Calvo 2018
Others								
ADAMTS-7	104	Prospective	day 1, day 3, day 7	TTE, 6 months	≥15% decrease in LVESV (reverse remodeling)	56 (53.8%) reverse	variable (positive day 7, none otherwise)	Wu 2018
Adiponectin	75	Not available	the next day after admission	TTE, 12 months	≥20% increase in LVEDVi	15 (20%)	negative, multivariate	Piestrzeniewicz 2010
Aortic CD34+ CD45dimKR+ cells levels	54	Prospective	during PCI	TTE, 12 months	≥20% increase in LVEDV	NA	none	Porto 2013
autoantibody against cardiac troponin-I	478	Not available	overnight after admission	TTE, 12 months	≥15% increase in LVEDV	226 (47.3%)	positive, multivariate	Fan 2017
blood coagulation factor XIII	75	Prospective	day 1, day 2, day 3, day 5, day 7, day 9	CMR, 12 months	none	NA	none	Frey 2020
Catestatin	31 (STEMI 67 % of the inital cohort of 93 patients)	Prospective	at admission, day 3 and day 7	TTE, 3 months	>20% increase in LVEDV	7 (22.6%)	positive	Meng 2013
Circulating endothelial cells	62	Prospective	within 24 hours	TTE, 1 month	≥20% increase in LVEDV	16 (26%)	positive	Abdel Hamid 2016
double-stranded deoxyribonucleic acid	272	RCT substudy	before and immediately after PCI, day 1	CMR, 4 months	change in LVEDVi or LVESVi	NA	none	Helseth 2019
endothelial nitric oxide synthase gene expression	62	Prospective	within 24 hours	TTE, 1 month	≥20% increase in LVEDV	16 (26%)	none	Abdel Hamid 2016
Fetuin-A	89	Prospective	48 hours	CMR, 4 months	≥20% increase in LVEDV	14 (15.7%)	negative, multivariate	Feistritzer 2015
FGF-23	88	Prospective	day 2	CMR, 4 months	≥20% increase in LVEDV	11 (12.5%)	positive, multivariate	Reindl 2017
Ficolin-2	55	RCT substudy	day 1-2, day 4, day 7	CMR, 6 months	none	NA	none	Schoos 2013
Ficolin-3	55	RCT substudy	day 1-2, day 4, day 7	CMR, 6 months	none	NA	none	Schoos 2013
Granzyme B	33 (AMI)	Not available	day 1, day 7	Left ventriculography, 6 months	unavailable	NA	none	Kondo 2009
Growth Arrest-Specific 6 protein	227	Prospective	day 1, day 7	CMR, 6 months	≥20% increase in LVEDV	29 (16%)	none	Caldentey 2019
Growth-differenciation factor 15	97	Prospective	at admission	TTE, 12 months	>20% increase in LVEDV	21 (21.6%)	positive, multivariate	Dominguez-Rodriguez 2011
	216	Prospective	day 2	TTE, 6 months	change in LVEDVi	NA	none	Lin 2014
Heart-type fatty acid binding protein	48	Prospective	day 2, day 7	CMR, 1 month and 3 months	none	NA	none	Mather 2013
Intracoronary CD34+ CD45dimKR+ cells levels	54	Prospective	during PCI	TTE, 12 months	≥20% increase in LVEDV	NA	none	Porto 2013
M30	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	positive, multivariate	Türkoğlu 2016
M65	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	positive	Türkoğlu 2016
M65/M30	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	negative	Türkoğlu 2016
Mannose-binding lectin	55	RCT substudy	day 1-2, day 4, day	CMR, 6 months	none	NA	none	Schoos 2013
MBL/Ficolin-associated Protein-1	55	RCT substudy	day 1-2, day 4, day 7	CMR, 6 months	none	NA	none	Schoos 2013
melatonin	161 (AMI)	Prospective	at admission	TTE, 12 months	>20% increase in LVEDV	24 (14.9%)	negative, multivariate	Dominguez-Rodriguez 2012

Table 5

neopterin	108	Prospective	before primary PCI	TTE, 12 months	>20% increase in LVEDV	21 (19%)	positive, multivariate	Dominguez-Rodriguez 2010
neprilysin	68	Prospective	during PCI	TTE, 7 months	none	NA	none	Legallois 2020
Oxidative Stress Index	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	positive, multivariate	Türkoğlu 2016
Peak adenosine	58	Not available	day 0, day 1, day 7	TTE, 6 months	change in LVEDV	NA	negative	Hatasa 2019
Peak tenascin-C	105	Prospective	unavailable	SPECT, 44 months	≥20% increase in LVEDV	25 (23.8%)	positive	Sato 2006
PGC-1α	31	Prospective	at admission and at 72 hours	CMR, 6 months	>10% increase in LVEDV	15 (48.4%)	positive (increase at 72 hours)	Fabregat-André 2015
serum connective tissue growth factor	42	Prospective	Day 2, week 1	CMR, 2 months and 12 months	none	NA	variable	Gravning 2012
Serum soluble ACE2 activity	88	Prospective	Between 24 and 48 hours and day 7	CMR, 6.4 months	≥20% increase in LVEDVi	15 (16.9%)	positive (day 7)	Ortiz-Perez 2013
soluble AXL	227	Prospective	day 1, day 7	CMR, 6 months	≥20% increase in LVEDV	29 (16%)	positive (d1 and d7), multivariate (d7)	Caldentey 2019
soluble FAS	48	RCT substudy	prior to PCI and 24 hours	CMR, 4 months	changes in LVEDVI and LVESVI	NA	none	Nilsson 2013
soluble FAS ligand	33 (AMI)	Not available	day 1, day 7 and day 14	Left ventriculography, 6 months	unavailable	NA	none	Kondo 2009
	48	RCT substudy	prior to PCI and 24 hours	CMR, 4 months	changes in LVEDVI and LVESVI	NA	none	Nilsson 2013
Soluble interleukin-1 receptor 2	255	RCT substudy	before and immediately after PCI, day 1	CMR, 4 months	change in LVEDVi and LVESVi	NA	positive	Orrem 2018
Soluble interleukin-1 receptor-like 1 (ST2)	109	Prospective	24 hours after reperfusion	CMR, 6 months	change in LVEDVi and LVESVi	NA	positive	Miñana 2018
Soluble Tumour Necrosis Factor Receptor 2	48	RCT substudy	prior to PCI and 24 hours	CMR, 4 months	changes in LVEDVI and LVESVI	NA	none	Nilsson 2013
Total Antioxydant Capacity	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	negative	Türkoğlu 2016
Total Oxidant Status	255	Retrospective	at admission, 24 hours	TTE, 6 months	≥20% increase in LVEDV	60 (23.5%)	positive	Türkoğlu 2016
Vascular endothelial growth factor B	290 (84% STEMI)	Prospective	before discharge (average day 4)	TTE, 6 months	increase in LVEDV	146 (50%)	negative, multivariate	Devaux 2012
Vascular endothelial growth factor	40 (AMI)	Not available	at admission, day 7, day 14	Left ventriculography, 3 months	an increase in LVEDVi ≥5 ml/m2	15 (37.5%)	none	Soeki 2002
Vascular endothelial growth factor-2 gene expression	62	Prospective	within 24 hours	TTE, 1 month	≥20% increase in LVEDV	16 (26%)	none	Abdel Hamid 2016
vonWillebrand factor	62	Prospective	within 24 hours	TTE, 1 month	≥20% increase in LVEDV	16 (26%)	none	Abdel Hamid 2016
β1-adrenoreceptor autoantibody	478	Not available	overnight after admission	TTE, 12 months	≥15% increase in LVEDV	226 (47.3%)	positive, multivariate	Fan 2017

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Relation entre taux de néprilysine et remodelage ventriculaire gauche

Cette annexe concerne l'article suivant: **Legallois D**, Macquaire C, Hodzic A, Allouche S, El Khouakhi I, Manrique A, Milliez P, Saloux E, Beygui F. Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction. BMC Cardiovasc Disord. 2020;20(1):316. doi: 10.1186/s12872-020-01578-y

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Serum neprilysin levels are associated with myocardial stunning after ST-elevation myocardial infarction

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Purpose. Left ventricular remodeling following ST-elevation myocardial infarction (STEMI) is associated with poor outcome. Neprilysin inhibition leads to improved outcome in patients with altered left ventricular ejection fraction (LVEF). We aimed to assess the association between serum levels of neprilysin and left ventricular (LV) volumes, function and remodeling in STEMI patients with successful myocardial reperfusion.

Methods. Sixty-eight patients were admitted for STEMI and had both plasma neprilysin measurement at baseline and 3D transthoracic echocardiogram at baseline and at follow-up (7 months). We compared 3 groups: a group with a low-level of plasma neprilysin (<125 pg/mL, i.e. the lower limit of detection of the assay, 38 patients) and the two other groups were defined as being below or above the median value of the remaining samples (15 patients each).

Results. Median age was 58.5±12.8 years and 56 (82.4%) were men. Median LVEF was 45.0±8.5%. Baseline characteristics were comparable among groups. At baseline there was a non-significant trend towards lower end-diastolic volume (p=0.07) but significantly lower LVEF in the high neprilysin group (46.4 ± 8.3%, 47.1 ± 8.1% and 39.1 ± 6.9%, p<0.01).

	Overall (n=68)	Neprilysin level ≤125 pg/mL (n=38)	Neprilysin level 126-450 pg/mL (n=15)	Neprilysin level >450 pg/mL (n=15)	Overall p.value	Highest-level vs. Lower groups p.value
Baseline EDV, mL/m²	53.8±13.0	55.1±12.4	56.0±13.5	48.3±13.3	0.18	0.07
Baseline ESV, mL/m²	28.2 [22.4, 34.7]	27.8 [23.2, 34.9]	28.8 [24.3, 32.8]	28.5 [21.1, 36.0]	0.97	0.82
Baseline LVEF, %	45.0±8.5	46.4±8.3	47.1±8.1	39.1±6.9	<0.01	<0.01
Follow-up EDV, mL/m²	56.6±15.0	57.8±13.6	58.7±19.9	51.6±12.6	0.35	0.15
Follow-up ESV, mL/m²	25.4 [19.0, 34.8]	25.8 [19.6, 32.7]	25.9 [18.9, 36.5]	25.1 [19.1, 32.3]	0.91	0.66
Follow-up LVEF, %	51.9±9.2***	53.0±8.9***	50.6±9.7	50.4±9.9***	0.55	0.49
%increase in LVEF	17.7±22.0	16.0±19.4	9.1±21.5	30.3±24.5	0.022	0.01
ΔLVEF, %	7.0±8.3	6.6±7.3	3.6±9.0	11.3±8.4	0.031	0.02

*Table. Echocardiographic data according to neprilysin levels at baseline. ***p<0.001 vs. baseline.*

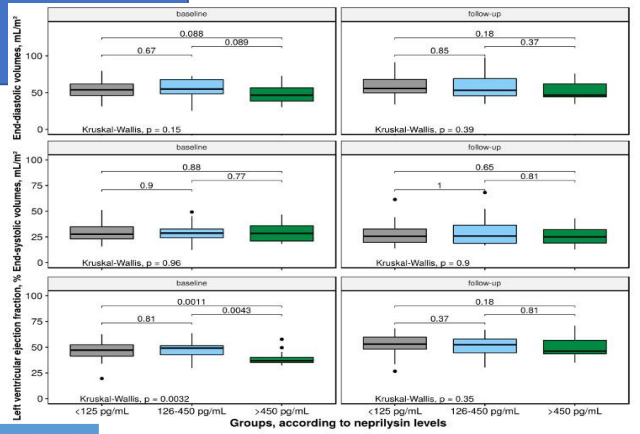

Figure. Relationship between neprilysin levels and LV volumes and function after STEMI

At follow-up, the magnitude of LVEF increase was significantly more important in the high neprilysin group compared to the other groups (p=0.022 for relative change in LVEF and 6.6 ± 7.3%, 3.6 ± 9.0% and 11.3 ± 8.4%, p=0.031 for absolute change in LVEF) resulting in similar LVEF levels at follow-up between all groups (53.0 ± 8.9%, 50.6 ± 9.7% and 50.4 ± 9.9%, p=0.55).

Conclusions. Initial high neprilysin levels may identify patients with stunned myocardium early after STEMI, with a recovery of contractility leading to improved LVEF at follow-up.

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Paramètres biologiques et échocardiographiques et remodelage ventriculaire gauche après syndrome coronarien aigu avec sus-décalage du segment ST

Biological and echocardiographic parameters and left ventricular remodeling after ST-elevation myocardial infarction

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Résumé Le remodelage ventriculaire gauche est une complication fréquente des patients ayant présenté un syndrome coronarien aigu, pouvant conduire à terme à une situation d'insuffisance cardiaque. Il est donc important de connaître les facteurs associés à la survenue d'un remodelage ventriculaire afin de dépister plus précocement les patients à plus haut risque d'insuffisance cardiaque et ainsi optimiser leur prise en charge. Ce travail comprend deux axes. Le premier porte sur la recherche de nouveaux paramètres d'imagerie associés à la survenue du remodelage. Nous avons dans un premier temps réalisé une revue de la littérature concernant la définition du remodelage ventriculaire gauche en imagerie par résonance magnétique. Puis, nous avons conduit deux études ayant pour but de rechercher une association entre (i) le strain atrial gauche et, (ii) le gradient de pression intraventriculaire gauche diastolique, évalués en échocardiographie 24-48 heures après le syndrome coronarien aigu et le remodelage ventriculaire gauche au cours du suivi. Le second axe porte sur les biomarqueurs associés au remodelage ventriculaire post-infarctus. Nous avons réalisé une revue de la littérature au sujet des biomarqueurs qui, dosés lors de l'hospitalisation initiale, sont associés à l'existence d'un remodelage lors du suivi. Nous avons ensuite étudié la valeur prédictrice de deux biomarqueurs (la néprilysine et le coenzyme Q10) pour la survenue d'un remodelage ventriculaire gauche.

Abstract Left ventricular remodeling is a common complication in patients following acute myocardial infarction and may lead to heart failure. Some baseline parameters are associated with remodeling at follow-up, allowing to better discriminate patients with an increased risk of heart failure to optimize therapeutics. This work has two axes, focused on imaging and biological parameters associated with left ventricular remodeling, respectively. First, we reviewed past studies that defined remodeling using cardiac magnetic resonance imaging. Then, we studied the association between some echocardiographic parameters (left atrial strain and diastolic intraventricular pressure gradient) and left ventricular remodeling after ST-elevation myocardial infarction. In the other axis, we reviewed biomarkers that have been associated with left ventricular remodeling in prior studies. Then, we investigated the association between neprilysin and coenzyme Q10 levels and left ventricular remodeling in STEMI patients.

Mots-clés remodelage ventriculaire gauche ; syndrome coronarien aigu avec sus-décalage du segment ST ; imagerie par résonance magnétique ; échocardiographie ; strain atrial ; fonction diastolique ; biomarqueurs ; néprilysine ; coenzyme Q10.

Key-words left ventricular remodeling ; ST-elevation myocardial infarction ; cardiac magnetic resonance imaging ; echocardiography ; atrial strain ; diastolic function ; biomarkers ; neprilysin ; coenzyme Q10.