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Désynchronisation et physiopathologie du remodelage ventriculaire gauche dans l'insuffisance cardiaque

Aymeric Menet

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Thèse de Doctorat

Mention : Biologie santé

Spécialité : Cardiologie

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de l'Université de Picardie Jules Verne

par

Aymeric MENET

pour obtenir le grade de Docteur de l'Université de Picardie Jules Verne

*Désynchronisation et physiopathologie du remodelage
ventriculaire gauche dans l'insuffisance cardiaque*

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Désynchronisation et physiopathologie du remodelage ventriculaire gauche dans l'insuffisance cardiaque

L'objectif de ce travail était de mieux appréhender les mécanismes impliqués dans la réponse à la resynchronisation biventriculaire en insistant sur la caractérisation écho-cardiographique du substrat éligible à un traitement par resynchronisation cardiaque (TRC). Afin de valider dans notre cohorte les critères de réponse au TRC, nous avons évalué l'impact pronostic au long cours de l'amélioration du strain longitudinal du ventricule gauche (VG), de la fraction d'éjection VG et des volumes VG 6 à 9 mois après un TRC. L'amélioration du volume téléstolique du VG (remodelage inverse) semble être le marqueur le plus pertinent du pronostic au long cours après TRC. De plus, l'insuffisance mitrale secondaire significative persistante malgré un TRC semble être un facteur pronostic important indépendant du remodelage VG. Nous avons démontré qu'il existe un certain degré de désynchronisation mécanique (fondé sur la mesure des délais entre paroi) dans les insuffisances cardiaques à fraction d'éjection préservée qui est semblable aux insuffisances cardiaques à fraction d'éjection basse à QRS fins et supérieur aux témoins hypertendus. Cependant, les paramètres de désynchronisation échographiques considérés comme les substrats de la réponse au TRC (fondés sur la contraction type bloc de branche gauche) ne sont que très rarement retrouvés chez ces patients. Ces paramètres sont fréquemment présents dans les insuffisances cardiaques à fraction d'éjection basse avec un QRS large et une indication de TRC. Le strain longitudinal du septum interventriculaire permet de caractériser 3 patterns de contraction septale eux même prédicteurs du remodelage inverse, des hospitalisations pour insuffisance cardiaque, de la mortalité cardiovasculaire et de la mortalité toute cause après un TRC. L'élargissement de la largeur du QRS après un TRC est quant à elle un prédicteur de l'absence de remodelage inverse, et d'un excès de mortalité cardiovasculaire et toute cause après un TRC. L'association d'un pattern de contraction septal peu prédicteur de réponse au TRC et d'un élargissement du QRS après le TRC permet d'identifier des patients avec une probabilité de réponse très faible au TRC.

Mots clés : Thérapie de resynchronisation cardiaque. Asynchronisme cardiaque. Insuffisance cardiaque. Echocardiographie. Electrocardiogramme.

Left ventricle dyssynchrony and remodeling physiopathology in heart failure

The objective of this work was to better understand the mechanisms involved in the response to biventricular resynchronization by focusing on the echocardiographic characterization of the substrate eligible for cardiac resynchronization treatment (CRT). In order to validate the CRT response criteria in our cohort, we evaluated the long-term prognostic impact of improvements in left ventricular (LV) longitudinal strain, LV ejection fraction and LV volumes 6 to 9 months after a CRT. The improvement of the LV endsystolic volume (reverse remodeling) appears to be the most relevant substrate for long-term prognostic after CRT. In addition, significant secondary mitral insufficiency despite a CRT appears to be a significant prognostic factor independent of LV remodeling. We have demonstrated that there is a degree of mechanical dyssynchrony (based on the measurement of delays between walls) in heart failure with a preserved ejection fraction that is similar to heart failure with low ejection fraction and thin QRS and superior to hypertensive controls. However, the ultrasound dyssynchrony parameters considered as the substrates of CRT response (based on left bundle branch block typical contraction) are seldom found in these patients. These parameters are frequently present in heart failure with low ejection fraction with a wide QRS and an indication for CRT. The longitudinal strain of the inter-ventricular septum allows to characterize 3 patterns of septal contraction that are predictors of reverse remodeling, hospitalizations for heart failure, cardiovascular mortality and all-cause mortality after CRT. The widening of the QRS after a CRT is a predictor of the absence of reverse remodeling, an excess of cardiovascular and all-cause mortality after CRT. The association of a septal contraction pattern with a low CRT response and a QRS enlargement after TRC can be used to identify patients with a very low probability of response to CRT.

Key words: Cardiac resynchronization therapy. Cardiac dyssynchrony. Heart failure. Echocardiography. Electrocardiogram.

A mon Directeur de thèse,

Monsieur le Pr Christophe Tribouilloy

Professeur des Universités - Praticien Hospitalier- CHU Amiens

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Monsieur le Pr Sylvestre Maréchaux

Professeur des Universités - Praticien Hospitalier- GHICL

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Monsieur le Pr Stéphane Lafitte

Professeur des Universités - Praticien Hospitalier- CHU de Bordeaux

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Professeur des Universités - Praticien Hospitalier- Hôpital Saint Antoine de Paris

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Menet A, Bernard A, Tribouilloy C, Leclercq C, Gevaert C, Guyomar Y, et al. Clinical significance of septal deformation patterns in heart failure patients receiving cardiac resynchronization therapy. *Eur Heart J Cardiovasc Imaging.* 29 déc 2016

Marechaux S, **Menet A**, Guyomar Y, Ennezat P-V, Guerbaai RA, Graux P, et al. Role of echocardiography before cardiac resynchronization therapy: new advances and current developments. *Echocardiogr Mt Kisco N.* nov 2016;33(11):1745-52.

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Thèse de science : Préambule

La désynchronisation cardiaque est la perte de synchronisation des différentes cavités et parois cardiaques. Cette asynchronisme peut être auriculo-ventriculaire : perte de synchronisation entre la contraction des oreillettes et des ventricules, interventriculaire : perte de synchronisation entre le ventricule droit et gauche ou intraventriculaire : perte de synchronisation entre les différentes parois d'un ventricule. La désynchronisation auriculo-ventriculaire est à l'origine d'un défaut de remplissage ventriculaire lié à une systole auriculaire trop précoce ou trop tardive. La désynchronisation inter et intraventriculaire entraîne une perte d'énergie à l'éjection ventriculaire. La désynchronisation cardiaque peut aboutir à l'insuffisance cardiaque si les réserves physiologiques pour compenser cette anomalie sont insuffisantes.

La désynchronisation cardiaque peut également être

-électromécanique : liée à un défaut de la propagation de l'influx électrique intracardiaque.

L'électrocardiogramme permet l'analyse électrique de la désynchronisation par l'analyse de l'espace PR et l'analyse de la largeur du QRS traduisant directement le temps de dépolarisation des ventricules.

-mécanique : qui n'est pas la résultante d'un défaut d'activation électrique mais d'un défaut de contractilité d'une paroi entraînant une dispersion dans le raccourcissement des fibres de différents segments du muscle cardiaque. Celle-ci est modifiée par les conditions de charges.(1)

La resynchronisation cardiaque est maintenant un standard du traitement de l'insuffisance cardiaque qui améliore la contractilité cardiaque, le remodelage cardiaque, la qualité de vie, les hospitalisations pour insuffisance cardiaque et la survie des patients ayant une cardiopathie hypokinétique (fraction d'éjection ventriculaire gauche (FEVG) $\leq 35\%$) avec un QRS large (≥ 120 ms) et recevant depuis 3 mois un traitement médical optimal (2). Ce traitement repose sur une stimulation simultanée du ventriculaire droit (apex ou septum inter ventriculaire) et du ventricule gauche (par une veine latérale du ventricule gauche). Il permet une resynchronisation inter et intra ventriculaire. Il diminue la largeur moyenne du QRS. Avec l'ajout d'une sonde auriculaire, si le rythme est sinusal, il permet une resynchronisation auriculo-ventriculaire. Ce traitement s'attaque au substrat électromécanique de la désynchronisation cardiaque.

Devant l'efficacité de ce traitement, il est paru légitime d'extrapoler aux autres cas d'insuffisance cardiaque à QRS fins sur la base d'une désynchronisation mécanique. Cette désynchronisation mécanique a été décrite chez les patients ayant une insuffisance cardiaque qu'elle soit systolique ou

diastolique.(3–5) Le premier objectif de notre travail a donc été de comparer les paramètres de désynchronisation cardiaque prédicteurs d'une réponse à la resynchronisation cardiaque des insuffisances cardiaques à fraction d'éjection conservée à : 1/ des cardiopathies dilatées à QRS fins, 2/ des cardiopathies dilatées à QRS larges, 3/ un groupe contrôle de cardiopathies hypertensives n'ayant jamais présenté d'insuffisance cardiaque. Nous verrons comment ce travail ainsi que les autres travaux scientifiques réalisés dans l'intervalle nous ont progressivement écartés de ce champs d'action pour nous amener à étudier la désynchronisation électromécanique des cardiopathies à FEVG basses.

Le remodelage du ventricule gauche après resynchronisation cardiaque et sa physiopathologie est le deuxième sujet d'intérêt de cette thèse. L'amélioration du volume télédiastolique, télésystolique ventriculaire gauche et de sa fraction d'éjection après resynchronisation sont des phénomènes bien connus. Ils sont utiles car ce sont des critères de substitution (« surrogates ») du pronostic du patient au long cours : les hospitalisations pour insuffisance cardiaque, la mortalité cardio-vasculaire et la mortalité totale sont réduites quand ces paramètres sont améliorés. La réponse à la resynchronisation cardiaque est le plus souvent définie comme étant une diminution de 15% du volume télésystolique du ventricule gauche à 6 mois du traitement par resynchronisation cardiaque (TRC) car il s'agit pour l'instant du meilleur critère de substitution. Cependant, un nouveau paramètre reproductible a vu le jour en échocardiographie : l'analyse de la déformation myocardique (« strain ») ventriculaire gauche par la méthode de traque des pixels échocardiographiques (« speckle tracking»). Nous avons étudié ce paramètre en le comparant au volume télésystolique du ventricule gauche et à la FEVG afin de préciser le paramètre le plus reproductible et le plus prédictif du pronostic au long cours et ainsi définir le meilleur critère de substitution.

Nous nous sommes ensuite intéressés à un aspect purement électrique de la désynchronisation cardiaque. Le primum movens de la désynchronisation cardiaque répondant au TRC est un phénomène électrique : l'élargissement du QRS. La physiologie nous amène à penser que dans les QRS large, la morphologie de bloc de branche gauche (BBG) est le meilleur prédicteur d'une réponse à un TRC. Ceci est soutenu par certaines études telle que l'analyse au long cours de MADIT-CRT(6,7) mais dans la méta-analyse des essais randomisés sur le TRC de Cleland et al.(8), la largeur du QRS est le seul paramètre prédictif en analyse multivariée de la réponse à la resynchronisation, la morphologie du BBG ne ressortant pas de manière significative probablement en raison de la grande proportion de BBG dans ces essais. L'affinement du QRS est donc légitimement un critère d'intérêt afin d'évaluer de manière précoce la réponse au TRC. Il s'agit d'ailleurs du paramètre le plus intuitif regardé par tous les électro-physiologistes lors de l'implantation d'un TRC. L'élargissement du QRS après TRC a déjà été décrit comme un paramètre prédictif du remodelage ventriculaire gauche

cependant il n'a jamais été relié à la mortalité au long cours.(9) Le troisième objectif de cette thèse a donc été d'analyser le lien entre affinement des QRS en post opératoire et les évènements cardio-vasculaires au long cours.

Enfin, même si l'anomalie princeps de la désynchronisation cardiaque est un phénomène électrique, la fonction altérée est hémodynamique. Malgré l'incapacité des paramètres classiques de désynchronisation échographiques à sélectionner les patients répondeurs à la resynchronisation (10), plusieurs nouveaux paramètres échographiques de désynchronisation comme le flash septal, l'apical rocking,(11), le pattern classique de désynchronisation en strain longitudinal du BBG (12) ou l'index de stretch systolique (13) ont été décrits comme étant de bons prédicteurs de la réponse à la resynchronisation. Leenders et al. ont affiné le flash septal en décrivant 3 patterns de contraction septal en strain dans le BBG.(14) L'utilité de ces patterns a été démontrée sur la prédiction du remodelage ventriculaire gauche après TRC.(15) La quatrième partie de cette thèse s'attache à décrire la valeur prédictive du pattern de contraction du septum interventriculaire en strain sur le pronostic au long cours après TRC.

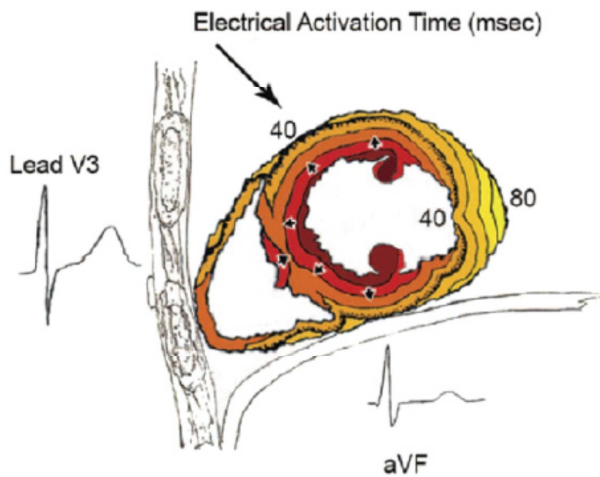
Notre base de travail est une cohorte prospective de l'ensemble des patients implantés d'une resynchronisation cardiaque depuis l'année 2010 à l'hôpital Saint Philibert de Lomme répondants aux indications de la société européenne de rythmologie.(2) 3 échographies étaient réalisées et implémentées sur station de travail de manière systématique : la première précédant le TRC, la deuxième immédiatement après le TRC et la troisième 9 mois après. Un suivi des évènements cardiovasculaires a été réalisé sous la forme de dates de point régulières (stade NYHA, hospitalisation pour insuffisance cardiaque, décès et cause du décès).

1 Physiopathologie, Mécanismes de l'asynchronisme cardiaque et resynchronisation cardiaque

1.1 Activation électrique normale

L'influx électrique naît du nœud sinusal, se propage au nœud auriculo-ventriculaire puis dans le faisceau de His-Purkinje dont les fibres sont isolées du myocarde jusqu'à l'apex. Les fibres du His-Purkinje possèdent de grandes cellules entourées de bandes de collagène avec de larges jonctions communicantes permettant une propagation rapide et linéaire du courant électrique. La dépolarisation de l'ensemble du myocarde prend moins de 80 ms et débute au niveau de la couche sous endocardique. L'ensemble de la couche sous-endocardique est dépolarisée en 30 ms puis la propagation se fait de l'endocarde vers l'épicarde, elle est plus lente car elle repose sur les ponts cellulaires transversaux dont la propagation électrique dépend de l'angle d'orientation des cardiomyocytes. (Figure 1) Pendant que l'endocarde se contracte, l'épicarde s'étire, c'est l'anisotropie de contraction myocardique. Cet asynchronisme mécanique endocarde-épicarde faciliterait la propagation de l'influx électrique au niveau des couches externes par une modification de l'orientation des fibres musculaires. La repolarisation suit le chemin inverse de la dépolarisation avec une durée des potentiels d'action plus courte pour les couches les plus tardivement activées.(16) Par ailleurs, l'anatomie des voies de conduction est variable d'un individu à l'autre. (Figure 1bis) rendant l'activation électrique également variable selon les individus..

A Normal Conduction



B Left Bundle Branch Block

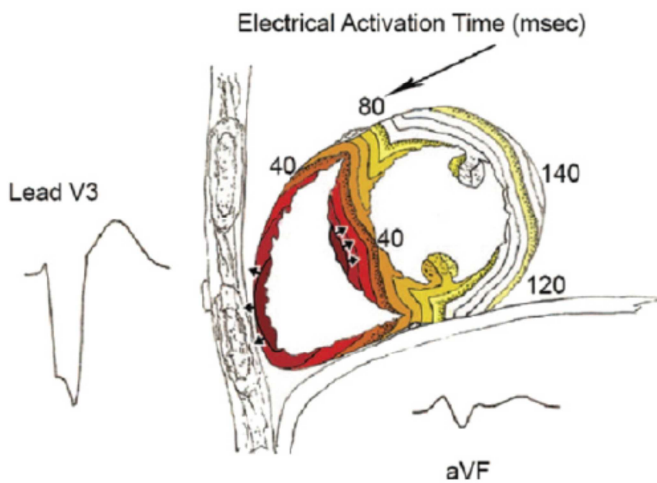


Figure 1. Durée du QRS pour une conduction normale (A) et un BBG complet (B). L'activation électrique commence au niveau des petites flèches et s'étend de façon circconférentielle. Chaque ligne colorée représente un temps de 10 ms. Pour la conduction normale, (A), l'activation commence au niveau de l'endocarde de VG et du VD, pour le BBG (B) l'activation commence au niveau du ventricule droit et doit traverser le septum pendant 40 à 50 ms avant d'atteindre le l'endocarde du ventricule gauche. Il a encore besoin de 50 ms pour pénétrer le réseau de Purkinje du ventricule gauche et se propager à l'endocarde de la paroi postéro-latérale puis encore 50 ms pour activer entièrement la paroi postéro-latérale. La durée du QRS étant alors de 140 à 150 ms. L'augmentation de l'épaisseur du septum ou de la paroi postéro-latérale ou de la surface de l'endocarde du VG augmente encore la largeur du QRS. La vitesse de conduction dans le myocarde humain étant de 3 à 4 mm toutes les 10 ms, une augmentation circconférentielle de l'épaisseur du VG de 3 mm augmentera la durée du QRS de 20 ms pour le BBG (10 ms pour le septum et 10 ms pour la paroi postéro-latérale). Figure issue de l'Am J Cardiol 2011, Strauss et al.

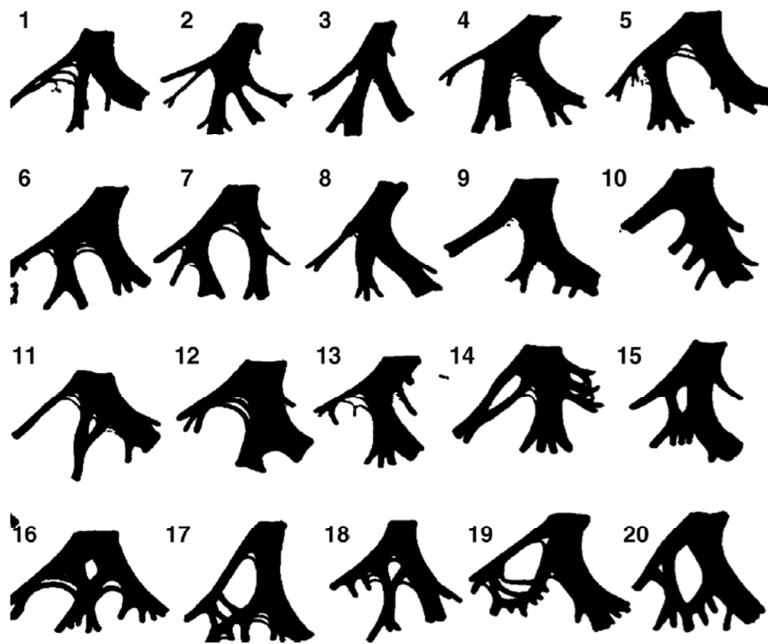


Figure 1 bis. Anatomie des voies de conduction chez 20 cœurs normaux. Figure issue du *Br Heart J* 1972, Demoulin et al.

1.2 Altération de la conduction électrique dans l'insuffisance cardiaque

Une fibrose des voies de conduction électrique entraîne l'apparition de blocs de conduction. Un QRS supérieur à 120 ms est retrouvé chez 30% des patients insuffisants cardiaques. Un QRS > 120 ms est associé à des événements rythmiques plus fréquents (17) et à une surmortalité lorsque la fraction d'éjection du ventricule gauche est inférieure à 35% (18,19).

1.2.1 Cas particulier du BBG

Le BBG est quant à lui retrouvé chez 0.3 à 1.2% de la population générale, le BBG isolé est rare et représente 0.1% de la population générale. Il est présent chez 25% patients porteurs d'une cardiomyopathie dilatée et 25 à 30% des patients ayant une insuffisance cardiaque avec FEVG de moins de 30%. On le retrouve chez 10 % des patients ayant une coronaropathie et 6% des patients avec une cardiopathie hypertensive.(20,21) Les patients insuffisants cardiaques porteurs d'un BBG et non resynchronisés ont une NYHA plus sévère, une FEVG plus basse et une surmortalité par rapport à ceux ayant un QRS fin.(19) En cas de présence d'un BBG sans insuffisance cardiaque, il existe un risque de 20% de développer une insuffisance cardiaque dans le suivi.(22)

Chez le chien, une radiofréquence de la branche gauche entraîne une hypoperfusion septale, un flash septal, un remodelage du VG avec une hypertrophie ventriculaire gauche asymétrique de 20%, une dilatation VG de 30% et une diminution de FE de 10%.(23,24)

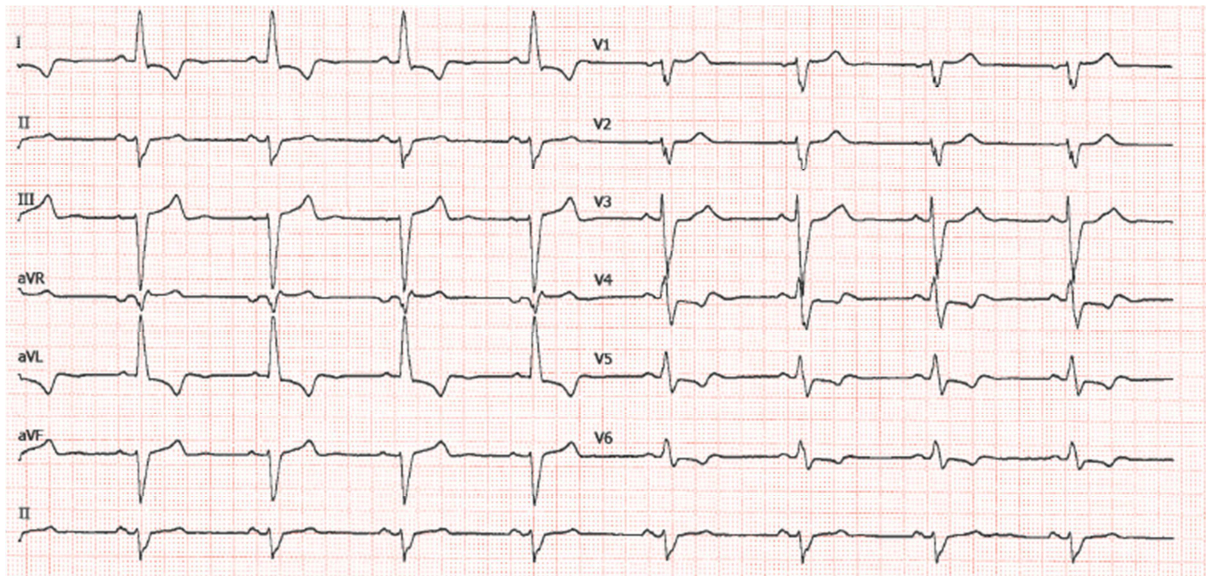
Il a été montré chez l'homme qu'un BBG isolé initialement et entraînant au long cours une insuffisance cardiaque et une altération de la FEVG peut être totalement corrigé par une resynchronisation cardiaque. Ceci introduit la notion de cardiopathie induite par un bloc de branche gauche.(25) Ce phénomène est très proche des cardiopathies induites par les faisceaux de Kent droit ou du septum interventriculaire avec une activation tardive du VG. Elles peuvent conduire à une dilatation du VG avec une altération de la FEVG et une insuffisance cardiaque. Ces cardiopathies régressent ad integrum après ablation du faisceau de Kent.(26–28)

1.2.2 Définition du BBG

La corrélation électro-anatomique du BBG a fait l'objet de débats donnant lieu à plusieurs définitions dont celle de Surawicz et al. qui est la plus utilisée dans les études sur le TRC. Cette définition du BBG associe : 1/ un QRS de plus de 120 ms chez l'adulte, 2/ une onde R large et crochetée sur les dérivations DI et aVL et habituellement sur les dérivations précordiales latérales (V5 et V6), l'aspect peut être RS en V5-V6 en raison d'une transition du QRS déplacée 3/ l'absence d'onde q sur les dérivations DI, V5, V6, mais une onde q étroite peut être présente en aVL en l'absence d'atteinte myocardique. 4/ Pic de l'onde R à plus de 60 ms dans les dérivations V5-V6 mais normal dans les dérivations V1, V2 et V3. 5/segment ST et onde T habituellement de polarité opposée à la polarité du QRS. 6/ des ondes T positives peuvent être présentes dans les dérivations ayant un QRS positif (concordance positive). 7/ Un sous décalage du segment ST ou une onde T négative avec un QRS négatif est anormal (concordance négative). 8/L'apparition d'une BBG peut changer l'axe frontal global du QRS à droite, à gauche ou vers un axe supérieur, parfois selon la fréquence cardiaque.(29)

Strauss et al. ont voulu affiner cette définition en ajoutant notamment un critère de durée de QRS plus stricte de 130 ms chez les femmes et 140 ms secondes chez les hommes afin d'augmenter la spécificité de détection du BBG (30). En effet, il s'avère que certain « faux BBG » à l'ECG sont la combinaison d'une hypertrophie ventriculaire gauche associée à un héli-bloc antérieur gauche. Dans ce dernier cas, la largeur du QRS augmente progressivement reflétant l'augmentation progressive de la masse myocardique globale dans le temps tandis que dans le vrai BBG, il passe de l'état fin à l'état large de manière brutale.

A.



B.

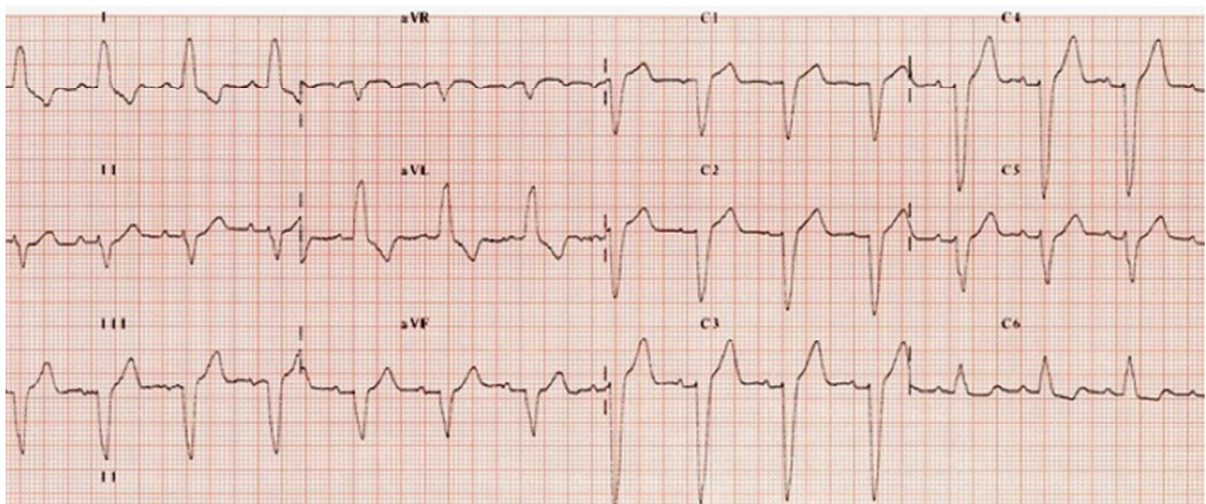


Figure 1 ter. Différence entre un vrai et un faux BBG. A : homme avec un QRS à 130 ms Pas de notch ou de slurring sur les dérivation latérales. Axe gauche. Ce patient présente une hypertrophie excentrique associée à un HBAG. B : homme avec un QRS à 160 ms et un aspect de notch dans les dérivation latérales.

1.2.3 Activation électrique dans le BBG

La présence d'un BBG a une conséquence électrique : l'activation électrique cardiaque commence au niveau du ventricule droit et du septum basal par la branche droite puis la conduction se fait par voie cellulaire lente : l'activation doit traverser le septum pendant 40 à 50 ms avant d'atteindre le l'endocarde du ventricule gauche. Il a encore besoin de 50 ms pour pénétrer le réseau de Purkinje du ventricule gauche et se propager à l'endocarde de la paroi postéro-latérale puis encore 50 ms pour activer entièrement la paroi postéro-latérale. La durée du QRS étant alors de 140 à 150 ms.

L'augmentation de l'épaisseur du septum ou de la paroi postéro-latérale ou de la surface de

l'endocarde du VG augmente encore la largeur du QRS. (Figure 1) Le premier pic visible sur l'ECG de surface d'un BBG reflète l'activation de l'endocarde du septum VG tandis que le deuxième pic représente l'activation de l'épicarde de la paroi postéro-latérale.

1.2.4 Conséquences mécaniques du BBG

La conséquence mécanique est une contraction précoce et énergique du septum durant la période de contraction iso-volumétrique appelé *septal flash* ; la pression dans le ventricule gauche étant alors faible. Les segments dont la dépolarisation est retardée ont une contraction post-systolique, l'ensemble de ces anomalies entraînent une diminution de la performance énergétique.(31) Ces mêmes segments subissent un étirement pendant la contraction septale appelé *stretching*. L'association de la contraction précoce septale et retardée de la paroi latérale entraîne un mouvement de rotation horaire de l'apex bien visualisé en échocardiographie sur la coupe apicale, appelé « *rocking apical* ». La perte de coordination des piliers mitraux peut entraîner ou aggraver une insuffisance mitrale préexistante.(32) Le BBG entraîne également une altération des protéines myocytaires, une hypertrophie, une apoptose et une fibrose myocytaire.(33)

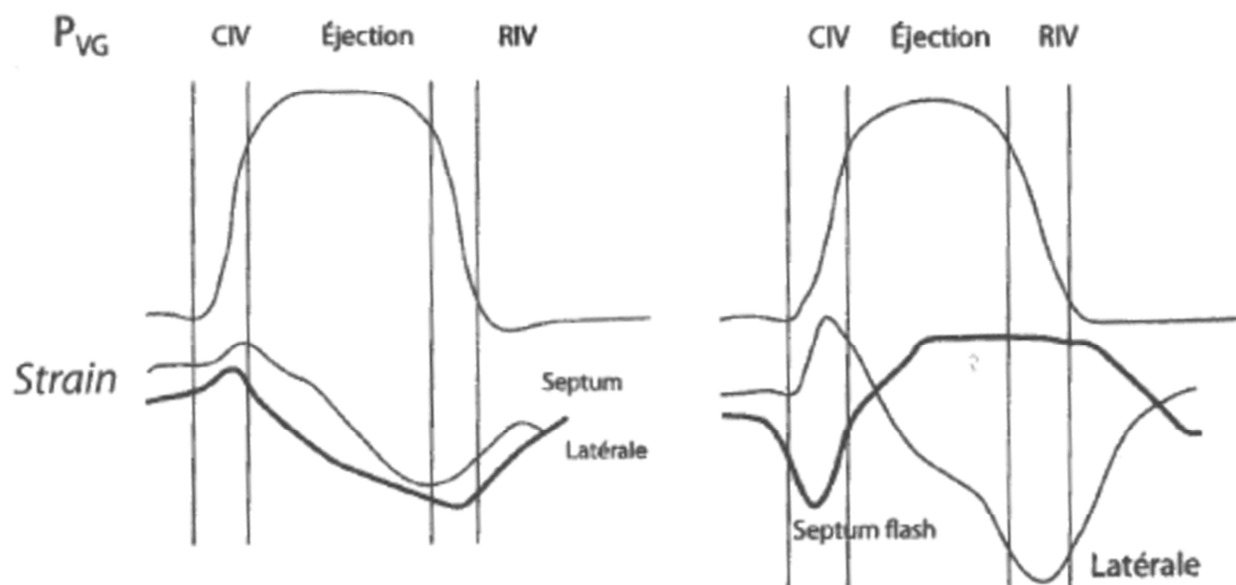


Figure 2. Conséquences mécaniques des blocs de branche gauche en imagerie paramétrique de la propagation électromécanique en rythme sinusal (à gauche) et avec un BBG induit par la stimulation ventriculaire droite (à droite). La dépolarisation et la contraction du myocarde sont homogènes en rythme sinusal, tandis qu'il existe un retard de contraction de la paroi latérale en cas de bloc de branche gauche. Les courbes de déformation montrent une brève contraction septale protosystolique (*septum flash*) suivie d'une contraction de forte amplitude de la paroi latérale. CIV : contraction iso-volumique ; RIV : relaxation iso-volumique. D'après Lim P. et Derumeaux G., *Echocardiographie clinique de l'adulte* Edition Lavoisier. Ariel Cohen Editeur.

1.3 Les paramètres écho-cardiographiques de désynchronisation cardiaque.

Les paramètres classiques (Figure 3) sont catégorisés en trois niveaux : auriculo-ventriculaire, interventriculaire et intraventriculaire.

1.3.1 Asynchronisme auriculo-ventriculaire :

Il est défini par la durée relative de la diastole (durée de l'onde E et A) par rapport à l'intervalle RR. Il existe un asynchronisme auriculo-ventriculaire significatif lorsque la durée du remplissage est inférieure à 40 %.

1.3.2 Asynchronisme inter-ventriculaire

Il est défini par le retard mécanique de l'éjection d'un ventricule par rapport à l'autre. Il est mesuré à l'aide du doppler pulsé dans les chambres de chasse. Il existe un asynchronisme inter-ventriculaire lorsque le délai entre l'éjection des deux ventricules est supérieur à 40 ms.

1.3.3 Asynchronisme intra-ventriculaire

Il se définit comme le déphasage temporel de contraction des parois du ventricule gauche. Il peut être mesuré en mode temps mouvement (TM) ou par une analyse plus sophistiquée de la déformation myocardique en 2D ou en 3D.

La méthode la plus simple consiste à mesurer **en TM** le retard latéral-septal et a été proposé par l'équipe de Pitzalis et al. (34). Le principe repose sur la mesure de l'intervalle de temps qui sépare le pic de contraction radiale de la paroi septale et latérale. (Figure 4) Un intervalle de temps de 130 ms a été identifié comme le meilleur prédicteur de réponse. Il existe une distribution bimodale de ce paramètre.(35)

D'autres méthodes utilisent le doppler tissulaire et le speckle tracking permettant d'analyser la déformation myocardique de plusieurs segments du myocarde et dans plusieurs directions de l'espace.

En doppler tissulaire

L'équipe de Bax et al. (36,37) a proposé de regarder le délai de contraction en doppler tissulaire entre les parois opposées du myocarde (septale/latérale, et antérieure/inférieure). L'équipe de Yu et al. (38) a proposé de regarder la dispersion (déviations standard) des temps au pic systolique de vélocité sur douze segments du myocarde (12SD-TDI), un seuil de 33 ms prédisait le mieux la réponse.

En speckle tracking (Figure 4)

Les études en speckle tracking ont fait suite aux résultats négatifs de l'étude PROSPECT pour répondre aux limites du doppler tissulaire. De la même manière qu'en doppler tissulaire, il est possible de regarder les temps aux pics des parois opposées ou de mesurer une dispersion des temps au pic systolique sur 6 ou sur 12 segments basaux. Bax et al. ont montré que la précision diagnostique la meilleure en speckle tracking était celle en déformation radiale en comparaison à la déformation longitudinale et circonférentielle.(39) Ces résultats sont cependant en désaccord avec la publication de la Mayo Clinic (40) qui montre que ces paramètres de dispersion temporelle ne sont pas assez précis pour prédire la réponse à la resynchronisation cardiaque. Bax et al. ont proposé un délai antéro-septal postérieur mesuré sur un strain radial (asynchronisme en cas de délai supérieur à 130 ms) et un pattern de contraction de type BBG en strain radial.(39) Cependant ce critère de délai antéro-septal postérieur en strain supérieur à 130 ms est retrouvé de manière très fréquente (25%) dans l'étude de resynchronisation avec des QRS fins et ne permet pas de trouver un substrat répondeur à la resynchronisation.(41) En effet, il s'agit probablement d'un substrat de désynchronisation mécanique plus que d'un substrat électromécanique. Le pattern radial de BBG est quant à lui défini par une déformation précoce du segment antéro-septal et une contraction post-systolique du segment postéro-latéral.

Risum et al. ont proposé un critère visant à reconnaître une contraction de type BBG en strain longitudinal. Il est défini par 1) un raccourcissement précoce d'au moins 1 segment basal ou mid-ventriculaire du septum et de l'étirement d'au moins un segment basal ou mid-ventriculaire de la paroi latérale ; 2) un pic de contraction septale précoce (dans les 70% initiaux de la phase d'éjection); et 3) un raccourcissement de la paroi latérale après la fermeture de la valve aortique.(12)

Enfin, Leenders et al. ont proposé de se centrer sur le septum interventriculaire et de décrire les mouvements du flash septal de manière plus précise et sous la forme de 3 types de contraction septale à l'aide du speckle tracking. Les patterns de contraction septale ont été classifiés sur la base d'une séquence de raccourcissement et d'étirement septal. Le pattern 1 était défini par un double pic systolique de raccourcissement septal. Le pattern 2 était défini par un pic pré-éjectionnel de contraction septale suivi par un étirement du septum prédominant durant la systole. Le pattern 3 était défini en cas de contraction pseudo-normale avec une contraction systolique tardive et un étirement septal moins prononcé en fin de systole.

Rotation , torsion et asynchronisme en 3D.

Ces approches sont attrayantes mais les études tentant de les valider ont pour l'instant des conclusions divergentes et non prédictives de la réponse à la resynchronisation.

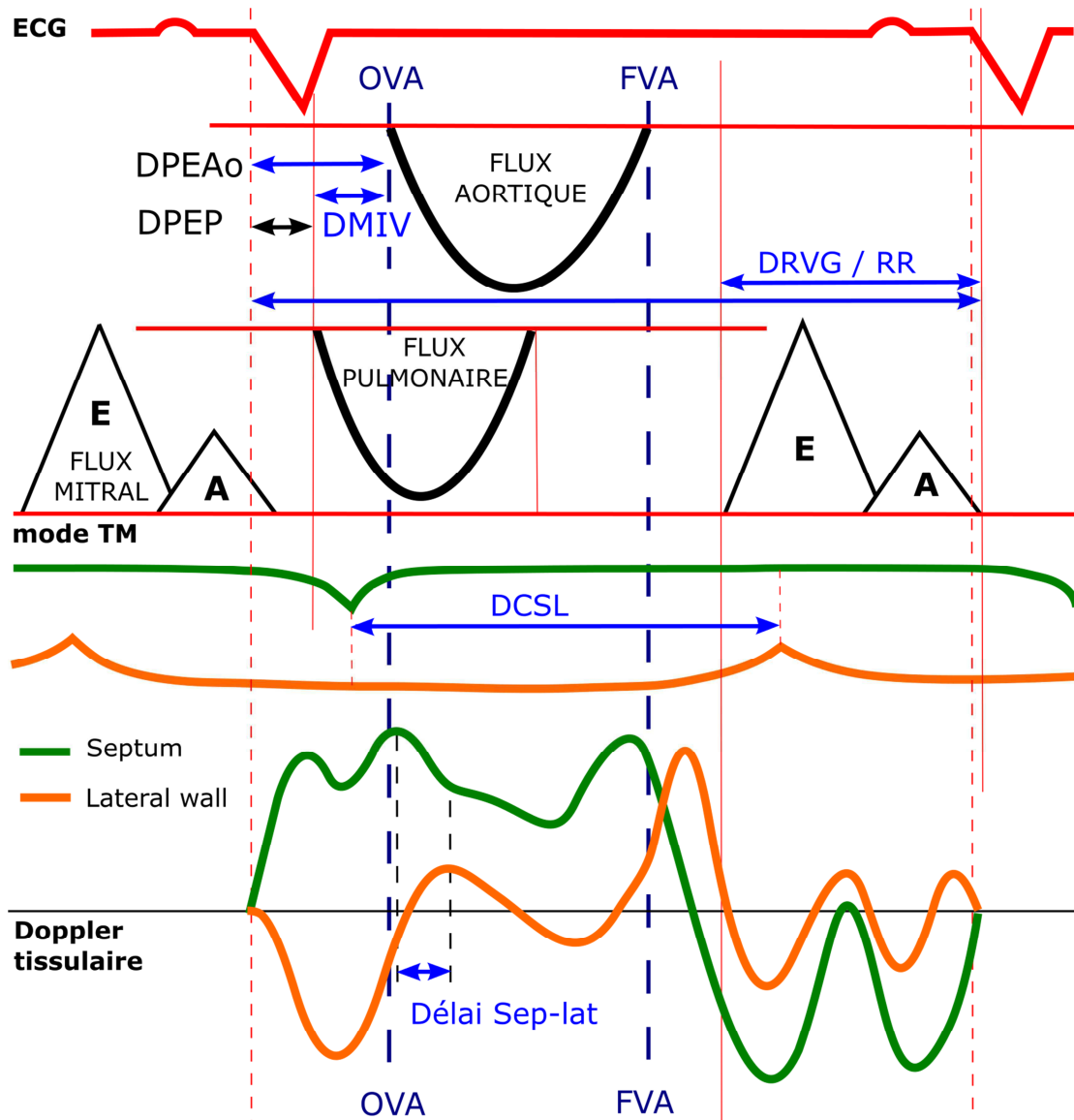


Figure 3. Indices de désynchronisation classiques : DPEAo: délai prééjectionnel aortique; DPEP: délai prééjectionnel pulmonaire; DMIV: Délai mécanique inter-ventriculaire; TRVG: durée de remplissage VG; DCSL: Délai de contraction septal-latéral; Délai Sep-Lat: délai de contraction septal-latéral en doppler tissulaire; OVA: ouverture valve aortique; FVA: fermeture valve aortique

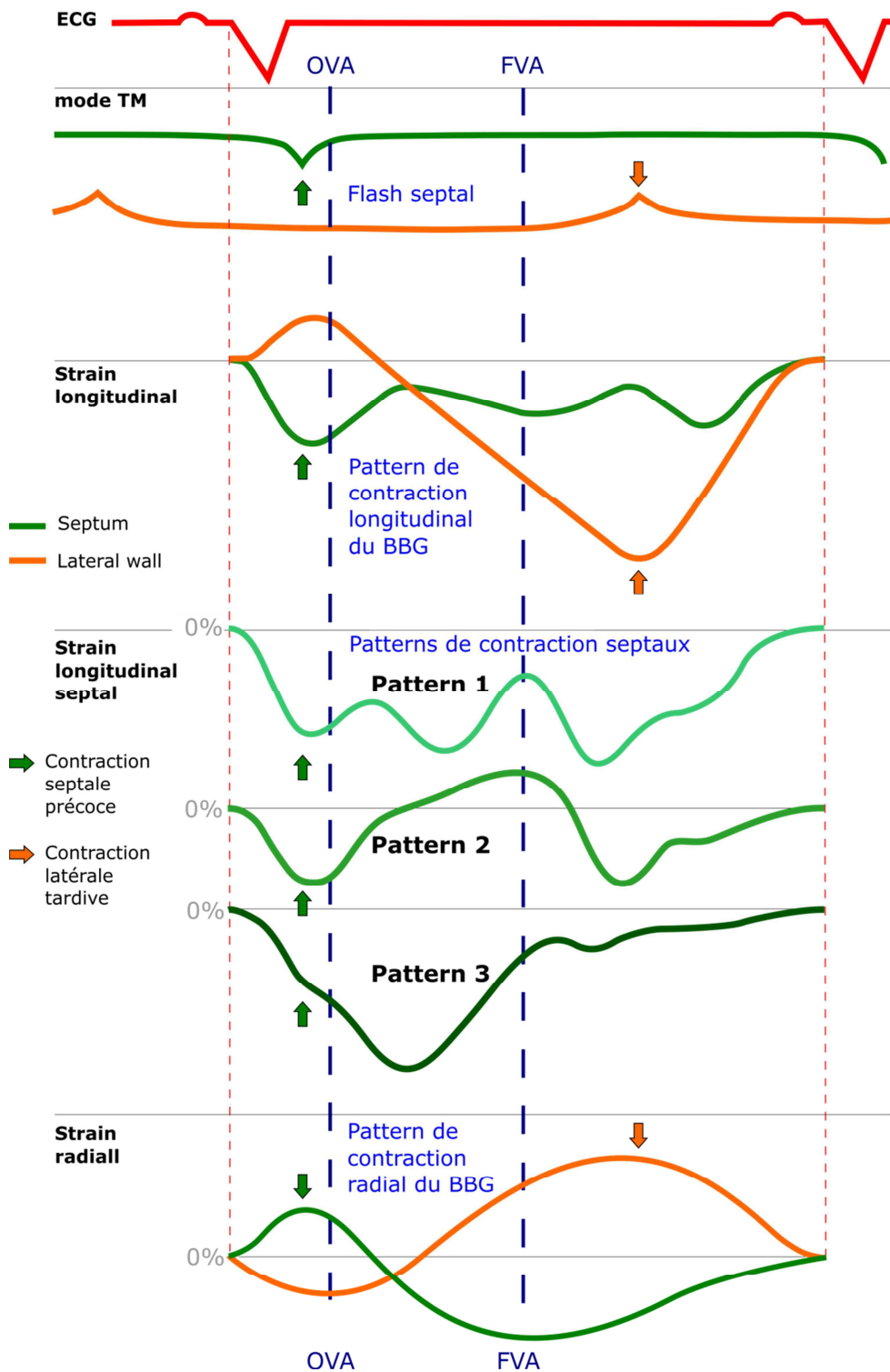


Figure 4. Nouveaux indices de désynchronisation: OVA: ouverture valve aortique ; FVC: fermeture valve aortique. Le septal flash (SF) correspond à un mouvement pré-systolique du septum vers le ventricule gauche. Le pattern de contraction longitudinal du BBG est défini par 1) raccourcissement précoce d'au moins 1 segment basal ou mid-ventriculaire du septum et de l'étirement d'au moins un segment basal ou mid-ventriculaire de la paroi latérale ; 2) pic de contraction septal précoce (dans les 70% initiaux de la phase d'éjection); et 3) un raccourci cément de la paroi latérale après la fermeture de la valve aortique. Les patterns de contraction septaux ont été classifiés sur la base d'une séquence de raccourcissement et d'étirement septal. Le pattern 1 était défini par un double pic systolique de raccourcissement septal. Le pattern 2 était défini par un pic pré-éjectionnel de contraction septal suivi par un étirement du septum prédominant durant la systole. Le pattern 3 était défini en cas de contraction pseudo normale avec une contraction systolique tardive et un étirement septal moins prononcé en fin de systole. Le pattern radial de BBG est défini par une déformation précoce du segment antéro-septal et une contraction post-systolique du segment postéro latéral.

1.4 Le traitement par resynchronisation cardiaque :

La resynchronisation cardiaque a été initialement décrite par Cazeau et al. en 1994 sur un patient de 54 ans avec une insuffisance cardiaque sévère qui s'est améliorée de façon spectaculaire avec une stimulation cardiaque des 4 cavités cardiaques.(42) Plus tard dans une étude en phase aigüe, Leclerc et al. ont montré qu'une resynchronisation cardiaque augmentait le volume d'éjection systolique et diminuait les pressions capillaires pulmonaires.(43) L'équipe d'Auricchio ont par la suite démontré que la resynchronisation améliorait la dP/dt ventriculaire gauche.(44)

En 2001, l'étude MUSTIC (MUltisite STImulation in Cardiomyopathies) est la première étude randomisée sur la resynchronisation cardiaque. Réalisée en cross over, elle montre que la resynchronisation améliore les hospitalisations pour insuffisance cardiaque, la classe NYHA, la qualité de vie, le pic de VO₂ et la capacité d'exercice.(45) L'étude CARE-HF (CARDiac RESynchronization in Heart Failure) a montré que la resynchronisation diminuait la mortalité de 36% comparée au traitement médical.(46) L'étude COMPANION (COMparison of medical therapy, PACing, and defibrillatION in heart failure) a montré un bénéfice de l'association du défibrillateur à la resynchronisation avec une amélioration de la mortalité en comparaison de la resynchronisation seule.(47) Mais l'étude DANISH publiée récemment suggère que le bénéfice du défibrillateur est surtout présent pour les cardiopathies ischémiques et les patients jeunes.(48,49)

L'ensemble des études randomisées sur le TRC sont résumées dans le tableau 1 issu des recommandations de l'ESC sur la resynchronisation cardiaque.(2)

Trial (ref)	No.	Design	NYHA	LVEF	QRS	Primary endpoints	Secondary endpoints	Main Findings
MUSTIC-SR ⁵²	58	Single-blinded, crossover, randomized CRT vs. OMT, 6 months	III	<35%	≥150	6MWD	NYHA class, QoL, peak VO ₂ , LV volumes, MR hospitalizations, mortality	CRT-P improved 6MWD, NYHA class, QoL, peak VO ₂ , reduced LV volumes and MR and reduced hospitalizations
PATH-CHF ⁵¹	41	Single-blinded, crossover, randomized RV vs. LV vs. BiV, 12 months	III-IV	NA	≥150	Peak VO ₂ , 6MWD	NYHA class, QoL hospitalizations	CRT-P improved NYHA class, QoL and 6MWD and reduced hospitalizations
MIRACLE ⁴⁹	453	Double-blinded, randomized CRT vs. OMT, 6 months	III-IV	≤35%	≥130	NYHA class, 6MWD, QoL	Peak VO ₂ , LVEDD, LVEF, MR clinical composite response	CRT-P improved NYHA class, QoL and 6MWD and reduced LVEDD, MR and increased LVEF
MIRACLE-ICD ⁵⁴	369	Double-blinded, randomized CRT-D vs. ICD, 6 months	III-IV	≤35%	≥130	NYHA class, 6MWD, QoL	Peak VO ₂ , LVEDD, LVEF, MR clinical composite response	CRT-D improved NYHA class, QoL, peak VO ₂
CONTAK-CD ⁵³	490	Double-blinded randomized CRT-D vs. ICD, 6 months	II-III-IV	≤35%	≥120	NYHA class, 6MWD, QoL	LV volume, LVEF composite of mortality, VT/VF, hospitalizations	CRT-D improved 6MWD, NYHA class, QoL, reduced LV volume and increased LVEF
MIRACLE-ICD II ⁶⁰	186	Double-blinded, randomized CRT-D vs. ICD, 6 months	II	≤35%	≥130	Peak VO ₂	VE/VCO ₂ , NYHA, QoL, 6MWD, LV volumes and EF, composite clinical endpoint	CRT-D improved NYHA, VE/VCO ₂ and reduced LV volumes and improved LVEF
COMPANION ⁵⁵	1520	Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D, 15 months	III-IV	≤35%	≥120	All-cause mortality or hospitalization	All-cause mortality, cardiac mortality	CRT-P and CRT-D reduced all-cause mortality or hospitalization
CARE-HF ⁵⁶	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III-IV	≤35%	≥120	All-cause mortality or hospitalization	All-cause mortality, NYHA class, QoL	CRT-P reduced all-cause mortality and hospitalization and improved NYHA class and QoL
REVERSE ⁶¹	610	Double-blinded, randomized CRT-ON vs. CRT-OFF, 12 months	I-II	≤40%	≥120	% worsened by clinical composite endpoint	LVESV index, heart failure hospitalizations and all-cause mortality	CRT-P/CRT-D did not change the primary endpoint and did not reduce all-cause mortality but reduced LVESV index and heart failure hospitalizations.
MADIT-CRT ³⁰	1820	Single-blinded, randomized CRT-D vs. ICD, 12 months	I-II	≤30%	≥130	All-cause mortality or heart failure hospitalizations	All-cause mortality and LVESV	CRT-D reduced the endpoint heart failure hospitalizations or all-cause mortality and LVESV. CRT-D did not reduced all-cause mortality
RAFT ⁶²	1798	Double-blinded, randomized CRT-D vs. ICD 40 months	II-III	≤30%	≥120	All-cause mortality or heart failure hospitalizations	All-cause mortality and cardiovascular death	CRT-D reduced the endpoint all-cause mortality or heart failure hospitalizations. In NYHA III, CRT-D only reduced significantly all-cause mortality

Table 1. Critères d'inclusion, design, objectifs, et principaux résultats des études randomisées évaluant la resynchronisation cardiaque chez les patients en rythme sinusal.

CARE-HF = Cardiac Resynchronization-Heart Failure; CONTAK-CD = CONTAK-Cardiac Defibrillator; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync Implantable Cardioverter Defibrillator trial; MR = mitral regurgitation; MUSTIC = Multisite Stimulation in Cardiomyopathies; No. = number of patients; NYHA = New York Heart Association; PATH-CHF = Pacing Therapies in Congestive Heart Failure trial; QoL = quality-of-life score; RAFT = Resynchronization-Defibrillation for Ambulatory Heart Failure Trial; VE/VCO₂ = minute ventilation/minute volume carbon dioxide production; VF = ventricular fibrillation; VO₂ = volume of oxygen; VT = ventricular tachycardia; 6MWD = 6-min walk distance.

1.4.1 Aspects techniques d'une resynchronisation cardiaque

Le TRC correspond la stimulation simultanée ou quasi simultanée des parois cardiaques du ventricule gauche en association à une stimulation synchrone de l'oreillette et du ventricule. Une sonde de stimulation est positionnée dans le ventricule droit et une deuxième sonde de stimulation est positionnée dans une veine latérale du ventricule gauche par l'intermédiaire du sinus coronaire.

De nombreuses modalités techniques ont été testées avec à chaque fois pour idée d'optimiser l'activation myocardique :

- Un placement de la sonde ventriculaire droite sur le septum inter-ventriculaire plutôt qu'à l'apex sans qu'une amélioration significative du remodelage ventriculaire ou du pronostic puisse être démontrée.(50,51) Cette technique continue d'être largement utilisée étant donné l'évidence empirique d'un QRS plus fin lors d'une stimulation septale comparée à une stimulation apicale.
- Une stimulation ventriculaire gauche variable soit dans le sens apex-base, soit dans le sens antéro-postérieur. La stimulation à l'apex est alors associée à une surmortalité par rapport à la stimulation au niveau de la base ou du segment moyen.(52,53) L'étude de Singh et al. ne retrouve pas de différence de mortalité entre la position antérieure, postérieure ou latérale(52) tandis que l'étude de Thébault et al. retrouve une différence à la limite de la significativité pour le critère mortalité/hospitalisations pour insuffisance cardiaque en faveur d'une position latérale vs non latérale.(53) La méthodologie était cependant différente entre les deux études puisque la première utilise des images en fluoroscopie pendant l'intervention tandis que la deuxième utilise des radiographies de thorax face profil après implantation d'interprétation difficile. La méthode de référence reste néanmoins une position latérale de la sonde VG afin qu'elle soit le plus éloignée possible de la sonde VD.
- Une stimulation multi-sites ventriculaire. Cette possibilité étant légitimement proposée puisqu'une augmentation du nombre de sites de stimulation diminue mécaniquement la durée d'activation de l'ensemble du myocarde et améliore donc la synchronisation de contraction des parois ventriculaires :
 - Une stimulation par deux sondes ventriculaires gauche dans deux veines différentes et une sonde ventriculaire droite a été réalisée par l'équipe de Leclercq et al. et n'a pas démontré d'intérêt pour améliorer la qualité de vie ou le test de marche de 6 minutes. Elle a par contre permis de montrer une amélioration des volumes télé-systoliques ventriculaires ((157±69 cm³ vs. 134±75 cm³; p=0.02) et de la FEVG ((27±11% vs. 35±11%; p<0.001).(54) Cette technique a été démontrée comme étant faisable en toute sécurité.

- Une stimulation par deux sondes ventriculaires droite et une sonde ventriculaire gauche a été réalisée par l'équipe d'Anselme et al. sur 76 patients et n'a pas démontré d'intérêt en terme d'amélioration de la qualité de vie, du test de marche de 6 minutes ou des paramètres échographiques excepté pour la proportion d'amélioration de FEVG de plus de 5%, 10% et 15%.⁽⁵⁵⁾ Cette technique a été démontrée comme étant faisable en toute sécurité.
- Une stimulation par plusieurs électrodes à l'aide d'une seule sonde ventriculaire gauche et une sonde ventriculaire droite. Cette technique s'appelle le « multipoint pacing ». Elle permet d'améliorer la réponse hémodynamique aiguë en comparaison à une stimulation VG en un seul site.^(56,57) Elle permet également d'améliorer la synchronisation cardiaque.^(58,59) Des études sont en cours pour connaître son utilité sur des paramètres échographiques et cliniques au long cours.

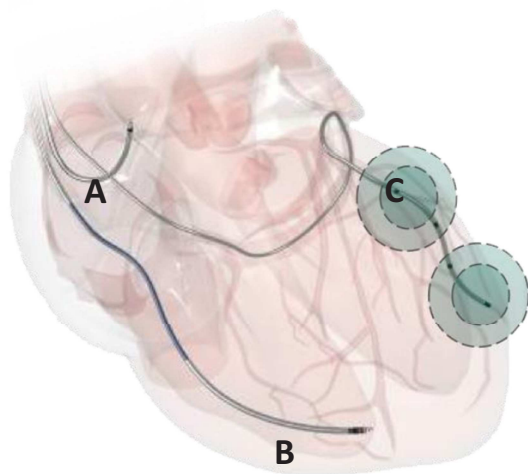


Figure 5. Schéma de la technique d'implantation actuellement standard d'une resynchronisation cardiaque. Une sonde auriculaire droite (A), une sonde ventriculaire droite (B) et une sonde ventriculaire gauche dans une veine latérale du ventricule gauche par l'intermédiaire du sinus coronaire (C). Cette sonde VG est le plus souvent quadripolaire plutôt que bipolaire afin de multiplier les sites possibles de stimulation du VG. Ceci diminue le risque de stimulation diaphragmatique, augmente la probabilité d'obtenir une stimulation avec un bon seuil, permet de choisir une zone de stimulation basale ou moyenne plutôt qu'apicale et offre la possibilité d'une stimulation multipolaire : le « le multipoint pacing ». Elle diminue également le taux de ré intervention.

Enfin la mise en place d'une sonde quadripolaire plutôt qu'une sonde bipolaire dans une veine latérale du VG permet de diminuer le risque de stimulation diaphragmatique, augmente la probabilité d'obtenir une stimulation avec un bon seuil, permet de choisir une zone de stimulation basale ou moyenne plutôt qu'apicale et diminue le taux de ré-intervention en plus d'offrir la possibilité d'une stimulation multipolaire.^(60–62) Elle est donc devenue un standard dans l'implantation d'un TRC.

1.4.2 Remodelage cardiaque après resynchronisation

Après un TRC, plusieurs paramètres témoignent de l'amélioration de la performance contractile du ventricule gauche : l'amélioration des volumes télédiastoliques et télésystoliques du VG ainsi que l'amélioration de la FEVG et du strain. Cette amélioration s'étend jusqu'au 18^{ème} mois (Figure 6). Dans l'étude CARE-HF, la réduction de volume télésystolique est de 18 % à 3 mois et de 26% à 18 mois. Le gain de FEVG est de 6.9% à 18 mois.(46)

Il existe une réduction de l'insuffisance mitrale qui peut être observée immédiatement après la resynchronisation cardiaque. Cette amélioration semble être liée à la diminution des volumes ventriculaires, à la resynchronisation de l'appareil sous valvulaire mitral et à l'augmentation des forces de fermeture mitrale liée à l'amélioration de la performance VG.

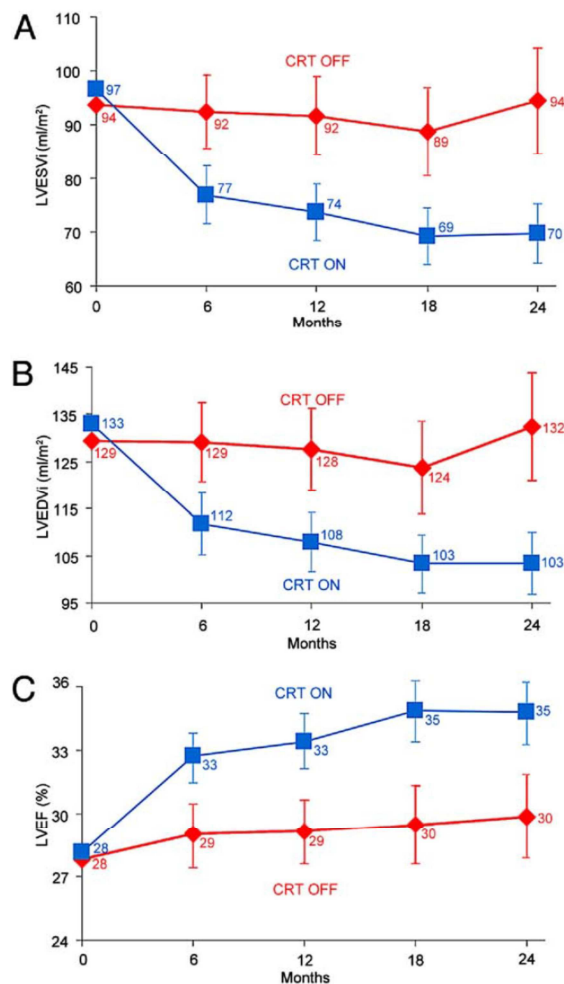


Figure 6. Effets de la resynchronisation cardiaque sur les volumes et la fonction ventriculaire gauche. LVESVi=Left ventricular end-systolic volume index. LVEDVi=Left ventricular end-diastolic volume index. LVEF=left ventricular ejection fraction. Les barres d'erreur montrent l'intervalle de confiance à 95%. CRT-ON= groupe traité. CRT-OFF=groupe contrôle.

1.5 Problématique de la non-réponse et paramètres permettant une prédiction de la non-réponse:

Les patients non répondeurs clinique et en terme de remodelage ventriculaire représentent 20 à 40 % de patients.(63). Cependant, étant donné le coût et les risques liés à l'intervention (jusque 14% de complications)(64), l'identification des facteurs de non réponse à la resynchronisation est un sujet de recherche important. La communauté des cardiologues imageurs tente de trouver des paramètres d'imagerie capables de prédire la réponse et la non-réponse à la resynchronisation.

En parallèle, le problème de la réponse et de la non réponse se pose moins pour les médicaments de l'insuffisance cardiaque tels que les bêtabloquants, les IEC ou encore la spironolactone même si le taux de répondeurs n'est pas plus élevé que pour le TRC : en effet, dans l'étude CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), 46.7% des patients traités par énalapril s'amélioraient d'au moins 1 classe NYHA.(65) Et malgré le traitement par IEC, 30% des patients présentaient après 1 an de suivi des surfaces VG plus importantes qu'à l'inclusion.(66) Dans l'étude CIBIS (Cardiac Insufficiency Bisoprolol Study), 21% des patients traités par bisoprolol s'amélioraient d'au moins 1 classe NYHA.(67) P De Groot et al. ont montré dans une étude de cohorte que 44% des patients avaient une amélioration de plus de 10% de FEVG sous traitement bêtabloquant.(68) Dans l'étude RALES (Randomized Aldactone Evaluation Study), 41% des patients traités par spironolactone s'amélioraient d'au moins 1 classe NYHA.(69) Le taux de non-répondeurs clinique s'élevait donc à 53 % pour l'énalapril, 79% pour le bisoprolol et 59% pour la spironolactone. Et si l'on compare le bénéfice net par rapport au placebo, le taux de répondeurs baisse à 24,9% pour l'énalapril, 6% pour le bisoprolol et 8% pour la spironolactone.

Une revue rapide des paramètres ayant été étudiés pour prédire la réponse/non réponse au TRC est décrite dans les paragraphes suivants.

1.5.1 Paramètres électriques : largeur des QRS et morphologie des QRS

1.5.1.1 Largeur des QRS

Il s'agit du seul paramètre prédicteur du pronostic au long cours (mortalité et hospitalisation pour insuffisance cardiaque) retrouvé dans l'analyse multivariée de la méta-analyse d'essais randomisés réalisée par l'équipe de Cleland et al. et comprenant 3782 patients.(8) Ces essais randomisés comprenaient MIRACLE, MIRACLE ICD, CARE-HF, REVERSE et RAFT et incluant 80% de patients avec un BBG. Lorsque le QRS est >140 ms, la réponse au TRC est claire alors qu'elle peut être débattue pour une durée <140 ms.

1.5.1.2 Morphologie du QRS

Dans une autre méta-analyse d'essais randomisés comprenant 5356 patients et conduite par Sipahi et al. la morphologie du QRS est retrouvée comme un facteur majeur de la réponse au TRC puisque l'effet du TRC sur la mortalité et les hospitalisations pour insuffisance cardiaque était très significatif pour les patients ayant un BBG alors qu'il était non significatif chez les patients ayant une morphologie autre.(70) Ces essais randomisés comprenaient COMPANION, CARE-HF, MADIT-CRT et RAFT.

Ce résultat est retrouvé dans la sous étude de MADIT-CRT réalisée par Zareba et al. (figure 7) (71) et dans l'étude de Mascioli et al. qui démontrent que les patients ayant un vrai BBG (durée du QRS ≥ 140 ms chez l'homme et ≥ 130 ms chez la femme avec un notch ou un slurring sur ≥ 2 dérivations latérales contiguës) ont un remodelage inverse plus important après le TRC que ceux avec un faux BBG (hypertrophie ventriculaire gauche et HBAG).(72)

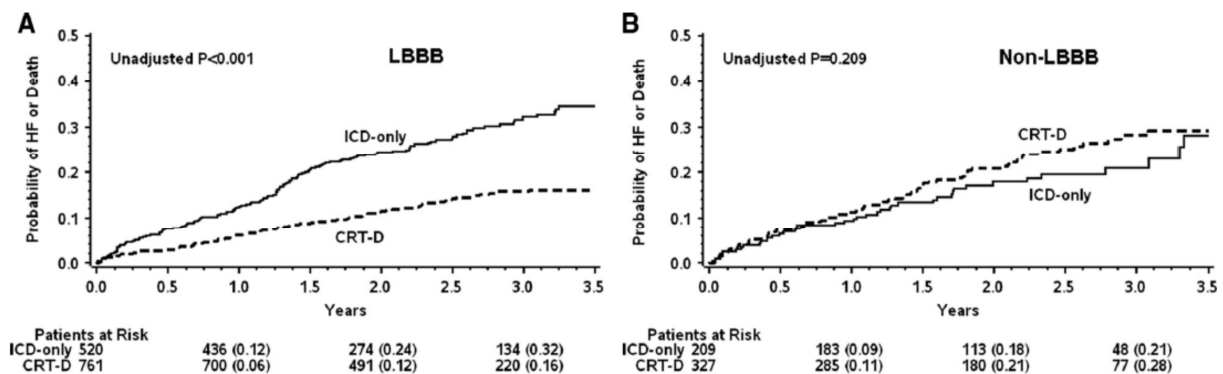


Figure 7. probabilité cumulative d'hospitalisation pour insuffisance cardiaque (HF) ou décès selon un traitement par défibrillateur automatique implantable simple (ICD-only) ou traitement par resynchronisation cardiaque en association au défibrillateur (CRT-D) chez des patients ayant un BBG (LBBB) (panneau A) ou chez des patients ayant une autre morphologie de QRS (Non-LBBB) (panneau B). Etude multicentrique MADIT-CRT (Boston scientific).(52)

1.5.1.3 Mapping épicaudique de l'activation électrique cardiaque

L'une des difficultés de la recherche de patients répondeurs est d'identifier avec précision les vrais BBG des « faux » BBG. En effet, le vrai BBG présente un délai d'activation de la paroi postéro-latérale du VG plus important que les BB droits (BBDt) ou les BB Indifférenciés. Même si Strauss et al. ont tenté d'optimiser la définition du BBG sur l'ECG, il reste un certain nombre de cas litigieux où un mapping de l'activation électrique myocardique serait utile. C'est l'objectif que s'est fixé l'université de Bordeaux avec le Cardioinsight®. Ploux et al. ont démontré sur 3 patients qu'un nouveau paramètre d'asynchronisme cardiaque : le VEU (ventricular electrical uncoupling) est plus prédictif que le BBG pour la prédiction des patients répondeurs au TRC sur un critère mixte NYHA, décès et hospitalisation pour insuffisance cardiaque.(73) Le VEU est défini comme la différence des temps d'activation moyens entre les deux ventricules. Un VEU positif correspond à un retard d'activation du

VG par rapport au VD et inversement. Plus le VEU est large, plus les ventricules sont découplés dans leur activation relative. Sur les courbes ROC, l'AUC du VEU est à 0.88 pour une AUC à 0.73 pour la largeur du QRS. Avec un cut-off de 50 ms de VEU, la sensibilité de ce paramètre à prédire les patients répondeurs était de 90% avec une spécificité de 82 %. Le VEU était en moyenne de 160±16 ms pour les BBG (pour une durée moyenne de QRS de 164±16 ms) et de 40±22 ms pour les BB indifférenciés (pour une durée moyenne de QRS de 137±20 ms).

1.5.2 Paramètres cliniques

Les paramètres cliniques classiquement reconnus comme étant prédictifs de la réponse à la CRT sont le sexe féminin et la cardiopathie dilatée non ischémique. Ils avaient été décrits par Goldenberg et al. sur 1761 patients de l'étude MADIT-CRT.(74) Ces paramètres ne sont pourtant pas retrouvés en analyse multivariée avec interaction sur le TRC dans la méta-analyse de Cleland et al.(8) L'effet du sexe féminin pourrait être lié à la plus faible masse myocardique chez la femme qui fait que les vrais BBG existent avec des largeurs de QRS plus fines (dès 130 ms)(30). L'effet de la cardiopathie ischémique a un effet propre sur la mortalité et les hospitalisations pour insuffisance cardiaque mais cet effet disparaît quand on ajoute l'interaction avec le TRC.(8)

Par ailleurs, en 2007, le United Kingdom National Institute of Clinical Excellence (NICE) Health Technology Appraisal (HTA) sur le TRC ont proposé une analyse du TRC associé à un pace maker (TRC-P) ou un défibrillateur (TRC-D) en comparaison à un traitement médical optimal au cours de la vie des patients (Table 2).(75) Dans ces analyses, la survie médiane après l'implantation d'un TRC était de 4,62 ans pour un pace maker et de 5,15 ans après un défibrillateur. Cependant, le gain en survie doit être comparé au traitement médical optimal et il est de 0,85 ans pour le TRC-P et de 1,39 ans pour le TRC-D. L'âge au moment de l'implantation a un impact significatif sur le gain attendu de survie : à 40 ans il était de 1,69 an pour le TRC-P contre 3,08 ans pour le TRC-D.

Age ^b	Survival			Additional life ^a	
	OPT	CRT-P	CRT-D	CTR-P	CRT-D
30	7.31	9.00	10.39	1.69	3.08
40	7.23	8.92	10.31	1.69	3.08
50	7.15	8.76	10.08	1.62	2.92
60	6.15	7.15	8.00	1.00	1.85
70	4.46	5.39	5.85	0.92	1.39
80	3.08	3.77	4.31	0.54	1.23
90	2.31	2.69	2.92	0.39	0.62
Overall	3.77	4.62	5.15	0.85	1.39

Table 2. Survie après un TRC en association à un pace maker (CRT-P) ou en association à un défibrillateur (CRT-D) au cours de la vie du patient. OPT : optimum pharmacological therapy.

1.5.3 Paramètres échocardiographiques

1.5.3.1 Paramètres de morphologie cardiaque

Goldenberg et al. avaient retrouvé deux critères échocardiographiques prédictifs d'une réponse au TRC : le volume téléstolique ventriculaire gauche ≥ 125 ml/m² et un volume d'oreillette gauche < 40 ml/m².(74) Cependant, le critère de dilatation ventriculaire est discordant avec l'étude de Rickard et al. qui retrouve au contraire que plus le ventricule gauche est petit plus il y a une forte probabilité de réponse au TRC et de survie.(76) Ces paramètres ne sont malheureusement pas étudiés dans la méta-analyse de Cleland.

1.5.3.2 Paramètres de contractilité cardiaque, la contractilité résiduelle

La FEVG est un paramètre étudié dans la méta-analyse de Cleland et a un effet propre très important sur la mortalité et l'insuffisance cardiaque, ce qui est connu de longue date. Lorsque l'on ajoute une interaction avec le traitement par TRC, il reste un effet significatif en analyse univariée mais pas en analyse multivariée.

Les patients répondeurs et super-répondeurs ont une contractilité évaluée par le strain global supérieure aux non répondeurs.(77) Ce paramètre n'est pas étudié par Cleland mais serait très intéressant car en rapport à la FEVG, le strain global est généralement étonnamment élevé avant un TRC en raison de la perte d'énergie importante secondaire au BBG. Cette perte d'énergie n'est pas visible dans le paramètre FEVG.

Nous retrouvons ces résultats dans notre travail

1.5.3.3 Paramètres de désynchronisation écho-cardiographique

L'ensemble des paramètres classiques de désynchronisation : asynchronisme auriculo-ventriculaire, interventriculaire et intra-ventriculaire en TM ou en doppler tissulaire sont de bons prédictifs de la réponse et du remodelage dans les études princeps de validation mais de mauvais prédictifs dans l'étude multicentrique de validation PROSPECT.(10) En effet, la précision diagnostique ne dépassait pas une AUC de plus de 0.62 qui correspond pour le paramètre « délai latéral septal en mode TM » à l'association d'une sensibilité à 64% et une spécificité à 52% pour prédire une amélioration du volume téléstolique ventriculaire de plus de 15%.

Lafitte et al. ont alors proposé une approche multiparamétrique en associant plusieurs critères d'asynchronisme pour augmenter la performance diagnostique. Cette étude montre qu'en associant

3 critères d'asynchronisme, on obtient une spécificité de 90% et une valeur prédictive positive de 65% mais en faisant baisser la sensibilité de façon majeure à 10%.(78)

L'échographie se fait prendre en défaut pour identifier les patients répondeurs probablement pour deux raisons : son manque de reproductibilité bien mise en évidence dans l'étude PROSPECT et son incapacité à différencier l'asynchronisme mécanique pur (hypokinésie ou augmentation de rigidité locale) de l'asynchronisme électromécanique (substrat électrique de la désynchronisation).(10) Le premier pouvant être considéré comme le substrat de la réponse au TRC alors que le second pas.

Parsai et al. démontrent dans une étude multicentrique qu'un retard mécanique (flash septal, asynchronisme auriculo-ventriculaire et interventriculaire) ne permet d'identifier les répondeurs que si ce retard est corrigible par un TRC, c'est-à-dire attribuable au substrat électrique.

De nouveaux paramètres de désynchronisation cardiaque analysables en échocardiographie ont vu le jour et tentent d'être spécifiques de la réponse au TRC. Ces nouveaux paramètres sont plus largement décrits dans le chapitre 6.1 de ce travail.

1.5.4 Paramètres de viabilité myocardique

La réserve contractile recherchée en échographie de stress ou d'effort dans les segments retardés permet d'améliorer l'identification des répondeurs.(79–82) En échographie d'effort, une augmentation de 6.5% de FEVG à l'effort permettrait d'identifier les répondeurs avec une sensibilité de 90% et une spécificité de 85%.(83)

Ce résultat est retrouvé en cherchant une viabilité du myocarde à la scintigraphie : une proportion de plus de 44% des segments viables permet d'identifier les répondeurs avec une sensibilité de 74% et une spécificité de 87%.(84)

La viabilité peut également être étudiée en IRM avec la prise de contraste tardive de gadolinium. L'équipe de Bleeker et al. montre en 2006 qu'une fibrose de la paroi postéro-latérale en IRM est un facteur de non réponse au TRC. Ce résultat a été redémontré par plusieurs autres équipes. Quelques années plus tard, Leyva et al. montrent que la fibrose myocardique endo-pariétale du VG est associée à la mortalité et la morbidité après TRC.(85)

Travaux personnels

2 Matériel et méthode

2.1 Critères d'inclusion et d'exclusion

Notre base de travail est une cohorte prospective de l'ensemble des patients implantés d'une resynchronisation cardiaque depuis l'année 2010 à l'hôpital Saint Philibert de Lomme répondants aux indications de la société européenne de rythmologie.(2) Patients insuffisants cardiaques avec FEVG $\leq 35\%$, gardant une dyspnée NYHA 2,3 ou 4 ambulatoires avec un traitement médical optimal et un QRS ≥ 120 ms ou une stimulation ventriculaire droite.

Les critères d'exclusion étaient : (i) un infarctus du myocarde, un syndrome coronaire aigu ou une revascularisation dans les 3 mois. (ii) une valvulopathie sévère mitrale ou aortique. (iii) une fibrillation atriale rapide non contrôlée. Les patients recevaient les doses maximales tolérées de bêtabloquant, d'IEC ou ARA 2 et de spironolactone.

2.2 Biologie

Les prélèvements sanguins étaient réalisées pour la créatinine et le Brain Natriuretic Peptide (BNP) dans une sous population (Triage assay ; Beckman, Villepinte, France).

2.3 Comité d'éthique

Le comité d'éthique du Groupement de Hôpitaux de l'Institut Catholique de Lille (GHICL) a accepté la réalisation de cette recherche. Le protocole est enregistré dans clinicaltrials.gov au numéro NCT02986633. Le consentement éclairé était obtenu pour tous les patients.

2.4 L'électrocardiogramme (ECG)

Un électrocardiogramme était systématiquement réalisé le jour précédant l'implantation du TRC et avant la sortie du patient après réglages optimaux. La mesure du QRS a ici été réalisée sur l'ECG directement avec une méthode visuelle aidée du papier millimétrique. Ceci pour deux raisons : 1/même si la mesure aurait été meilleure en salle d'électrophysiologie, celle-ci ne reflète pas la pratique clinique. Par ailleurs, en post implantation précoce d'un TRC (en salle d'électrophysiologie), les réglages des paramètres ne sont pas forcément définitifs. 2/nous avons testé la mesure avec l'aide d'un compas et celle-ci s'est avérée similaire. En effet, la concordance inter-juge retrouve un ICC à 0.922 pour la méthode visuelle vs un ICC à 0.919 pour la méthode au compas.

2.5 Echocardiographies transthoraciques (ETT)

Trois échocardiographies transthoraciques (ETT) étaient réalisées avec un appareil GE Vivid E9 ou 7 (General Electric healthcare, Velizy, France). Ces ETT étaient implémentées sur station de travail de manière systématique et étudiées sur une station de travail dédiée (EchoPAC PC version BT12; GE Vingmed Ultrasound AS). La première ETT était réalisée le jour précédant le TRC, la deuxième immédiatement après le TRC et la troisième 9 mois après.

Toutes les mesures standard ont été réalisées selon les recommandations américaines de Lang et al. de 2006 (86).

Le strain global longitudinal strain était calculé comme la moyenne des pics de strain longitudinaux segmentaires mesurés sur les 3 coupes apicales. Un logiciel de traque des marqueurs sonores était utilisé pour analyser la déformation des différentes parois myocardiques. En ce qui concerne le strain septal, la région d'intérêt sélectionnée était positionnée le long de l'endocarde septal de la base à l'apex en excluant la pointe et en s'adaptant à l'épaisseur septale. La moyenne de la déformation des trois segments septaux basal, moyen et apical était utilisée pour l'analyse.

2.6 Suivi clinique et dates de point

Un suivi des événements cardiovasculaires a été réalisé sous la forme de dates de point régulières afin d'éviter un biais de suivi. Les événements évalués étaient : le stade NYHA, les hospitalisations pour insuffisance cardiaque, les décès et causes du décès. Ces événements étaient enregistrés par des consultations présentes ou téléphoniques avec le patient et éventuellement avec leur médecin généraliste, cardiologue ou proche familial si besoin.

Une mortalité était considérée comme cardiovasculaire si elle était reliée à une insuffisance cardiaque, un infarctus du myocarde, une arythmie ou une mort subite.

3 La désynchronisation mécanique est-elle une cible thérapeutique dans l'insuffisance cardiaque à FE préservée.*

*Menet A, Greffe L, Ennezat P-V, Delelis F, Guyomar Y, Castel AL, et al. Is mechanical dyssynchrony a therapeutic target in heart failure with preserved ejection fraction? Am Heart J. déc 2014;168(6):909-916.e1 (87)

3.1 Introduction

Devant l'efficacité du TRC sur la mortalité, les hospitalisations pour insuffisance cardiaque et les symptômes, il a paru légitime d'extrapoler aux autres cas d'insuffisance cardiaque à QRS fins sur la base d'une désynchronisation mécanique. Cette désynchronisation mécanique est retrouvée chez les patients ayant une insuffisance cardiaque qu'elle soit systolique ou diastolique.(3–5) Par contre le substrat électromécanique de désynchronisation qui présente une potentielle réponse au TRC n'est pas connu dans cette population. Le premier objectif de cette thèse a donc été de comparer les paramètres de désynchronisation cardiaque prédicteurs d'une réponse à la resynchronisation cardiaque des insuffisances cardiaques à fraction d'éjection conservée à : 1/ des cardiopathies dilatées à QRS fins, 2/ des cardiopathies dilatées à QRS larges, 3/ un groupe contrôle de cardiopathie hypertensive.

3.1.1 Désynchronisation mécanique

Le concept de désynchronisation mécanique est né lors de la découverte de la présence d'asynchronisme de contraction sur des critères échocardiographiques chez des sujets normaux et chez les patients ayant des QRS fins. Cette désynchronisation n'est donc pas spécifique du BBG et on peut la retrouver en cas d'hypokinésie ou d'akinésie de parois myocardiques notamment dans la cardiopathie ischémique. Skulstad et al. démontrent de manière élégante sur 15 chiens après provocation d'une sténose de l'artère interventriculaire antérieure (IVA), d'une sténose de l'IVA associée à une constriction aortique et enfin d'une occlusion de l'IVA. Cet asynchronisme lié à une contraction post-systolique dans les segments ischémiques est réversible après reperfusion de l'IVA. (88) (Figure 8) Park et al. montrent sur 37 patients avec des cardiopathies dilatées non ischémiques que l'asynchronisme mécanique est un phénomène dynamique qui varie avec les conditions de pré et de post-charge.(1) En effet, ils utilisent pour ce faire une compression pneumatique des membres inférieurs pour augmenter la post charge puis utilisent de la trinitrine sublinguale pour diminuer la précharge et mesurent la différence maximale de temps au pic en strain radial ainsi que le stress

pariétal télésystolique du VG. Ces deux mesures augmentent avec l'augmentation de la post charge et baissent avec la diminution de la précharge marquant une augmentation de la désynchronisation cardiaque en cas d'augmentation de la post charge et une diminution de celle-ci en cas de diminution de la précharge.

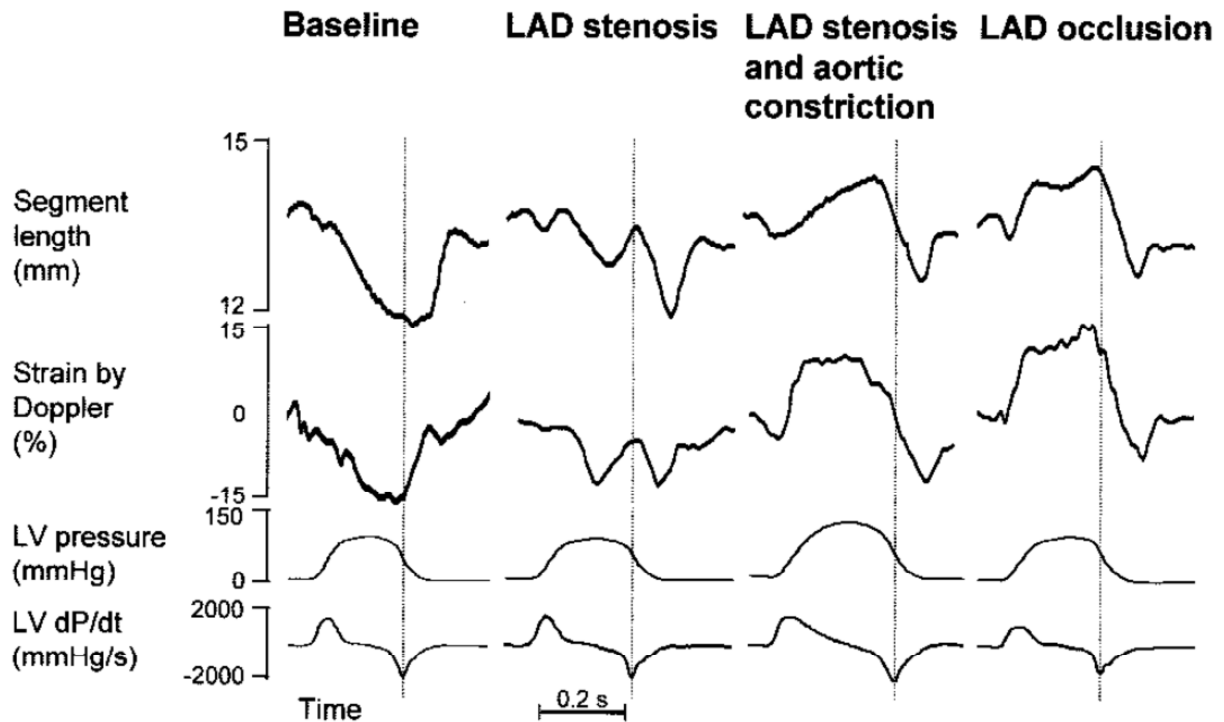


Figure 8. Asynchronisme mécanique observé au cours de l'ischémie et de l'infarctus induit expérimentalement. LAD : Left anterior descendant. LV : left ventricular. *Figure tirée de l'article de Skulstad et al. Circulation 2002, 6;106(6):718-24.*

3.1.1.1 Les 3 substrats de la désynchronisation mécanique du VG

Lumens et al. montrent par un modèle mathématique l'effet de 3 substrats responsables de désynchronisation sur la contraction des parois du VG en strain radial : le BBG (un substrat électrique), et deux substrats non électriques : l'hypo-contractilité et la rigidité myocardique de la paroi latérale du VG.(13) (Figure 9). Chacun de ces substrats est responsable d'un mouvement particulier des parois myocardiques avec une augmentation du temps maximal entre les pics de contraction en strain radial mais avec un mouvement des parois ventriculaires très différent.

Dans le substrat électrique du BBG, la contraction septale est pré-systolique avec un étirement de la paroi latérale pré-systolique tandis que dans les substrats non électriques, l'étirement est systolique. L'auteur tente ainsi de différencier une incoordination mécanique sans substrat électrique et sans

probabilité de réponse à la resynchronisation cardiaque du véritable asynchronisme cardiaque qui peut être amené à répondre à un traitement par resynchronisation cardiaque (TRC).

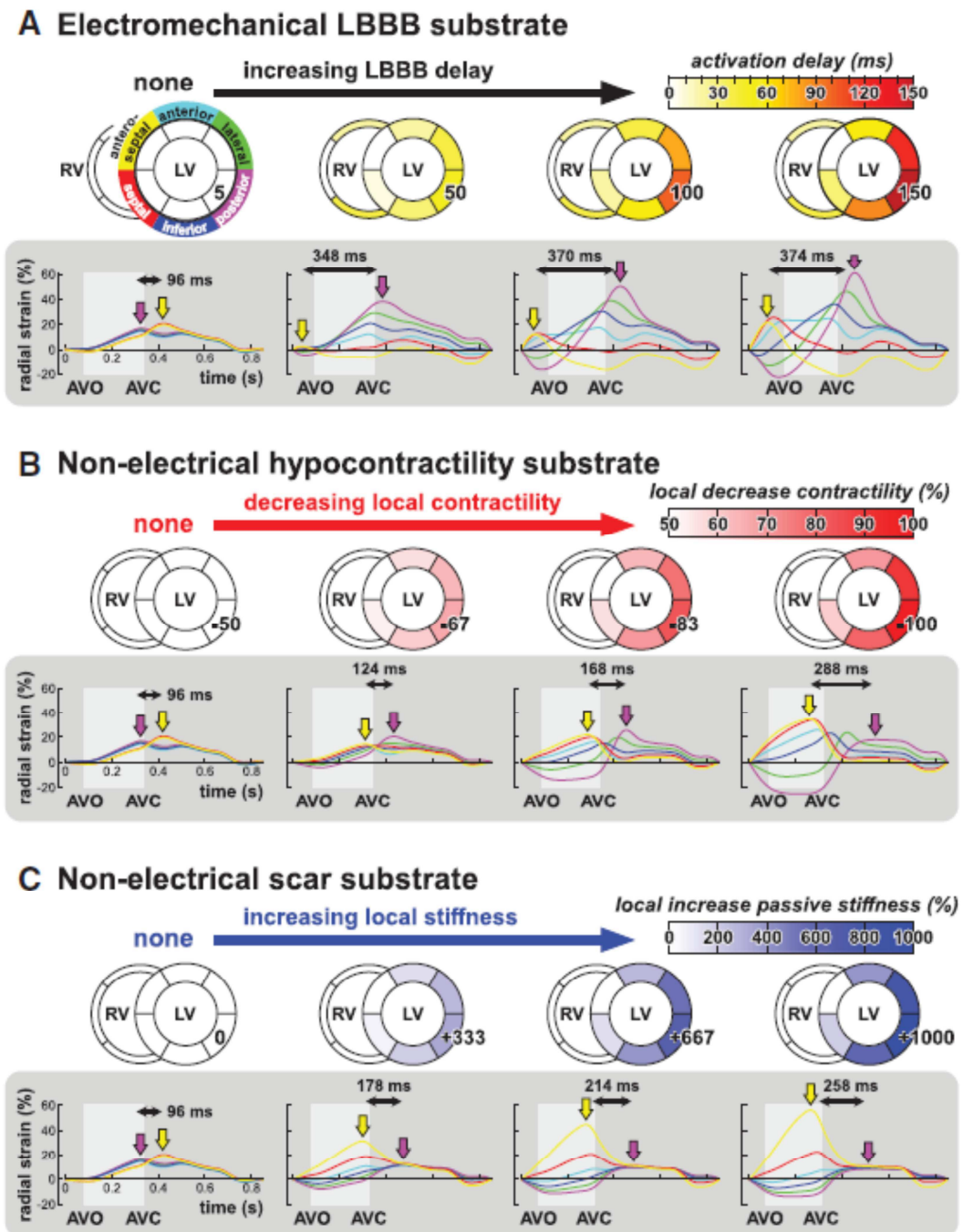


Figure 9. Substrats de la désynchronisation mécanique simulés par ordinateur. A : asynchronisme électromécanique induit par un BBG. B : désynchronisation mécanique induite par une diminution de la contractilité de la paroi latérale par rapport à la paroi septale. C : désynchronisation mécanique induite par une augmentation de la rigidité de la paroi latérale du ventricule gauche. AVO : aortic valve opening. AVC : aortic valve closure. Les flèches jaune et violette montrent les temps au pic les plus éloignés. *Figure tirée de Lumens et al., Circ Cardiovasc Imaging. 2015, 8(9):e003744.*

3.1.2 Cas de la cardiopathie à fraction d'éjection préservée

Dans la cardiopathie à fraction d'éjection conservée, dès le début des années 2000, plusieurs auteurs mettent en évidence un asynchronisme en échocardiographie. De Sutter et al. en 2005 montrent chez 60 patients avec une insuffisance cardiaque à fraction d'éjection préservée (ICFEP) que la prévalence de l'asynchronisme interventriculaire par la mesure du délai pré-éjectionnel aorto-pulmonaire ≥ 40 ms est de 17% et l'asynchronisme intraventriculaire par la mesure en doppler tissulaire d'une dispersion ≥ 60 ms du temps entre le pied du QRS et le début du mouvement de 4 segments basaux du VG est de 18%. Si les QRS sont ≥ 120 ms, ce taux atteint presque 50%.⁽⁸⁹⁾ Yu et al. montrent à leur tour en 2007 chez 92 patients ICFEP avec des QRS fins que 39 % des patients ont un asynchronisme de contraction par la mesure des déviations standard des temps au pic en doppler tissulaire sur 6 segments basaux et 6 segments médians.⁽⁴⁾ Wang et al. le retrouvent chez 33% des patients.⁽⁹⁰⁾ Santos et al. retrouvent des résultats similaires et trouvent une association entre l'asynchronisme et la largeur du QRS, la masse myocardique et l'amplitude du trouble de relaxation par la mesure de la vélocité de l'anneau mitral (E').⁽⁵⁾ Lee et al, retrouvent un asynchronisme systolique sur les déviations standard des 12 segments en doppler tissulaire chez 36% des patients et une proportion identique chez des patients ayant une cardiopathie hypertensive avec hypertrophie du VG. Par contre, après réalisation d'une échographie de stress par dobutamine, ce taux s'élève à 85% chez les patients ayant une ICFEP contre 52% chez les patients ayant une cardiopathie hypertensive. ⁽⁹¹⁾

La question d'une possibilité de traitement par resynchronisation cardiaque était donc devenu légitime, il fallait construire une cohorte multicentrique de patients avec une ICFEP pour évaluer leur pronostic. C'est ce que se sont attelés à faire Donal et al. avec le registre prospectif KaRen. Sur 539 patients inclus, la prévalence du BBG était de 3,8% et du BBDt de 7,6%. Les paramètres de désynchronisation échographiques mesurés dans cette étude étaient peu altérés: le délai pré-éjectionnel aorto-pulmonaire (84 ± 31 ms), les délais de contraction entre le septum et la paroi latérale du VG en doppler tissulaire (35 ± 58 ms) et en strain (18 ± 192 ms). ^(92,93)

Aucune de ces études ne s'était attachée à mesurer l'ensemble des paramètres classiques de désynchronisation et les nouveaux paramètres de désynchronisation qui sont prédicteurs de la réponse à la CRT. Nous nous sommes donc attachés à réaliser ce travail sur 40 patients avec une insuffisance cardiaque à fraction d'éjection préservée et en les comparant à i) 40 patients avec une indication à la resynchronisation cardiaque : fraction d'éjection $\leq 35\%$, NYHA 2-4 malgré un traitement médical optimal et des QRS ≥ 120 ms. ii) 40 patients avec une cardiopathie hypokinétique

avec FE<50% et des QRS < 120 ms et *iii*) 40 patients contrôles avec une hypertension artérielle chronique sans antécédent d'insuffisance cardiaque.

3.2 Résultats

Ce travail confirme que les patients atteints d'une insuffisance cardiaque à FE préservée présentent une désynchronisation mécanique plus importante que les sujets contrôles (étudiée par la dispersion du pic de contraction des parois du cœur en doppler tissulaire). Ils ne présentent par contre que peu des autres critères de désynchronisation et notamment pas les critères de désynchronisation considérés comme les substrats de la réponse au TRC.

Les indices d'asynchronisme étaient identiques entre les patients ayant une ICFEP, les patients hypertendus contrôles et les patients ayant une insuffisance cardiaque à FEVG basse (ICFEb) à QRS fins. Ils étaient par contre très différents du groupe d'ICFEb et QRS large ayant une indication pour le TRC.

Par ailleurs, l'analyse en composante principale met en évidence de manière visuelle qu'il existe un lien étroit entre les paramètres de désynchronisations spécifiques d'un substrat électromécanique de désynchronisation (notamment le BBG): le flash septal, le pattern de contraction classique de BBG et les patterns 1 ou 2 de contraction septale. Ces paramètres sont très corrélés au groupe ayant une indication de TRC mais peu corrélés aux trois autres groupes étudiés. Cela souligne qu'en termes de désynchronisation pouvant répondre à la stimulation biventriculaire, l'insuffisance cardiaque à FE préservée est proche du groupe de cardiopathie hypokinétique à QRS fins ou au groupe contrôle de patients ayant une hypertension artérielle chronique sans antécédent d'insuffisance cardiaque.

3.3 Discussion

Les résultats négatifs de l'étude menée par Ruschitzka et al. qui étudiait de manière randomisée le TRC chez des patients insuffisants cardiaques NYHA 3 ou 4 avec une FEVG \leq 35%, un QRS < 130 ms et une désynchronisation en échographie viennent confirmer cette impression. En effet, ces patients ont des paramètres de désynchronisation mécanique supérieurs aux patients avec une ICFEP.(41) Les critères de désynchronisation échographique dans cette étude étaient le délai de pic de contraction entre les parois antéro-septale et postérieure en strain radial supérieur à 130 ms et un délai de pic de contraction en doppler tissulaire entre deux parois opposées en apical 4 cavités ou 2 cavité supérieur à 80 ms. L'un de ces deux critères a été retrouvé chez 66% des patients. En outre, 76 % des patients inclus dans cette étude avaient un asynchronisme écho-cardiographique persistant ou aggravé 6

mois après le TRC. Cette aggravation était retrouvée dans les groupes TRC-off et TRC-on. Ces résultats montrent que la désynchronisation mécanique sans désynchronisation électrique est fréquente dans les insuffisances cardiaques à FEVG basse (ICFEB) est qu'elle n'est pas affectée par le TRC. Elle n'est donc pas une bonne cible pour ce traitement.

Même si la désynchronisation échographique amenable au TRC est rare chez le patient à QRS < 130 ms, elle peut tout de même se retrouver. (Figure 10) Le bénéfice du TRC chez ces patients est indémontrable étant donné le peu de patients concernés : il faudrait screener 1000 patients de ce type pour inclure 10 patients dans un essai thérapeutique.



Figure 10 : Présence d'une désynchronisation cardiaque présentant des indices de désynchronisation amenable au TRC chez un patient ayant des QRS à 115 ms. En haut : ECG montrant des QRS à 115 ms avec un aspect d'HBAG. En bas à gauche : strain longitudinal en coupe apicale 3 cavités. En bas à Droite : strain longitudinal en coupe apical 4 cavités. Ces strains montrent un aspect net de contraction précoce septal et antéro septal avec un étirement et une contraction post systolique des parois postérieure et latérale.

Un petit groupe de patients mériterait une attention particulière : les patients avec une FE >35% mais gardant une insuffisance cardiaque clinique malgré un traitement optimal et la présence d'un BBG. Le BBG est présent chez 3,8 à 8,1% des patients ayant une ICFEP.(93,94) Sa prévalence est probablement plus élevée pour les patients ayant une FEVG entre 35 et 45%. Leur pronostic et leur

éventuelle réponse au TRC méritent d'être évalués. L'étude MIRACLE-HF tentant de répondre à cette question a été interrompue du fait d'un défaut d'inclusion (44 patients inclus en 13 mois alors que l'étude devait en randomiser 2300).(95)

Is mechanical dyssynchrony a therapeutic target in heart failure with preserved ejection fraction?



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Background Previous studies have found a high frequency of mechanical dyssynchrony in patients with heart failure (HF) with preserved ejection fraction (HFpEF), hence suggesting that cardiac resynchronization therapy (CRT) may be considered in HFpEF. The present study was designed to compare the amount of mechanical dyssynchrony between HFpEF patients and (1) HF with reduced EF (HFrEF) patients with an indication for CRT (HFrEF-CRT(+)) group, (2) HFrEF patients with QRS duration <120 ms (HFrEF-QRS <120 ms) group, and (3) hypertensive controls (HTN).

Methods Electrical (ECG) and mechanical dyssynchrony (atrio-ventricular dyssynchrony, interventricular dyssynchrony, intraventricular dyssynchrony) were assessed using conventional, tissue Doppler, and Speckle Tracking strain echocardiography in 40 HFpEF patients, 40 age- and sex-matched HTN controls, 40 HFrEF-QRS <120 ms patients, and 40 HFrEF-CRT(+) patients.

Results The frequency of left bundle branch block was low in HFpEF patients (5%) and similar to HTN controls (5%, $P = 0.85$). Indices of dyssynchrony were similar between HFpEF and HTN patients or HFrEF-QRS <120 ms patients. In contrast, most indices of dyssynchrony differed between HFpEF and HFrEF-CRT(+) patients. The principal components analysis on the entire cohort of 160 patients yielded 2 homogeneous groups of patients in terms of dyssynchrony, the first comprising HFrEF-CRT(+) patients and the second comprising HTN, HFrEF-QRS <120 ms and HFpEF patients.

Conclusions Mechanical dyssynchrony in HFpEF does not differ from that of patients with HTN or patients with HFrEF and a narrow QRS. This data raises concerns regarding the role of dyssynchrony in the pathophysiology of HFpEF and thereby the potential usage of CRT in HFpEF. (*Am Heart J* 2014;168:909-916.e1.)

Chronic heart failure (CHF) affects about 2% of the western population, increasing sharply from 1% in those aged 50 years to a 10% prevalence in those aged 75 years and older.^{1,2} CHF is the most common cause of hospitalization in patients aged over 65 years.^{1,2} As many as 50% of patients with CHF have a preserved ejection fraction (HFpEF). Epidemiological surveys show that the prognosis of patients with HFpEF is nearly as poor as those with heart failure and with a reduced ejection fraction (HFrEF).³ Despite use of similar drugs, outcomes of recent heart failure (HF) trials were consistently neutral in HFpEF in

contrast to HFrEF.⁴ The multifaceted pathophysiology of HFpEF remains debatable. The role of combined ventricular and arterial stiffening, subtle longitudinal and torsional LV systolic dysfunction,⁵ chronotropic incompetence,⁶ and renal impairment⁷ have been previously highlighted in HFpEF pathogenesis. Preliminary landmark studies have also reported a high frequency of mechanical dyssynchrony in patients with HFpEF, hence suggesting that myocardial dyssynchrony may contribute to the pathophysiology of HFpEF. Thus, the present study was designed to compare the amount of mechanical dyssynchrony between HFpEF patients and (1) HFrEF patients with an indication for CRT according to current guidelines and (2) HFrEF patients with a narrow QRS (QRS <120 ms) and (3) hypertensive controls (HTN). We hypothesized that HFpEF patients resemble to HTN and HFrEF patients with a narrow QRS in terms of dyssynchrony but not to HFrEF patients with a CRT indication.

Methods

Study population

HFpEF patients. The first cohort included patients who were hospitalized for heart failure and were found to

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have a LV ejection fraction ≥ 0.50 . Patients with HFpEF were studied as outpatients 2 months after the index hospitalization. Data was collected at the time of the outpatient examination. Every patient met the Framingham HF criteria and had physical and radiographic evidence of pulmonary congestion. Exclusion criteria are detailed in the appendix. Forty patients were included in this study.

Hypertensive control patients. Hypertensive patients (HTN) were randomly recruited among patients with hypertension who were followed in the outpatient department of our institution over a time period similar to the recruitment of HFpEF patients. Hypertension patients were age- and sex- matched to HFpEF patients.

HFrEF patients with QRS <120 ms (HFrEF-QRS <120 ms). HFrEF patients were randomly recruited among patients who, were hospitalized for heart failure at our institution and found to have a LV ejection fraction < 0.50 and a narrow QRS on ECG (< 120 ms). None of these patients had an indication for CRT according to current guidelines.

HFrEF patients with indication for CRT (HFrEF-CRT (+)). This cohort was retrospectively built by random sampling of HFrEF patients referred to our institution for CRT, according to the European Society of Cardiology guidelines; these patients were enrolled in a prospective study evaluating CRT response.^{8,9} CRT had been considered for patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$ who remained in New York Heart Association class II, III, and ambulatory IV, despite optimal medical treatment and QRS duration ≥ 120 ms with a left bundle-branch block (LBBB) morphology or with QRS duration ≥ 150 ms with a non LBBB morphology. A part of the results regarding this group of patients has been previously reported.⁸

Exclusion criteria were identical for HFpEF patients, HTN patients, HFrEF-QRS < 120 ms and HFrEF-CRT(+) patients.

Clinical and ECG data obtained in the present study is detailed in the appendix.

Echocardiography

Every examination was performed on a GE Vivid E9 ultrasound system with a M5S probe (GE Healthcare, Velizy, France) and stored on a PACS. All measurements were off-line performed on a dedicated EchoPAC workstation equipped with the BT12 version (GE Medical Systems). Standard echocardiographic measurements, speckle tracking and tissue Doppler methods are detailed in the appendix.

Dyssynchrony measurements. As shown in Figure 1, indices of ventricular dyssynchrony were measured as follows:

1. Atrio-ventricular dyssynchrony (ratio of the LV filling time [mitral Doppler inflow] and RR interval [LVFT/RR] less than 0.40).
2. Inter-ventricular dyssynchrony:
 - a. Left ventricular pre-ejection interval (LPED), as the time interval between QRS onset and onset of aortic ejection (predefined cut-off value > 140 ms).¹⁰
 - b. Inter-ventricular mechanical delay (IVMD), defined as the difference between left and right ventricular pre-ejection delays (predefined cut-off value > 40 ms).
3. Intraventricular dyssynchrony
 - a. LV dyssynchrony by tissue Doppler imaging (TDI) was defined as the maximum delay between peak systolic velocities of the septal and the lateral walls (Ts lateral-septal). Ts-SD (the standard deviation of time to peak systolic velocity of 12 segments of the left ventricular wall at the basal and medial levels) was also calculated.^{11,12}
 - b. The difference between time to peak-systolic longitudinal strain by speckle tracking of the basal-septal and basal-lateral LV segment (BS-BL delay) and the standard deviation of time to peak-systolic longitudinal strain by speckle tracking for the 12 basal and medial segments ($SD_{t_{12s}}$) were accordingly calculated.⁸
 - c. The septal flash was defined as an early septal thickening/thinning within the isovolumic contraction period as detected both visually from the gray-scale SAX and 4CH views and from the PSLAX, SAX, and 4CH views obtained by M-mode (Figure 1).¹³
 - d. A classical LBBB pattern of contraction was searched using longitudinal strain waveforms (Figure 1) and was defined as an early contraction of the septal or anteroseptal wall and early stretching in the opposing wall.¹⁴
 - e. Septal deformation patterns were systematically investigated. Three septal deformation patterns have been described in patients with a LBBB. Pattern 1 was considered if there was a double peak systolic shortening, pattern 2 was defined early pre-ejection shortening peak followed by prominent systolic stretch and pattern 3 was defined as a normalized pattern with a late systolic peak.^{8,15}

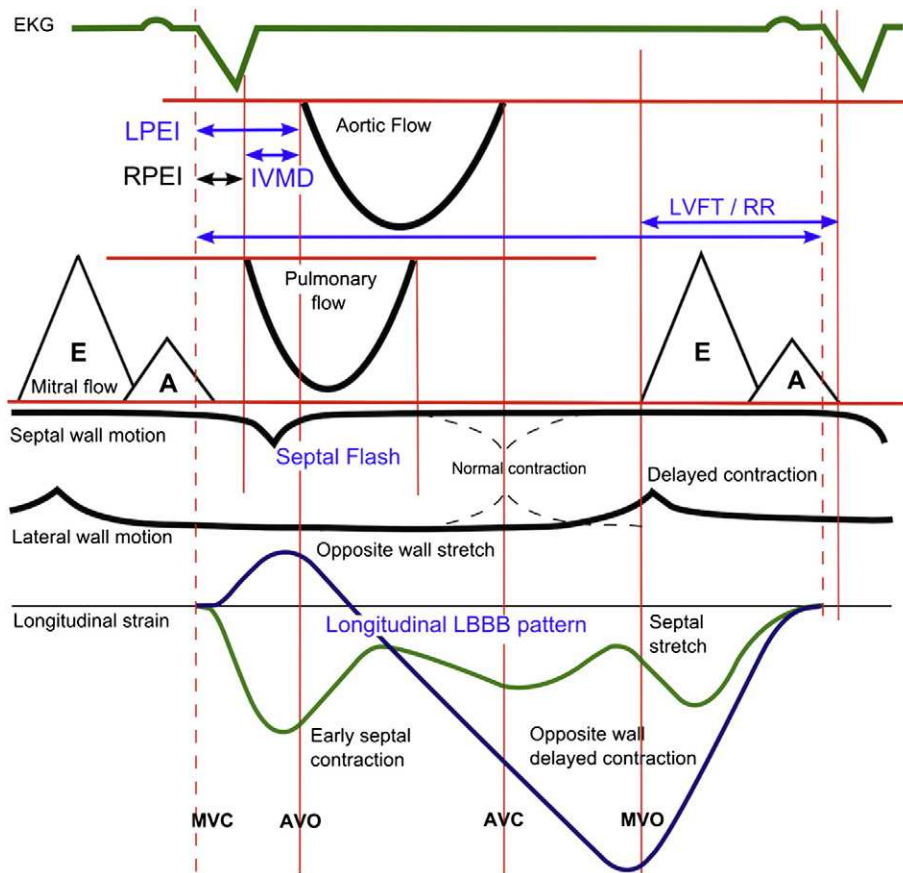
Statistical analysis

Quantitative data is presented as mean \pm SD or median [25-75th]. Qualitative data is presented as absolute numbers and percentages. Comparison of the means was carried out using a paired two-sided Student *t* test or Mann-Whitney *U* test as appropriate. Comparison of categorical variables was carried out using a χ^2 test or a Fisher exact test, as appropriate.

To identify the association between electrical dyssynchrony (QRS duration) and each continuous variable of mechanical dyssynchrony, multiple linear regression analysis with adjustment on the group of patients were performed.

Principal components analysis (PCA) is a multidimensional exploratory method and allows to comprehensively link the network of relationships that exist among many variables, which was the case in this analysis of dyssynchrony. From a geometrical point of view, variables in a correlation matrix correspond to points in a high-dimensional space. PCA enables the projection of these points on a plan with minimal

Figure 1



Doppler, M-mode, and speckle tracking indices of dyssynchrony. Abbreviations of indices of dyssynchrony are detailed within the text in the methods section. MVC/O: mitral valve closure/opening. AVC/O: aortic valve closure/opening.

distortion: 2 principal components which adequately explain the variance of all dyssynchrony variables, are used to build the axes of the plan.

Thus, dyssynchrony variables and groups of patients are presented in a subject plan determined by the 2 main components which are orthogonal within one plan and draw a circle.

The closer the point is to the circle, the better the quality of the representation. Two close points are positively correlated. When two points are close to the circle and orthogonal to the origin (O), these two underlying variables are uncorrelated. When two points are diametrically opposed and close to the circle, these two underlying variables are negatively correlated. No conclusion can be drawn if a point is close to the origin O. We can thus find groups of variables having the same meaning and link groups with variables.

For all tests, a 2-tailed $P \leq .05$ or less was considered statistically significant. Statistical analysis was performed with R 3.0.3 (Youngstown, OH).

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conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Clinical characteristics, ECG and biological data

Clinical characteristics, ECG and biological data are detailed in Table I. HF_rEF-QRS <120 ms and HF_rEF-CRT(+) patients were more frequently male, had a lower body mass index and were less frequently hypertensive compared with HF_pEF patients. The frequency of enlarged QRS (QRS ≥ 120 ms) was similar in HF_pEF patients and HTN controls (15% vs 10%, $P = .85$ respectively).

Echocardiographic data

Echocardiographic data of the 4 groups of patients is shown in Table II. LVEF and Global Longitudinal Strain were lower in HF_pEF compared with HTN patients. As expected, left atrial volume index and E/e' ratio were higher in the three groups of HF patients compared with HTN controls.

Table I. Demographic and clinical data of the study population

		HFpEF	HTN	HFrEF-QRS < 120 ms	HFrEF CRT(+)	P	HFpEF vs HTN	HFpEF vs HFrEF-QRS < 120 ms	HFpEF vs HFrEF-CRT(+)
Clinical data	No. of patients	40	40	40	40				
	Age (year)	70 ± 13	68 ± 11	62 ± 12	70 ± 12	.005	0.432	0.002	0.94
	Male (n, %)	9 (23)	9 (23)	32 (80)	28 (70)	<.001	1	<0.001	<0.001
	Body mass index (kg/m ²)	31 ± 6	29 ± 6	27 ± 5	27 ± 5	.007	0.274	0.004	0.004
	Hypertension (n, %)	37 (93)	40 (100)	21 (54)	13 (33)	<.001	0.651	<0.001	<0.001
	Diabetes (n, %)	24 (60)	15 (38)	14 (36)	11 (28)	.022	0.073	0.043	0.006
	Dyslipidemia (n, %)	28 (70)	19 (48)	18 (46)	13 (33)	.009	0.069	0.041	0.002
	COPD (n, %)	7 (18)	1 (3)	5 (13)	5 (13)	.142	0.057	0.756	0.755
	Coronary artery disease (n, %)	9 (23)	2 (5)	20 (50)	13 (33)	<.001	0.025	0.0184	0.453
	Systolic blood pressure (mmHg)	142 ± 23	138 ± 18	126 ± 21	124 ± 19	<.001	0.317	<0.001	<0.001
	Diastolic blood pressure (mmHg)	77 ± 10	79 ± 11	72 ± 14	71 ± 12	.005	0.291	0.093	0.028
	Heart rate (beat/min)	72 ± 15	72 ± 11	72 ± 13	73 ± 13	.998	0.903	0.964	0.943
	ECG	QRS width (ms)	92 ± 23	91 ± 18	97 ± 10	157 ± 25	<.001	0.696	0.297
QRS Morphology (n, %)						<.001	0.845	0.026	<0.001
LBBB		2 (5)	2 (5)	0 (0)	38 (95)				
Right bundle-branch block		4 (10)	2 (5)	0 (0)	0 (0)				
Intraventricular conduction delay		0 (0)	0 (0)	0 (0)	2 (5)				
Biological data	Creatinine (mg/L)	16 ± 12	9 ± 2	12 ± 4	14 ± 9	<.001	<0.001	0.038	0.362
	Brain natriuretic peptide (pg/mL)	471 ± 679	54 ± 52	722 ± 900	959 ± 1066	<.001	0.024	0.213	0.009

Abbreviation: COPD, Chronic obstructive pulmonary disease.

Dyssynchrony

Dyssynchrony variables of the 4 groups of patients are shown in Table III. A significant heterogeneity was found between the four groups of patients. Indices of dyssynchrony were similar in HFNEF and HTN patients. Similar findings were found for the comparison of dyssynchrony indices between HFpEF and HFrEF QRS < 120 ms patients. In contrast, most indices of dyssynchrony differed between HFpEF and HFrEF-CRT (+) patients. In the 2 patients with HFpEF and a LBBB, a septal flash was found in 1 patient and a longitudinal LBBB classical pattern was found in both patients. In contrast, no patient with HFpEF without a LBBB had a septal flash (0%) and only 1 had a longitudinal LBBB classical pattern (2%).

In the whole cohort of patients and after adjustment of groups, QRS duration did correlate with LPEI ($P = .0001$), IVMD ($P = .008$) and Sdt12d ($P = .02$) whilst Ts lateral septum ($P = .09$), Ts-SD ($P = .71$), BS-BL ($P = .06$) and LVFT/RR ($P = .52$) did not. In contrast, the proportion of patients with a septal flash, a LBBB longitudinal classical pattern and a septal pattern 1 or 2 was significantly higher in patients with QRS duration ≥ 120 ms compared with those with a QRS duration <120 ms (Figure 2).

Principal components analysis

A graphical representation of the correlations between dyssynchrony variables and correlation between groups

of patients and variables based on a principal component analysis is shown in Figure 3 and summarizes the information contained in Table III. This figure illustrates dyssynchrony variables (dyssynchrony variables plan) and the groups of patients (groups of patients plan) that resemble one another. The HFpEF group is very close to the HTN group and to HFrEF-QRS <120 ms group. In contrast, the three other groups largely differ from HFrEF-CRT (+) patients in terms of dyssynchrony. Thus, the PCA yielded 2 homogeneous groups of patients in terms of dyssynchrony, the first comprising HFrEF-CRT(+) group and the second comprising HTN, HFrEF-QRS < 120 ms and HFpEF patients. The HFrEF-CRT(+) group strongly correlates with most echocardiographic indices of dyssynchrony (Figure 3).

Discussion

The present data confirm that mechanical dyssynchrony is a key feature in patients with HFrEF and a wide QRS who are therefore candidates for CRT, whilst providing evidence that mechanical dyssynchrony in HFpEF does not significantly differ from that of patients with HTN or patients with HFrEF and a narrow QRS.

Recently, landmark studies have reported mechanical dyssynchrony in patients with HFpEF,¹⁶⁻¹⁸ hence suggesting a pathophysiological role of dyssynchrony and thereby room for CRT in HFpEF. At first glance the present findings differ from previous reports on mechanical dyssynchrony

Table II. Echocardiographic data of the study population

	HFpEF	HTN	HFrEF-QRS <120 ms	HFrEF-CRT(+)	P	HFpEF vs HTN	HFpEF vs HFrEF-QRS <120 ms	HFpEF vs HFrEF-CRT(+)
LV ejection fraction (%)	63 ± 9	69 ± 9	30 ± 7	25 ± 4	<.001	<0.001	<0.001	<0.001
Global longitudinal strain (%)	-17 ± 3	-19 ± 3	-9 ± 4	-7 ± 3	<.001	<0.001	<0.001	<0.001
LV end-diastolic diameter (mm)	47 ± 7	47 ± 6	64 ± 8	69 ± 8	<.001	0.64	<0.001	<0.001
LV end-systolic diameter (mm)	33 ± 8	33 ± 8	54 ± 9	59 ± 9	<.001	0.846	<0.001	<0.001
LV mass index (g/m ²)	92 ± 33	83 ± 19	143 ± 37	172 ± 49	<.001	0.273	<0.001	<0.001
LV end-diastolic volume index (mL/m ²)	43 ± 13	39 ± 9	121 ± 31	143 ± 33	<.001	0.466	<0.001	<0.001
LV end-systolic volume index (mL/m ²)	16 ± 7	12 ± 5	86 ± 27	108 ± 28	<.001	0.372	<0.001	<0.001
Cardiac output index (L/m ²)	3.2 ± 0.9	3.2 ± 0.8	2.3 ± 0.9	2.4 ± 0.7	<.001	0.961	<0.001	<0.001
Left atrial volume index (mL/m ²)	33 ± 10	23 ± 7	33 ± 12	41 ± 14	<.001	<0.001	0.83	0.002
E-wave deceleration time (ms)	218 ± 67	245 ± 85	171 ± 65	181 ± 81	<.001	0.102	0.006	0.031
E/A	1.1 ± 0.7	0.8 ± 0.3	1.6 ± 1.1	1.3 ± 0.9	.010	0.136	0.009	0.318
E/E'	16 ± 6	7 ± 3	13 ± 6	15 ± 7	<.001	<0.001	0.026	0.297
RV S-wave (cm)	12 ± 3	13 ± 3	10 ± 4	10 ± 4	<.001	0.105	0.061	0.003

Abbreviations: LV, left ventricle. RV, right ventricle.

Table III. Mechanical dyssynchrony data of the study population

	HFpEF	HTN	HFrEF-QRS < 120 ms	HFrEF-CRT(+)	P	HFpEF vs HTN	HFpEF vs HFrEF-QRS < 120 ms	HFpEF vs HFrEF-CRT(+)	
Atrio-ventricular dyssynchrony	LVFT/RR <40% (n, %)	6 (15)	4 (10)	8 (20)	22 (57.5)	<.001	0.737	0.77	<0.001
	LPEI (ms)	89 ± 19	83 ± 21	125 ± 28	169 ± 31	<.001	0.319	<0.001	<0.001
Inter-ventricular dyssynchrony	LPEI >140 ms (n, %)	0 (0)	2 (5)	10 (25)	32 (82)	<.001	0.494	0.001	<0.001
	IVMD (ms)	-9 ± 21	1 ± 21	11 ± 22	46 ± 28	<.001	0.080	<0.001	<0.001
	IVMD >40 ms (n, %)	0 (0)	2 (5)	4 (10)	24 (60)	<.001	0.494	0.116	<0.001
Intra-ventricular dyssynchrony	Ts lateral-septal (ms)	69 ± 53	48 ± 44	65 ± 36	66 ± 40	.235	0.033	0.623	0.718
	Ts-SD (ms)	55 ± 24	47 ± 21	51 ± 27	54 ± 22	.434	0.108	0.485	0.742
	BSBL (ms)	18 ± 110	-2 ± 98	21 ± 88	116 ± 186	.025	0.491	0.92	0.00078
	Sdrl2d (ms)	62 ± 21	54 ± 15	72 ± 34	115 ± 51	<.001	0.231	0.219	<0.001
Septal flash (n, %)	1 (3)	2 (5)	3 (8)	31 (80)	<.001	1	0.358	<0.001	
Longitudinal LBBB classical pattern (n, %)	3 (8)	2 (5)	9 (23)	32 (82)	<.001	1	0.066	<0.001	
Septal deformation pattern 1 or 2 (n, %)	0 (0)	0 (0)	4 (10)	26 (65)	<.001	NA	0.116	<0.001	

Abbreviations of indices of dyssynchrony are detailed within the text in the methods section.

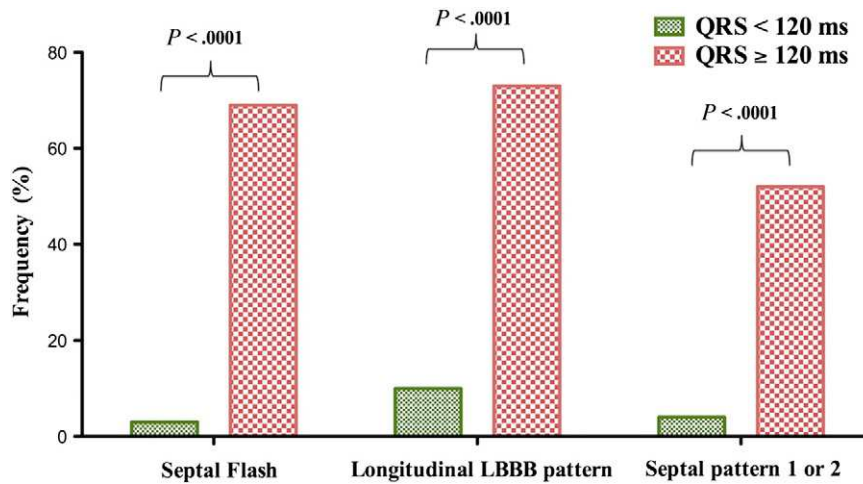
in HFpEF.^{16,19,22} Yu et al, measured time standard deviation of tissue Doppler peak myocardial systolic velocity (Ts-SD) to assess systolic asynchrony in 92 HFpEF patients, 281 HFrEF patients and 100 healthy volunteers.²⁰ The Ts-SD was significantly prolonged in both the HFrEF and HFpEF groups when compared with the healthy volunteers but was more severely prolonged in HFrEF than in HFpEF. Using 2D speckle tracking as standard deviation of time to peak longitudinal systolic strain in 12 ventricular segments, Santos and coworkers found greater systolic dyssynchrony in 130 HFpEF patients compared to 40 healthy controls.¹⁸ In contrast and similar to our findings, Lee and coworkers using TDI did not find any difference in systolic dyssynchrony between patients with HFpEF and hypertensive patients with LV hypertrophy.²¹

In the design of this study, attention was sought to study ambulatory stable patients with a definite diagnosis of HFpEF. Global longitudinal strain, left atrial volume index, and E/e' ratios were greater in our HFpEF patients than in our hypertensive patients who served as relevant

controls. In contrast to the present study, controls were age matched to normotensive healthy subjects in Yu's and Santos's study.^{18,20} Lee et al compared HFpEF patients with both HTN patients and normal controls.²¹

CRT is currently recommended in New York Heart Association II-IV patients with HFrEF and prolonged QRS duration. The presence of a LBBB is a strong predictor of outcome in most reports including the long-term follow-up of the MADIT-CRT.^{23,24} Conversely a recent report has demonstrated the detrimental effect of CRT in patients with HFrEF and narrow QRS.²⁵ We reported that besides a septal flash from M-mode and 2D strain derived LBBB pattern, a LV septal deformation pattern 1 or 2 has a high positive predictive value for predicting reverse remodeling and outcome in patients with wide QRS receiving CRT.^{8,15} These indices of dyssynchrony (septal flash, classical LBB pattern, septal pattern 1 or 2) amenable to CRT were consistently found in patients with increased QRS duration and very rare in patients with HFrEF and QRS <120 ms. Hence, these indices of dyssynchrony are

Figure 2



Proportion of patients with a septal flash, a longitudinal LBBB classical pattern and a septal deformation pattern 1 or 2 according to QRS duration <120 or ≥120 ms.

harbingers of electrical dyssynchrony and significantly differed between patients with HFrEF and wide QRS from HFrEF patients with narrow QRS but also from patients with HFpEF.

Park et al demonstrated that ventricular loading conditions altered LV dyssynchrony in patients with non ischemic cardiomyopathy.²⁶ Therefore one expects to find an amount of increased dyssynchrony in HFpEF patients compared to hypertensive patients without heart failure. Despite having higher pre- and after-load conditions only the T's lateral-septal was found greater in patients with HFpEF than in hypertensive patients. Importantly the echocardiographic indices of dyssynchrony amenable to CRT were rare and similar between HFpEF and HTN patients, indicating their close relationship with electrical dyssynchrony but not with loading conditions.

The principal component analysis allows finding clusters in a set of data from multiple groups. It is worthy to note that this analysis does not depend on any variable outcome but relies on the dependence of variables in the dataset. Indices of dyssynchrony amenable to CRT were strongly correlated and represented within the same component, indicating that they convey the same information. Hence, this component allowed for identifying 2 groups of patients other than the 4 initial groups, HFrEF-CRT (+) patients and others (HFpEF, HFrEF-QRS <120 ms and HTN patients), hence demonstrating that HFpEF patients are similar in terms of dyssynchrony to HTN and HFrEF-QRS <120 ms patients and are very different from HFrEF-CRT (+) patients.

Clinical implications

The amount of mechanical dyssynchrony in patients with HFpEF does not significantly differ from hyperten-

sive patients without signs or symptoms of heart failure and from patients with HFrEF and narrow QRS. Our results do not support the use of CRT in HFpEF patients; this has to be tested in future randomized trials. The small subset of patients with HFpEF and LBBB should be specifically evaluated in prospective multicenter studies.

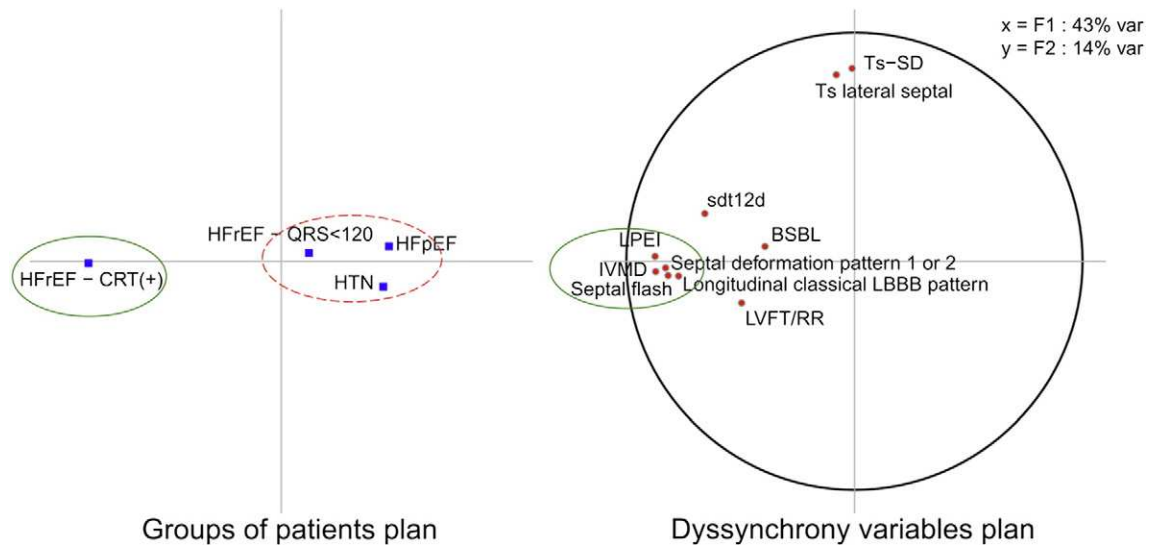
Study limitations

The study population was small in size. Of note in spite of the small size of our HFpEF group the proportion of patients with wide QRS (15%) was similar to that of Yu's (11%),¹⁶ Santos's (13%)¹⁸ or Lee's (15%)²¹ studies. In addition, HFpEF patients were prospectively included and well characterized to avoid the enrollment of patients with specific causes of HF other than HFpEF. Clinical and echocardiographic outcome after CRT cannot be evaluated in patients with HFNEF, HTN or HFrEF-QRS <120 ms from the present study. As CRT is aimed at specifically correcting systolic dyssynchrony diastolic dyssynchrony was not evaluated. The small subset of HFpEF patients with LBBB is likely to show increased mechanical dyssynchrony. Dyssynchrony was found dynamic during exercise or dobutamine challenge in HFpEF as well as in HFrEF.²¹ Only resting dyssynchrony was assessed in our series. The subset of patients with QRS width ≥120 ms and without CRT indication (LVEF between 0.35 and 0.50) was not studied as the group of patients with HFrEF and enlarged QRS was retrospectively built with patients receiving CRT according to current guidelines (LVEF ≤0.35).⁹

Conclusion

This study is the first to evaluate mechanical dyssynchrony amenable to CRT in patients with HFpEF. Patients

Figure 3



Graphical representation of correlation between groups, between groups and dyssynchrony variables and between dyssynchrony variables with a PCA. The following graph shows the correlations of the original variables with the principal components. More point is close to the circle the better the quality of representation. Two close points are positively correlated. We can thus find groups of variables that provide the same information. Here, x (abscise = main component 1) represents 43% of variance and y (main component 2) represents 14% of variance. The 3 groups “HFrEF-QRS <120 ms”, “HTN” and “HFpEF” (red circle) are opposite (no correlation) from “HFrEF-CRT(+)” and from the group of most dyssynchrony variables (green circles).

with HFpEF are similar to HTN or HFrEF-QRS < 120 ms patients in terms of mechanical dyssynchrony and widely differ from HFrEF-CRT(+) patients. This data may raise concerns about the potential usefulness of CRT in HFpEF patients.

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Appendix

Exclusion criteria

Exclusion criteria were history of myocardial infarction, atrio-ventricular or sino-atrial conduction defects, atrial fibrillation or flutter, cardiac pacemaker, primary valvular disease, prosthetic heart valves, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, end-stage kidney disease, nephrotic syndrome, cor pulmonale or other causes of isolated right ventricular failure, liver cirrhosis, congenital heart diseases, high-output heart failure and patients with poor echocardiographic windows.

Clinical data

Significant coronary artery disease was defined as the presence of a luminal narrowing greater than 50% on coronary angiography. LBBB was defined as QRS duration greater than or equal to 120 ms, broad notched/slurred R in DI, aVL, V₆; absent q in DI, V₅, V₆; R-peak time >60 ms in V₆ and <60 ms in V₁-V₃.²⁷ Right bundle branch block (RBBB) was defined as QRS duration greater than or equal to 120 ms, rsr', rsR', or rSR' in leads V₁ or V₂, S wave of greater duration than R wave or greater than 40 ms in leads I and V₆ and normal R peak time in leads V₅ and V₆ but >50 ms in lead V₁.²⁷ Intraventricular conduction delay (IVCD) was defined by a QRS duration ≥ 120 ms with no criteria for RBBB or LBBB.²⁷

Echocardiographic methods

Three cardiac cycles were stored for each measurement and for subsequent off line analysis by one investigator blinded for the clinical status of the patient. The LV ejection fraction was measured using the Simpson biplane method. Septal wall, posterior wall thickness, and LV minor axis dimensions at end-diastolic and end-systolic, were obtained with the use of M-mode recordings obtained at a sweep speed of 100 mm/s. The LV mass was accordingly calculated using the American Society of Echocardiography corrected formula and indexed for body surface area.²⁸ Cardiac output was calculated as the product of the forward stroke volume (time-velocity integral * $\pi * D^2/4$, D being the diameter of the LV outflow tract) and heart rate. Pulsed-wave Doppler was performed in the apical

4-chamber view at end-expiration with a 3-mm sample volume to obtain mitral inflow velocities (E and A waves). Pulse-wave tissue Doppler imaging was sequentially performed to acquire lateral and septal mitral annular velocities (e' waves), and both velocities were averaged to calculate the E/e' ratio (which correlates reasonably well with LV end-diastolic pressure) as previously described. Left atrial diameter (LAD1) was measured at ventricular end-systole in the parasternal long-axis view using M-mode. Left atrial volume was calculated using the ellipse formula: $\pi/6 (LAD1 \times LAD2 \times LAD3)$, where LAD2 and LAD3 are measurements of the short axis and long axis, respectively, in the apical 4-chamber view, and was indexed to body surface area.

Apical chamber views were recorded at a frame rate between 55 and 90 frame per second (65±10 fps) and were used for strain analysis. Longitudinal strain values were computed after determining aortic valve opening and closure onset using Doppler recordings. Automatic tracking of the endocardial contour on an end-systolic frame was carefully verified and the region of interest was manually corrected to ensure optimal tracking and to cover the entire thickness of the LV myocardium. Color-coded TDI was also performed. For TDI data acquisition, color Doppler frame rates were minimally set at 150 fps; pulse repetition frequency was 1 KHz, resulting in aliasing velocities at 16 cm/s.

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4 Valeur pronostique du remodelage et de l'amélioration de la performance ventriculaire gauche après resynchronisation cardiaque.*

* Menet A, Guyomar Y, Ennezat P-V, Graux P, Castel AL, Delelis F, et al. Prognostic value of left ventricular reverse remodeling and performance improvement after cardiac resynchronization therapy: A prospective study. *Int J Cardiol.* 1 févr 2016;204:6-11.(96)

4.1 Introduction

Le TRC étant à la fois très efficace mais avec un taux de non répondeurs qui représentent 20 à 40 % des patients.(63) Etant donné le coût et les risques liés à l'intervention (jusqu'à 14% de complications)(64), l'identification des patients répondeurs et non répondeurs a considérablement attiré l'attention de la communauté des chercheurs. La réponse au TRC peut être évaluée en termes : 1/de réponse clinique, de qualité de vie ou bien 2/en termes de pronostic au long cours : mortalité toute cause, mortalité cardio-vasculaire, hospitalisation pour insuffisance cardiaque et transplantation cardiaque. Alors laquelle choisir ? Il est difficile de répondre à cette question, les études le démontrent bien puisqu'elles utilisent de multiples critères. La réponse au long cours mérite d'être prédite précocement afin de pouvoir adapter le traitement. Cette prédiction passe par l'utilisation de critères de substitution (appelés « surrogates »).

4.1.1 La réponse clinique : NYHA et qualité de vie

Si l'on considère la réponse clinique, le TRC diminue la classe NYHA de 3,06 à 2,1 à 90 jours post implantation dans l'étude CARE-HF.(46) En ce qui concerne la qualité de vie, l'étude COMPANION a montré une amélioration de 8,8% avec le TRC-P et 9,3% avec le TRC-D contre 3,7% avec le traitement médical seul.(47) On peut donc s'attendre avec le TRC à gagner 1 classe NYHA et 5 à 6% de qualité de vie. Ce critère est en lui-même très important et répond à un des objectifs majeurs du TRC.

Cependant il existe souvent une discordance entre le pronostic et la réponse clinique. Une bonne réponse clinique ne prédit pas forcément un bon pronostic et inversement. En outre, la réponse escomptée sera différente selon le type patient ; chez le sujet très âgé, la qualité de vie est priorisée

à la survie tandis que les deux sont recherchées chez un jeune patient. Pour faire un parallèle, à un extrême, les traitements palliatifs améliorent les symptômes sans améliorer la survie et à l'autre extrême, les chimiothérapies dans les cancers prolongent la vie mais donnent des effets secondaires et altèrent la qualité de vie. Si l'on donne le choix au patient, il pourra préférer l'amélioration des symptômes surtout s'il a une qualité de vie très altérée à cause des symptômes.

Pour le TRC, ce problème existe et a été soulevé par Yu et al qui ont retrouvé une amélioration similaire de la classe NYHA, de la qualité de vie et du test de marche de 6 minutes dans les deux groupes survivants et non survivants à distance d'un traitement par TRC.(97) Faut-il alors se baser sur la réponse clinique pour modifier ou arrêter un TRC ?

4.1.2 La réponse au long cours.

Elle représente un critère « dur » avec une très faible variabilité de jugement pour les hospitalisations pour insuffisance cardiaque et aucune variabilité de jugement pour la mortalité. D'autres critères pourraient être utilisés tels que les événements thromboemboliques, les troubles du rythme ventriculaires mais semblent moins pertinents. L'augmentation de contractilité, le remodelage ventriculaire sont des éléments assez intuitifs d'évaluation de l'efficacité du TRC chez un patient donné même si ces critères ne sont pas cliniques et n'ont pas d'intérêt mesurable par le patient lui-même.

4.1.3 Les critères de substitution

Un bon critère de substitution pour être utile en pratique clinique doit être reproductible, fiable, facilement accessible et facilement mesurable. Il doit être un vrai marqueur de la maladie et non la réflexion d'un facteur confondant. Enfin, le lien entre le critère de substitution et le vrai critère de jugement doit être validé de façon interne et externe.

Les critères de substitution testés dans le TRC sont nombreux : amélioration des volumes ventriculaire et de la fraction d'éjection VG, du pic de consommation d'oxygène (VO₂), du test de marche de 6 minutes, de paramètres hémodynamiques invasifs, ou de neurohormones.

Les paramètres hémodynamiques sont améliorés de manière certaine par le TRC cependant son caractère invasif et difficilement accessible fait qu'ils n'ont jamais été évalués dans leur caractère

prédictifs du pronostic au long cours. Le pic de consommation d'oxygène (VO₂) est amélioré par le TRC de 0,6 à 1,4 ml/kg/min mais les modifications temporelles de cette mesure en font un mauvais critère de substitution.(98) Pitzalis et al ont montré que le BNP était plus bas chez les patients qui présentent un remodelage VG en comparaison de ceux qui n'en présentent pas.(99) Il est également prédicteur de la mortalité au long dans une sous-étude de CARE-HF cours avec un HR de 5,7 pour le tertile le plus élevé par rapport au tertile le plus bas.(100) Cependant, un problème de variabilité de mesure inter-individuel le rend vulnérable en qualité de critère intermédiaire avec des variations chez le sujet sain de 92% pour le NT-proBNP à 168% pour le BNP(101) et de 35% chez le patient insuffisant cardiaque.(102) Le test de marche de 6 minutes a été beaucoup utilisé pour mesurer la réponse au TRC et a été amélioré dans 4 des 6 études randomisées sur le TRC avec une bonne corrélation avec les symptômes cliniques.(103) Il est également prédicteur de la mortalité cardiovasculaire après implantation d'un TRC avec un HR de 5,6, $p=0,026$ en analyse multivariée lorsqu'il est inférieur à 225m.(104)

4.1.4 Le remodelage cardiaque comme critère de substitution

Le remodelage cardiaque (ou dilatation du VG) est la voie d'évolution finale qui survient après un infarctus du myocarde, une surcharge en pression, une maladie inflammatoire du muscle, une myocardiopathie dilatée idiopathique ou une surcharge en volume.(105) Le remodelage cardiaque est prédicteur de la mortalité chez les patients insuffisants cardiaques.(106) Le remodelage cardiaque en volume est retrouvé avec les médicaments améliorant l'insuffisance cardiaque tels que les IEC(107), les bêtabloquants et les anti-aldostérone.(105)

Pour le TRC, de nombreuses études ont montré le remodelage cardiaque dès un mois(108) et maintenu à 24 mois(109). Ce remodelage disparaît après arrêt de la resynchronisation.(110) Il est prédicteur de la survie et des hospitalisations pour insuffisance cardiaque. Le cut-off initialement trouvé par Yu et al est de 9,5% d'amélioration de volume téléstolique du VG (VTSVG). (97) Il existe un lien linéaire entre l'amplitude du remodelage et le pronostic au long cours.(111) Toutes ces caractéristiques font du VTSVG un bon critère de substitution. Cependant sa capacité à prédire la mortalité avec un cut-off de 9,5% reste faible avec une sensibilité et une spécificité de 70%.(97) Par ailleurs la reproductibilité de la mesure du VTSVG est imparfaite avec une variabilité de mesure intra-observateur de 5.3 ml et inter-observateur de 7.4 ml.(112)

4.1.5 La performance myocardique comme critère de substitution

4.1.5.1 La FEVG

En ce qui concerne l'amélioration de FEVG utilisée comme critère de substitution, les résultats sont discordants. Dans l'étude CARE-HF, l'amélioration de la FEVG à 3 mois n'était pas prédictive du pronostic au long cours en analyse multivariée.(46) Dans l'étude TRUST-CRT comparant les prédicteurs du pronostic au long cours du TRC, les variations de FEVG n'étaient pas différentes entre les patients qui avaient eu un évènement cardiovasculaire grave et ceux qui n'en n'avaient pas eu.(113) D'autres auteurs tels que Yu et al. retrouvent la FEVG comme un paramètre prédictif de la mortalité au long cours.(97) La principale limite de cette mesure est toutefois sa reproductibilité notoirement mauvaise surtout chez les patients porteurs d'un trouble conducteur.

4.1.5.2 Le Strain myocardique

Les fibres du ventricule gauche ont une orientation en spirale, les fibres sous-endocardiques et sous-épicaudiques sont orientées de manière longitudinale et les fibres du milieu de la paroi sont orientées de manière circonférentielle. Il y a donc une contraction longitudinale qui ramène la base vers l'apex et une contraction circonférentielle durant la systole ventriculaire gauche. L'épaississement du myocarde résulte du raccourcissement longitudinal et circonférentiel. Il existe également un mouvement de « twist » lié à la rotation antihoraire de l'apex et de la rotation horaire de la base. Ces mouvements peuvent être quantifiés par le strain myocardique qui décrit la déformation myocardique.

Le strain longitudinal global (SLG) est la moyenne de la composante longitudinale du strain dans l'ensemble du myocarde, il peut être approximé en faisant la moyenne des strains segmentaires.

L'utilité clinique du SLG a été démontrée dans plusieurs champs de la clinique. Un nombre croissant d'études a démontré une valeur importante du SLG comme prédicteur de mortalité et d'évènements cardiaques.(114–117)Le SLG donne une information pronostique indépendante de la FEVG chez les patients ayant une dysfonction systolique du VG.(114) La combinaison du SLG et de l'index de contractilité des parois apporte une amélioration de la performance diagnostique dans la maladie coronaire.(118) L'altération du SLG est associée au pronostic chez les patients valvulaires tels que l'insuffisance mitrale organique (119) et le rétrécissement aortique sévère asymptomatique. (120) Le SLG identifie l'atteinte infra-clinique chez les patients ayant un diabète ou une cardiomyopathie.(121,122) Le SLG est un prédicteur précoce de l'atteinte cardiaque dans les chimiothérapies cardiotoxiques.(123)

La reproductibilité du SLG était excellente dans les études publiées avec un coefficient de variation entre 5 et 7% environ. Cette reproductibilité est moins bonne pour le strain circonférentiel et nettement moins bonne pour le strain radial.(124) Il existe cependant une variabilité significative entre les différents vendeurs sur les valeurs obtenues pour le SLG chez les cœurs sains ou pathologiques.(104,125–128) Cependant, cette variabilité lors d’une comparaison systématique entre 9 vendeurs reste modérée et inférieure à d’autres mesures échographiques. (129)

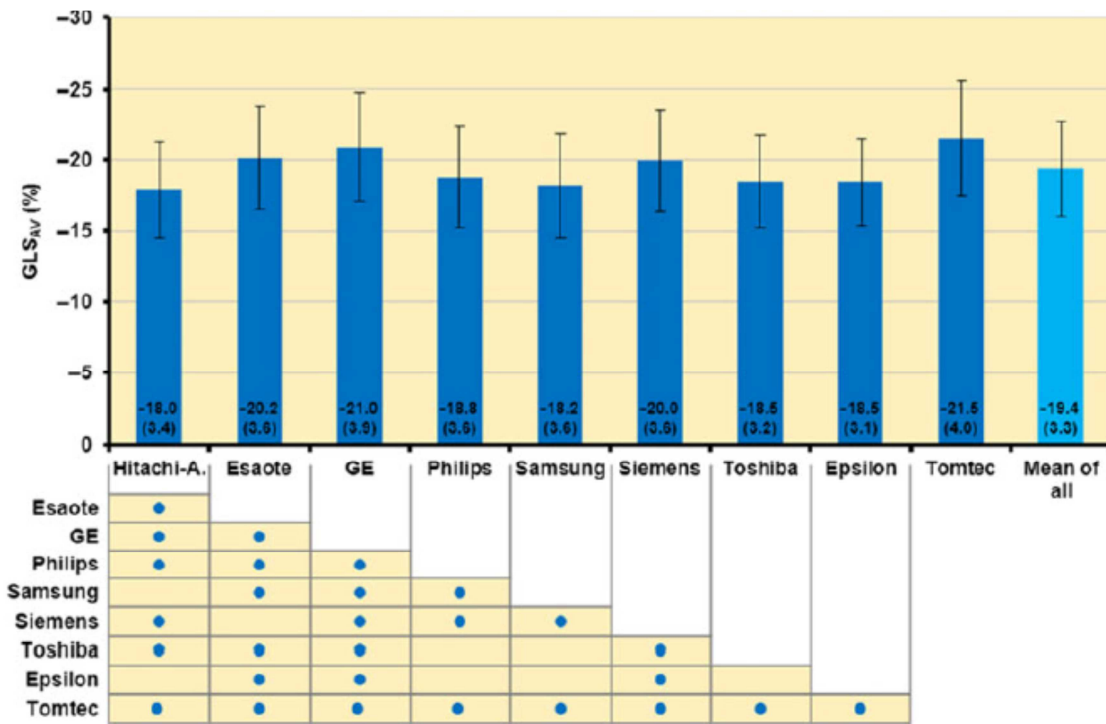


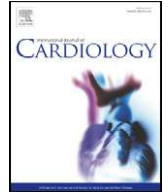
Figure 11. Moyenne (\pm déviation standard) du strain longitudinal global par vendeur. Cette étude a été réalisée chez des patients ayant une fonction ventriculaire gauche normale à très altérée. Comme le montre cette figure, il existe une différence significative entre la plupart des vendeurs, point bleu = $p < 0,05$.

Les variations absolues de SLG moyenné sur les 3 coupes variaient de 18.0% à 21.5 % tandis que la variabilité du SLG en apicale 4 cavités variait de 17.9 à 21.4%. La différence absolue entre les vendeurs pouvait monter à 3.7%. Les coefficients de variabilité inter-observateurs allaient de 5.4% à 8.4% pour le GLS moyenné sur les 3 coupes et de 6.2% à 11% pour le SLG en apical 4 cavités. Les coefficients de variabilité intra-observateurs allaient de 4.9% à 7.3% et 7.2 à 11.3%.(129) La reproductibilité était très variable en fonction des segments cardiaques étudiés avec des coefficients de variabilité allant de 7.6% à 49.2%.(127) Ces variations étaient inférieures à celles de la FEVG et de la plupart des paramètres conventionnels de mesure écho-cardiographique.

Le SLG semble donc être légitimement un bon paramètre à évaluer dans son apport pronostic après resynchronisation cardiaque. Nous avons donc réalisé une étude de validation de ce paramètre en comparaison à la FEVG et au volume ventriculaire gauche sur notre cohorte de patients.

4.2 Résultats

L'étude a été réalisée sur une cohorte de 170 patients avec un suivi de 32 mois. 20 patients sont morts et 27 ont été hospitalisés pour insuffisance cardiaque. Les trois paramètres étudiés : variation de volume télésystolique du VG (Δ VTSVG), variation de FEVG (Δ FEVG) et variation de SLG (Δ SLG) évalué à 9 mois de l'implantation du TRC étaient associés à la mortalité toute cause, à la mortalité cardiovasculaire et aux hospitalisations pour insuffisance cardiaque en analyse univariée et multivariée. Des cut-off de Δ VTSVG \geq 15%, Δ FEVG \geq 10% et Δ SLG \geq 1% ont été identifiés comme étant les plus discriminants du décès et/ou de l'hospitalisation pour insuffisance cardiaque (respectivement, HR ajusté = 0.25 (0.12–0.51), $p < 0.001$, HR ajusté = 0.26 (0.13–0.54), $p < 0.001$ et HR ajusté = 0.38 (0.19–0.75), $p = 0.006$). La performance des modèles multivariés était meilleure en utilisant le Δ VTSVG ou le Δ FEVG que pour le Δ SLG. La concordance inter-juge était excellente pour le Δ VTSVG (Coefficient de corrélation intra-classe (CCI) 0,91) et pour le Δ SLG (CCI 0,90) mais modeste pour le Δ FEVG (CCI 0,76) sur un échantillon de 20 patients. Le Δ VTSVG est donc un prédicteur reproductible et robuste du pronostic au long cours après le TRC. Il est supérieur au Δ FEVG de par sa meilleure reproductibilité et au Δ SLG de par sa meilleure discrimination. Néanmoins, l'échographie reste une approche multiparamétrique et ces 3 paramètres sont utiles en pratique clinique.



Prognostic value of left ventricular reverse remodeling and performance improvement after cardiac resynchronization therapy: A prospective study



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ABSTRACT

Background: The present study was designed to evaluate the respective value of left ventricular (LV) reverse remodeling (changes in LV end-systolic volume relative to baseline (Δ LVESV)) or LV performance improvement (Δ LV ejection fraction (Δ LVEF) or Δ Global longitudinal strain (GLS)) to predict long-term outcome in a prospective cohort of consecutive patients receiving routine cardiac resynchronization therapy (CRT).

Methods: One hundred and seventy heart failure patients (NYHA classes II–IV, LVEF \leq 35%, QRS width \geq 120 ms) underwent echocardiography before and 9 months after CRT. The relationships between Δ LVESV, Δ LVEF, Δ GLS and outcome (all-cause mortality and/or CHF hospitalization, overall mortality, cardiovascular mortality, CHF hospitalization) were investigated.

Results: During a median follow-up of 32 months, 20 patients died and 27 were hospitalized for heart failure. Δ LVESV, Δ LVEF or Δ GLS were significantly associated with all-cause mortality or CHF hospitalization (adjusted hazard's ratio (HR) per standard deviation 0.58 (0.43–0.77), 0.39 (0.27–0.57) or 0.55 (0.37–0.83) respectively, all $p < 0.01$) and all other endpoints (all $p < 0.01$). Patients with Δ LVESV \geq 15%, Δ LVEF \geq 10% and Δ GLS \geq 1% had a reduced risk of mortality or CHF hospitalization (adjusted HR = 0.25 (0.12–0.51), $p < 0.001$, adjusted HR = 0.26 (0.13–0.54), $p < 0.001$ and adjusted HR 0.38 (0.19–0.75), $p = 0.006$ respectively). Overall performance of multivariate models was better using Δ LVESV or Δ LVEF compared with Δ GLS. Interobserver agreement was excellent for Δ LVESV (Intraclass correlation coefficient – ICC-0.91) and Δ GLS (ICC 0.90) but modest for Δ LVEF (ICC 0.76) in a sample of 20 patients from the study population.

Conclusions: LV reverse remodeling assessed by Δ LVESV is a strong and reproducible predictor of outcome following CRT. Compared with Δ LVESV, Δ LVEF and Δ GLS have important shortcomings: poorer reproducibility or lower predictive value.

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1. Introduction

Cardiac resynchronization therapy (CRT) is currently recommended to improve symptoms, and prognosis in patients with moderate-to-severe heart failure, left ventricle (LV) systolic dysfunction and prolonged QRS duration [1]. Identification of 'responders' and 'non-

responders' to CRT has attracted considerable attention as 20 to 40% of patients fail to respond to CRT [2]. The CRT response can be measured in terms of clinical outcome or alternatively, in terms of LV response. Numerous studies have shown a significant reduction in left ventricle end-systolic volume (LVESV) after CRT [3–5] which translated consistently into a more favorable outcome [3,6]. Although mechanically attractive, the relationship between LV performance improvement assessed by changes in LV ejection fraction (LVEF) and outcome in heart failure remains a matter of debate [7], with studies reporting conflicting results in patients receiving CRT [8–10]. Lastly, one report from a post hoc analysis of the randomized control MADIT-CRT trial suggested that LV performance improvement as assessed by changes in speckle tracking-derived global longitudinal strain (GLS) may be powerfully

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linked to an improved outcome on top of changes in LVESV and LVEF [11]. Accordingly, the present study was designed to evaluate the respective prognostic value of each of these parameters (changes (Δ) in LVESV, LVEF and GLS) in a prospective cohort of patients receiving CRT according to current guidelines in the context of routine clinical practice.

2. Methods

2.1. Study population

The cohort included ambulatory patients with stable heart failure with indication for CRT according to the European Society of Cardiology guidelines consecutively referred to the Saint Philibert Catholic University Hospital for CRT implantation. Briefly, CRT was considered for patients whose LVEF was $\leq 35\%$ who remained in New York Heart Association (NYHA) classes II, III and ambulatory IV despite optimal medical treatment and QRS duration ≥ 120 ms in case of left bundle branch block (LBBB) morphology or with QRS duration ≥ 150 ms in case of a non-LBBB morphology, as recommended by current guidelines [1].

Exclusion criteria were (1) myocardial infarction, acute coronary syndrome, or coronary revascularization during the previous 3 months; (2) primary mitral or aortic valvular disease; (3) uncontrolled rapid atrial fibrillation; and (4) poor echocardiographic window. The study was approved by the Lille Catholic University ethics committee for non-interventional research. Informed consent was obtained for all patients.

2.2. Echocardiography

Echocardiography was performed the day before CRT implantation and at nine-month follow-up. All exams were performed on a GE Vivid E9 ultrasound system with a M5S probe (GE Healthcare, Velizy, France) by experienced echocardiographers. All echocardiographic data were stored on a PACS. All measurements were off-line performed on a dedicated EchoPAC workstation equipped with the BT12 version (GE Medical Systems). Three cardiac cycles were stored for each measurement for subsequent off-line analysis by one investigator blinded for the clinical status of the patient. LVEF was obtained by Simpson biplan method. LVESV was obtained by contouring LV end systolic volume in two orthogonal plans. All standard echocardiographic data were obtained according to current ASE/EACVI recommendations for performance of echocardiography [12].

Apical chamber views recorded at a frame rate between 55 and 90 frames per second (65 ± 10 fps) were used for strain analysis. Longitudinal strain values were computed after determining aortic valve opening and closure onset using Doppler recordings. Automatic tracking of the endocardial contour on an end-systolic frame was carefully verified and the region of interest was manually corrected to ensure optimal tracking and to cover the entire thickness of the LV myocardium. GLS was the average of segmental peak systolic longitudinal strains from the three apical views.

Δ LVEF and Δ GLS were defined as the differences between baseline and nine-month follow-up values. Δ LVESV was defined as the extent of reduction in LVESV between baseline and nine-month follow-up relative to baseline LVESV.

Interobserver variability of Δ LVESV, Δ LVEF and Δ GLS was tested in a randomly selected set of 20 patients from the study population.

2.3. Clinical data

Clinical data included age, sex, documented history of hypertension, hypercholesterolemia (patients on cholesterol-lowering medication or with a low-density lipoprotein cholesterol concentration greater than 160 mg/dL in the absence of treatment), diabetes mellitus (fasting blood glucose greater than 126 mg/dL on two occasions or patients currently receiving an oral hypoglycemic medication or insulin). Body mass index was calculated as weight in kilogram divided by height in meter square. Significant coronary artery disease was defined as the presence of a luminal narrowing greater than 50% on coronary angiography.

Patients received maximum tolerated doses of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and spironolactone, as recommended by current guidelines. Blood was sampled in the supine position for serum creatinine on the day before CRT device implantation.

2.4. CRT device implantation

Boston Scientific (Natick, MA), Medtronic (Minneapolis, MN), St. Jude (St Paul, MN), Sorin (Milan, Italy), and Biotronik (Berlin, Germany) CRT devices were implanted by electrophysiologists targeting a basal lateral, antero-lateral or postero-lateral coronary sinus vein for LV lead positioning. To promote biventricular pacing, CRT devices were commonly programmed with short atrioventricular delays. Interventricular timing was set to zero. Other parameters were set to nominal values or at the clinician's discretion. Using pulsed Doppler mitral inflow, the atrioventricular delay was selected before hospital discharge to allow adequate E-wave and A-wave separation and termination of the A-wave before mitral valve closure.

2.5. Outcomes

During follow-up, patients were monitored by their personal physicians. Events were ascertained by clinical interviews and/or by phone calls to physicians, patients, and (if necessary) next of kin. The endpoint of the study was all-cause mortality and/or congestive heart failure (CHF) hospitalization. Follow-up was complete in 100% of cases.

2.6. Statistical analysis

Quantitative data are presented as mean \pm standard deviation or median [25–75th]. Qualitative data are presented as absolute numbers and percentages. Student paired t-test was performed for paired continuous variables.

For the sake of clarity, Δ GLS has been converted in absolute value in all presented analyses [13]. As a consequence, Δ GLS ("improvement in GLS") positively correlates with improvement in LV systolic function in the present report.

The mean duration of follow-up was computed using the reverse Kaplan–Meier method. Univariate Cox regression survival analysis was used to identify the relationship between Δ LVESV, Δ LVEF and Δ GLS and occurrence of events during follow-up. We used a time-to-first-event approach for composite criteria. Cox regression multivariable survival analysis was thus performed; we did not use model building techniques, and entered covariates that were considered of potential prognostic impact on an epidemiological basis in the models. These covariates were: QRS width, NYHA III or IV, age, coronary artery disease, creatinine serum levels and baseline LVEF (%). The proportional hazards assumption was confirmed using statistics and graphs on the basis of Schoenfeld residuals. Cut-off values for Δ LVESV and Δ LVEF were based on cut-offs from previous published reports [14,15]. In the absence of previously published cut-offs for Δ GLS, the cut-off value was chosen as the value minimizing the Bayesian Information Criteria (BIC) in Cox regression analysis. Univariate survival curves using these categorical values were obtained using the Kaplan–Meier method. To allow comparison of Δ LVESV, Δ LVEF and Δ GLS used as continuous variables, all hazard ratios (HRs) of all Cox models were rescaled by the within-study standard deviation to represent a standardized change in the value of each parameter (either Δ LVESV, Δ LVEF and Δ GLS). Each model discrimination was assessed using Harrell's C statistics. Goodness of fit of Cox multivariate models was assessed by using the R^2 . Intraclass correlation coefficient (ICC) was obtained to assess interobserver agreement of Δ LVESV, Δ LVEF and Δ GLS. For all tests, a 2-tailed p-value of 0.05 or less was considered statistically significant. Statistical analysis was performed with R 3.0.3 (Youngstown, Ohio, USA).

3. Results

3.1. Clinical characteristics, EKG, biological and echocardiographic data

One hundred and eighty two patients were initially enrolled in the present study. However, 12 patients died before the nine-month echocardiography examination. The final study population consisted in 170 patients (mean age 70 ± 11 years, 71% male) with heart failure due to LV systolic dysfunction (mean LVEF $26 \pm 5\%$, mean GLS $-8.0 \pm 2.8\%$) who received CRT (CRT-P 13%, CRT-D 87%). Clinical characteristics, ECG, biological and echocardiographic data are summarized in Table 1. Fifty percent of the patients were in NYHA functional class III or IV. Mean QRS width was 162 ± 26 ms, 74% of patients had QRS width of ≥ 150 ms and 81% had a LBBB. Mean values of LVESV, LVEF and GLS at baseline and 9 months of follow-up are detailed in Table 2. Among the 3060 myocardial segments studied at baseline, longitudinal strain analysis was feasible in 3001 (98%). Similarly, among the 3060 myocardial segments studied at nine-month follow-up, longitudinal strain analysis was feasible in 3002 (98%). Δ GLS poorly correlated with Δ LVEF ($r = 0.45$, $p < 0.001$) and Δ LVESV ($r = 0.48$, $p < 0.001$). In contrast Δ LVEF strongly correlated with Δ LVESV ($r = 0.80$, $p < 0.001$). Mean NYHA functional class decreased from baseline to 9-month follow-up from 2.5 ± 0.6 to 1.9 ± 0.7 ($p < 0.0001$) in the overall study population. Among patients in NYHA functional classes III–IV at baseline, 78% experienced an improvement in one or more NYHA functional class at 9-month follow up. Among patients in NYHA functional class II, 35% experienced an improvement in NYHA functional class at 9-month follow-up. At 9 month follow-up, median [25–75th] biventricular pacing rate was 99 [98;100] %. Seventy nine percent of the study patients achieved biventricular pacing of $>97\%$.

Table 1
Demographic, clinical, laboratory and echocardiography data of the study population. NYHA = New York Heart Association; LV = left ventricular; sPAP = systolic pulmonary artery pressure.

Demographic and clinical data	n = 170
Age (years)	70 ± 11
Male (n, %)	121 (71%)
Body mass index (kg/m ²)	28 ± 5.4
Diabetes mellitus (n, %)	50 (29%)
Hypertension (n, %)	71 (42%)
Hypercholesterolemia (n, %)	68 (40%)
Coronary artery disease (n, %)	66 (39%)
Atrial fibrillation (n, %)	32 (19%)
NYHA III or IV (n, %)	85 (50%)
Heart rate (b.p.m.)	72 ± 13
Systolic blood pressure (mm Hg)	124 ± 21
Diastolic blood pressure (mm Hg)	70 ± 12
QRS width (ms)	162 ± 26
Left bundle branch block (n, %)	138 (81%)
Laboratory data	
Serum creatinine (mg/dL)	13 ± 6
Echocardiography data	
LV ejection fraction (%)	26 ± 5
Global longitudinal strain (%)	−8.0 ± 2.8
LV end-diastolic diameter (mm)	67 ± 8
LV end-diastolic volume (mL)	250 ± 68
Indexed cardiac output (L/min/m ²)	2.4 ± 0.8
E/Ea	13 ± 5.5
Indexed left atrial volume (mL/m ²)	40 ± 13
Tricuspid annular plane systolic excursion (TAPSE) (mm)	20 ± 5
sPAP (mm Hg)	37 ± 14

3.2. Outcome

During a median follow-up of 32 months, 20 patients died (13 with-out preceding heart failure) and 27 patients were hospitalized for heart failure. At one, two and three years, survival free from death and/or CHF hospitalization was 91 ± 4%, 83 ± 6% and 69 ± 9% respectively. Eleven patients died from cardiovascular causes.

3.3. Prognostic value of Δ LVESV

LVESV decreased in average from 186 ± 58 to 127 ± 69 mL, $p < 0.001$ (Table 2). Mean Δ LVESV were lower in patients who experienced all-cause mortality or CHF hospitalization than in those who did not (Table 3). As shown in Table 4, by Cox univariate analysis, Δ LVESV was associated with reduced all-cause mortality or CHF hospitalization (HR = 0.57 (0.45–0.72), $p < 0.001$). After adjustment, Δ LVESV remained significantly associated with all-cause mortality or CHF hospitalization (adjusted HR = 0.58 (0.43–0.77), $p < 0.001$). Kaplan–Meier event free survival according to a relative reduction of LVESV at $\geq 15\%$ vs $< 15\%$ is represented in Fig. 1. Patients with a relative reduction of LVESV at $\geq 15\%$ had a better outcome than those with a relative reduction of LVESV at $< 15\%$ (HR = 0.20 (0.10–0.37), $p < 0.001$, adjusted HR = 0.25 (0.12–0.51), $p < 0.001$).

As shown in Supplementary Tables 1, 2 and 3, Δ LVESV was also associated with reduced all-cause mortality (HR = 0.58(0.40–0.84), $p = 0.004$), cardiovascular death (HR = 0.44 (0.28–0.68), $p < 0.001$) and

Table 2
Left ventricular (LV) reverse remodeling and functional indices at baseline, follow-up and their absolute changes (mean ± standard deviation).

	Baseline	Follow-up	Changes (Δ)	p-Value
Global longitudinal strain (%)	−8.0 ± 2.8	−9.9 ± 4.0	1.9 ± 3.5	<0.001
LV end-systolic volume (mL)	186 ± 58	127 ± 69	59 ± 53	<0.001
LV ejection fraction (%)	26 ± 5	39 ± 12	13 ± 11	<0.001

CHF hospitalization (HR = 0.52 (0.40–0.68), $p < 0.001$). After adjustment, Δ LVESV remained significantly associated with reduced all-cause mortality (adjusted HR = 0.59 (0.37–0.92), $p = 0.022$), cardiovascular death (adjusted HR = 0.42 (0.23–0.75), $p = 0.003$) and CHF hospitalization (adjusted HR = 0.54 (0.39–0.77), $p < 0.001$). A relative reduction of LVESV at $\geq 15\%$ was accordingly associated with reduced all-cause mortality (adjusted HR = 0.31 (0.12–0.83), $p = 0.019$), cardiovascular death (adjusted HR = 0.14 (0.03–0.61), $p = 0.008$) and CHF hospitalization (adjusted HR = 0.18 (0.07–0.45), $p < 0.001$).

3.4. Prognostic value of Δ LVEF

LVEF increased in average from 26 ± 5% to 39 ± 12%, $p < 0.001$ (Table 2). Mean Δ LVEF was lower in patients who experienced all-cause mortality or CHF hospitalization than in those who did not (Table 3). As shown in Table 4, by Cox univariate analysis, Δ LVEF was associated with reduced all-cause mortality or CHF hospitalization (HR = 0.42 (0.30–0.60), $p < 0.001$). After adjustment, Δ LVEF remained significantly associated with all-cause mortality or CHF hospitalization (adjusted HR = 0.39 (0.27–0.57), $p < 0.001$). Kaplan–Meier event free survival according to an increase in LVEF at $\geq 10\%$ vs $< 10\%$ is represented in Fig. 2. Patients with an increase in LVEF at $\geq 10\%$ had a better outcome than those with an increase in LVEF at $< 10\%$ (HR = 0.35 (0.18–0.66), $p < 0.001$, adjusted HR = 0.26 (0.13–0.54), $p < 0.001$).

As shown in Supplementary Tables 1, 2 and 3, by Cox univariate analysis, Δ LVEF was also associated with reduced all-cause mortality (HR = 0.40 (0.24–0.65), $p < 0.001$), cardiovascular death (HR = 0.19 (0.09–0.43), $p < 0.001$) and CHF hospitalization (HR = 0.38 (0.25–0.58), $p < 0.001$). After adjustment, Δ LVEF remained significantly associated with reduced all-cause mortality (adjusted HR = 0.33 (0.19–0.60), $p < 0.001$), cardiovascular mortality (adjusted HR = 0.13 (0.04–0.39), $p < 0.001$) and CHF hospitalization (adjusted HR = 0.38 (0.25–0.58), $p < 0.001$). An increase in LVEF at $\geq 10\%$ was not associated with reduced all-cause mortality (adjusted HR = 0.42 (0.15–1.16), $p = 0.095$), but was associated with reduced cardiovascular death (adjusted HR = 0.05 (0.01–0.48), $p = 0.009$) and with reduced CHF hospitalization (adjusted HR = 0.14 (0.05–0.39), $p < 0.001$).

3.5. Prognostic value of Δ GLS

As shown in Table 2, GLS improved in average from baseline to 9 months of follow-up from −8.0 ± 2.8% to −9.9 ± 4.0%, $p < 0.001$. Mean Δ GLS was lower in patients who experienced all-cause mortality or CHF hospitalization than in those who did not (Table 3). As shown in Table 4, by Cox univariate analysis, Δ GLS was positively associated with reduced all-cause mortality or CHF hospitalization (HR = 0.62 (0.43–0.88), $p = 0.007$). After adjustment, Δ GLS remained significantly associated with all-cause mortality or CHF hospitalization (adjusted HR = 0.55 (0.37–0.83), $p = 0.004$). Kaplan–Meier event free survival according to an improvement in GLS at $\geq 1\%$ vs $< 1\%$ is represented in Fig. 3. Patients with an improvement in GLS at $\geq 1\%$ had a better outcome than those with an improvement in GLS at $< 1\%$ (HR = 0.43 (0.23–0.82), $p = 0.011$, adjusted HR 0.38 (0.19–0.75), $p = 0.006$).

As shown in Supplementary Tables 1, 2 and 3, by Cox univariate analysis, Δ GLS was also associated with reduced all-cause mortality (HR = 0.51 (0.30–0.87), $p = 0.013$), cardiovascular death (HR = 0.37 (0.18–0.77), $p = 0.008$) and CHF hospitalization (HR = 0.58 (0.39–0.89), $p = 0.011$). After adjustment on QRS width, NYHA functional class III or IV, age, coronary artery disease, creatinine serum level and LVEF, Δ GLS remained significantly associated with reduced all-cause mortality (adjusted HR = 0.48 (0.25–0.91), $p = 0.025$), cardiovascular mortality (adjusted HR = 0.34 (0.14–0.81), $p = 0.015$) and CHF hospitalization (adjusted HR = 0.53 (0.33–0.83), $p = 0.006$). An improvement in GLS at $\geq 1\%$ was not associated with reduced all-cause mortality (adjusted HR = 0.42 (0.16–1.12), $p = 0.081$), but was

Table 3

Left ventricular (LV) reverse remodeling and functional indices according to the occurrence of clinical endpoints (mean \pm standard deviation). Δ LVESV = relative changes in left ventricular end-systolic volume; Δ LVEF = changes in left ventricular ejection fraction; Δ GLS = changes in global longitudinal strain; CHF = congestive heart failure.

Endpoints	Δ GLS	p-Value	Δ LVEF	p-Value	Δ LVESV	p-value
All-cause mortality and/or CHF hospitalization						
Event (n = 39)	0.6 \pm 2.6		6 \pm 10		16 \pm 23	
No event	2.3 \pm 3.6	0.002	15 \pm 10	<0.001	37 \pm 26	<0.001
All-cause mortality						
Event (n = 20)	0.2 \pm 2.5		5 \pm 11		17 \pm 26	
No event	2.2 \pm 3.5	0.003	14 \pm 10	0.004	34 \pm 27	0.012
Cardiovascular mortality						
Event (n = 11)	-0.6 \pm 2.5		-0.4 \pm 8		5 \pm 19	
No event	2.1 \pm 3.5	0.005	14 \pm 10	<0.001	34 \pm 26	<0.001
CHF hospitalization						
Event (n = 27)	0.4 \pm 2.9		5 \pm 10		11 \pm 20	
No event	2.2 \pm 3.5	0.006	14 \pm 10	<0.001	36 \pm 26	<0.001

associated with reduced cardiovascular death (adjusted HR = 0.16 (0.03–0.83), $p = 0.029$) and with reduced CHF hospitalization (adjusted HR = 0.32 (0.14–0.75), $p = 0.009$).

3.6. Comparison of the predictive value of Δ GLS, Δ LVESV and Δ LVEF

As shown in Table 4, the Harrel C statistics was lower in both univariate and Cox multivariate models (mortality and/or CHF hospitalization) including Δ GLS in the models as compared with Δ LVESV and Δ LVEF, hence indicating a poorer discrimination using Δ GLS as compared with Δ LVESV or Δ LVEF. Similar findings were obtained for all-cause mortality, cardiovascular mortality and CHF hospitalization (Supplementary Tables 1, 2 and 3). In addition, goodness of fit of the Cox multivariate models assessed by the R^2 was better in the multivariate models including Δ LVESV or Δ LVEF than in those including Δ GLS (Table 4 and Supplementary Tables 1, 2 and 3).

3.7. Reproducibility

Interobserver agreement was excellent for Δ GLS and Δ LVESV (ICC 0.90 and 0.91 respectively) but was modest for Δ LVEF (ICC 0.76).

4. Discussion

The present study is the first to the best of our knowledge to evaluate the respective prognostic value of Δ LVESV, Δ LVEF and Δ GLS in patients with heart failure and LV systolic dysfunction receiving CRT in the context of routine clinical practice. The present study reinforces the major importance of Δ LVESV as a strong and reproducible surrogate marker of outcome in CHF patients receiving CRT. Δ LVEF or Δ GLS emerged also as powerful predictors of outcome following CRT. However, the predictive value of Δ GLS was lower than that of Δ LVESV or Δ LVEF. In addition, the poor reproducibility of Δ LVEF is likely to be an issue.

Cardiac remodeling is the final common pathway of chamber dilatation and failure that occurs after myocardial infarction, pressure overload, inflammatory muscle disease, idiopathic dilated cardiomyopathy or volume overload [16]. Maladaptive remodeling, identified by a progressive increase in LV end-diastolic and end-systolic volume results in poor outcome in CHF patients [17]. Prevention and reversal of remodeling is an established therapeutic target in CHF patients. Besides angiotensin-converting enzyme inhibition and beta-adrenergic blockade [18,19], CRT is strongly indicated in patients with a reduced ejection fraction of $\leq 35\%$, and wide QRS complex to induce reverse remodeling and thereby improve outcome [20–22]. Nevertheless, 30 to 40% of patients fail to respond after CRT [3,6,23,24]. Yu and coworkers found lower long-term mortality and heart failure events in CRT patients with a reduction in LVESV of 9.5% or more [3]. The REVERSE study found a 68% long-term mortality reduction in the 183 patients with $\geq 15\%$ LVESV decrease at six-month follow-up [6]. Conversely the mortality was more than 4-fold higher in the 25% of the REVERSE patient cohort with further LV dilation despite CRT. Similarly in our cohort a LVESV reduction of $\geq 15\%$ translated into a better outcome.

The relationship between improvement in LV function and outcome in heart failure remains a matter of debate. In the MOCHA trial, carvedilol produced dose-related improvements in LV function and dose-related reductions in mortality and hospitalization rate [25]. In the randomized controlled CARE-HF trial, CRT mediated improvement in LVEF at 3 months was not associated with improved outcome in multivariate analysis [26]. In a recent report from the TRUST CRT trial comparing predictors of outcome in CRT, changes in LVEF were not significantly different between patients who experienced major adverse cardiac events during follow-up and those who did not [10]. In our study, CRT improved LVEF beyond beta-adrenergic blockade. Similar to the findings of the REVERSE study, a strong association was found between the magnitude of change in LVEF and long-term outcome with CRT in the present report. In Yu et al.'s report, survivors had a mean

Table 4

Cox regression univariate and multivariate analyses for the relationship between relative changes left ventricular end-systolic volume (Δ LVESV), changes in left ventricular ejection fraction (Δ LVEF), improvement in global longitudinal strain (Δ GLS) and all-cause mortality or congestive heart failure hospitalization. LV = left ventricle; HR = hazard ratio; SD = standard deviation; CI = confidence interval; NYHA = New York Heart Association.

Analysis	Increment	Δ LVESV		Δ LVEF		Δ GLS		
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	
Univariate	Δ GLS/ Δ LVEF/ Δ LVESV respectively	SD	0.57 (0.45–0.72)	<0.001	0.42 (0.30–0.60)	<0.001	0.62 (0.43–0.88)	0.007
	Discrimination (C stat de Harrell)		0.748		0.726		0.748	
Multivariate	Δ GLS/ Δ LVEF/ Δ LVESV respectively	SD	0.58 (0.43–0.77)	<0.001	0.39 (0.27–0.57)	<0.001	0.55 (0.37–0.83)	0.004
	QRS width	SD	0.98 (0.70–1.36)	0.897	0.91 (0.64–1.30)	0.610	0.80 (0.59–1.10)	0.178
	NYHA III or IV	Yes/No	1.67 (0.79–3.54)	0.181	1.83 (0.86–3.89)	0.115	1.93 (0.93–4.04)	0.079
	Age	SD	0.89 (0.60–1.31)	0.549	0.97 (0.66–1.43)	0.870	0.92 (0.63–1.35)	0.667
	Coronary artery disease	Yes/No	0.76 (0.36–1.62)	0.477	0.85 (0.41–1.76)	0.667	0.92 (0.44–1.93)	0.825
	Creatinine serum	SD	1.62 (1.29–2.03)	<0.001	1.61 (1.25–2.07)	<0.001	1.60 (1.28–2.00)	<0.001
	LV ejection fraction (%)	SD	0.57 (0.38–0.87)	0.009	0.48 (0.32–0.72)	<0.001	0.48 (0.32–0.73)	<0.001
	Discrimination (C stat de Harrell)		0.790		0.815		0.729	
	Goodness of fit (R^2)		0.205		0.262		0.196	

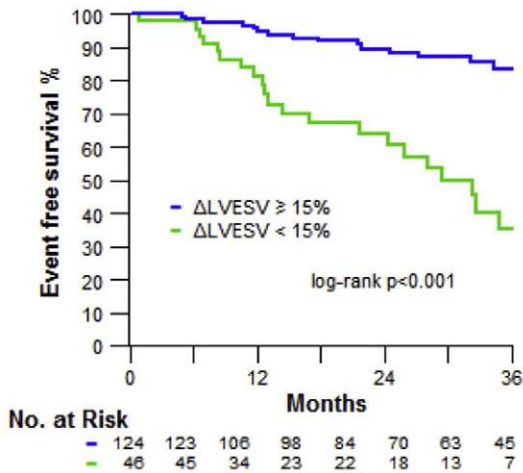


Fig. 1. Kaplan–Meier event – free survival (mortality or CHF hospitalization) according ΔLVESV ≥ 15 and < 15%.

increase in LVEF of 7% whereas non-survivors had only 2.8%. However the reproducibility of LVEF has been repeatedly questioned [27]. Consistently, the reproducibility of ΔLVEF was modest in the present report and was lower than the reproducibility of ΔLVESV. The recently developed 2-dimensional strain based on speckle tracking is an innovative method for assessing LV systolic function based on the assessment of GLS. GLS can be reliably obtained in 90 to 95% of cases [28]. The reproducibility of GLS has been shown to be excellent in most reports, with coefficients of variation of about 7% [29]. Importantly, similar to our findings the reproducibility of GLS has been shown to be higher than the reproducibility of LVEF [28]. In a recent report, interobserver variability of LVEF was greater than GLS (coefficients of variations (CV) at 9.1% versus 4.1%) [28]. In one report from a post hoc analysis of the randomized control MADIT-CRT trial, LV functional improvement as assessed by ΔGLS was powerfully linked to an improved outcome on top of ΔLVEF or CRT response assessed by ΔLVESV [11]. Despite the strong prognostic value of ΔGLS in the present report, the predictive value of ΔGLS was lower than ΔLVESV. Apart from differences in study population (100% of patients were in NYHA I–II functional class in Pouleur's report versus 50% in our study) and design (randomized versus consecutive patients) there are no obvious explanations for the divergent findings.

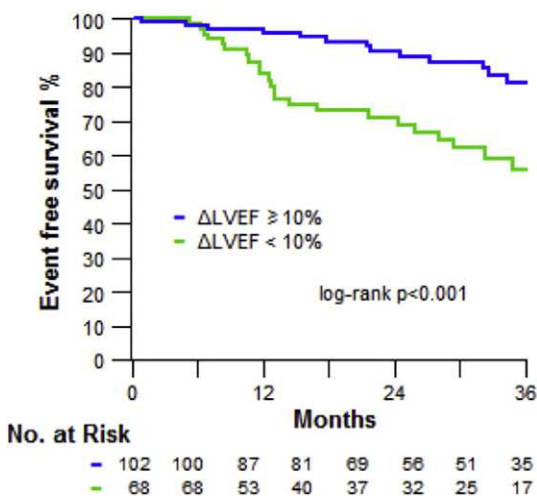


Fig. 2. Kaplan–Meier event – free survival (mortality or CHF hospitalization) according ΔLVEF ≥ 10 and < 10%.

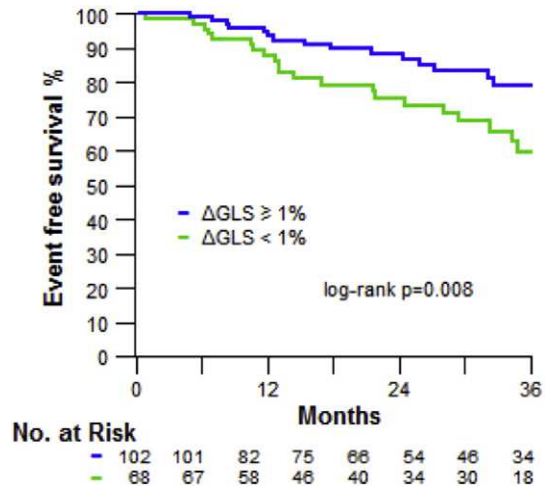


Fig. 3. Kaplan–Meier event – free survival (mortality or CHF hospitalization) according ΔGLS ≥ 1 and < 1%.

4.1. Limitations

Limitations of this study are inherent to observational studies. This prospective single-center study included a relatively small number of patients. However, clinical and echocardiographic data were prospectively collected with off-line analysis and the follow-up of patients was prospectively planned. Changes in plasma B type natriuretic levels might also have refined the prognostic assessment of these patients [30], but were not fully available. We acknowledge that multiple intricate factors influence changes in LVESV after a therapeutic intervention including changes in LV preload, afterload and contractility. Hence, changes in LVESV do not purely correlate with LV reverse remodeling. However, reductions in LVESV appear to be the most useful measure of reverse remodeling in clinical studies [3,31]. Although postimplantation optimization of atrial and ventricular stimulation by altering atrioventricular and interventricular pacing intervals is theoretically an advantageous process, CRT pacing settings were commonly not changed or adjusted during the time period of the study. Actually, three large multicenter trials (a frequent optimization study using the QuickOpt method [32]; SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy [33]; and adaptive CRT [34]) failed to show superiority of intracardiac electrographic optimization over nominal settings. Consistently, a recent meta-analysis of 12 trials comparing atrioventricular and/or interventricular delay optimization and conventional CRT device programming found that atrioventricular and/or interventricular delay optimization had a neutral effect on clinical and echocardiographic outcomes [35].

5. Conclusion

LV reverse remodeling assessed by ΔLVESV is a strong and reproducible predictor of outcome following CRT. Compared with ΔLVESV, ΔLVEF and ΔGLS have important shortcomings: poorer reproducibility or lower predictive value.

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Conflict of interest disclosures

The authors report no relationships that could be construed as a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2015.11.091>.

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5 Importance pronostique de l'élargissement du QRS post-opératoire immédiat chez les patients insuffisants cardiaques traités par resynchronisation cardiaque.*

* Menet A, Bardet-Bouchery H, Guyomar Y, Graux P, Delelis F, Castel A-L, et al. Prognostic importance of postoperative QRS widening in patients with heart failure receiving cardiac resynchronization therapy. *Heart Rhythm Off J Heart Rhythm Soc.* août 2016;13(8):1636-43. (130)

5.1 Introduction

Le primum movens de la désynchronisation cardiaque répondant au traitement par resynchronisation est un phénomène électrique : l'élargissement du QRS. Même si la physiologie (cf Figure 1 dans le chapitre Activation électrique normale) et certaines études telles que l'analyse au long cours de MADIT-CRT(6,7) retrouvent l'aspect du QRS (et notamment le BBG) comme un facteur prédictif de réponse au TRC, la méta-analyse des essais randomisés sur le TRC de Cleland et al.(8), nous rappellent que la largeur du QRS est capitale car elle est dans cette étude le seul paramètre prédictif en analyse multivariée de la réponse à la resynchronisation.

L'évolution de la largeur du QRS est donc légitimement un critère d'intérêt afin d'évaluer de manière précoce la réponse au traitement par resynchronisation. Il a été montré par Rickard et al. que l'élargissement du QRS après resynchronisation est associé à une détérioration de la fonction ventriculaire gauche (9) et son affinement à une amélioration du remodelage chez les patients ayant une stimulation ventriculaire droite permanente(131). Cependant, l'évolution de la largeur du QRS après resynchronisation n'a jamais été reliée au pronostic au long cours et notamment à la mortalité au long cours. Nous avons donc analysé notre cohorte de patients implantés d'un TRC pour répondre à cette question.

5.2 Résultats

Nous avons constitué une cohorte de 237 patients implantés d'un TRC pour insuffisance cardiaque à fraction d'éjection basse $\leq 35\%$, NYHA 2 à 4 et des QRS ≥ 120 ms. Nous avons analysé l'évolution de la largeur des QRS avant et immédiatement après implantation d'un TRC. La durée de suivi médiane de l'étude était de 24 mois, 39 patients sont décédés. 50 (21%) patients ont présenté un élargissement de leur QRS. L'élargissement des QRS était en moyenne de $13\% \pm 15$ dans le groupe

des QRS élargis et il était affiné en moyenne de $32\% \pm 19$ dans le groupe des QRS affinis. En analyse univariée et après ajustement sur les variables confondantes, cet élargissement était prédicteur de la mortalité toute cause (HR ajusté 2.67; IC à 95% 1.07–6.65; P = 0,035) et de la mortalité cardiovasculaire HR ajusté 3.63; IC 95% 1.13–11.65; P = 0,03). Les patients ayant élargis leurs QRS étaient moins souvent répondeurs au TRC sur l'ensemble des critères de remodelage et de performance myocardique (Δ VTSVG, Δ FEVG, Δ SLG). Cette étude met en évidence une association entre l'élargissement des QRS et la mortalité mais ne permet pas de conclure qu'il s'agit d'un objectif thérapeutique même si en pratique clinique, il s'agit du premier paramètre facilement accessible en salle de cathétérisme pour s'assurer de l'effectivité de la resynchronisation. Malgré l'aspect très intuitif de l'objectif thérapeutique « affinement du QRS » lors de la pose d'un TRC, c'est la première fois qu'une étude évalue son impact sur la mortalité au long cours. Cette étude repose néanmoins sur un nombre limité de patients et mériterait d'être confirmée par d'autres.

Prognostic importance of postoperative QRS widening in patients with heart failure receiving cardiac resynchronization therapy



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BACKGROUND Landmark reports have suggested that patients with QRS widening immediately after cardiac resynchronization therapy (CRT) experienced less frequently reverse left ventricular remodeling during follow-up.

OBJECTIVE We sought to investigate the relationship between postoperative QRS widening relative to baseline and mortality in a prospective cohort of heart failure patients receiving CRT.

METHODS A 12-lead electrocardiogram was recorded for 237 heart failure patients (New York Heart Association class II to IV, left ventricular ejection fraction $\leq 35\%$, and QRS width ≥ 120 ms) before and immediately after CRT device implantation. The relationships between QRS widening, all-cause and cardiovascular mortality, and echocardiographic response to CRT were studied.

RESULTS During a median follow-up of 24 months, 39 patients died. Fifty patients (21%) experienced QRS widening after CRT [QRS (+) group]. During follow-up, all-cause mortality was higher in QRS (+) patients than in QRS(−) patients (36-month survival free from

death $81\% \pm 7\%$ vs $64\% \pm 16\%$; log rank, $P = .029$). After adjustment for important prognostic confounders, QRS(+) patients remained associated with an excess overall mortality (adjusted hazard ratio [HR] 2.67; 95% confidence interval 1.07–6.65; $P = .035$) and cardiovascular mortality (adjusted hazard ratio 3.63; 95% confidence interval 1.13–11.65; $P = .03$). QRS(+) patients were less frequent responders to CRT than were QRS(−) patients (20 [47%] vs 136 [83%]; $P < .0001$).

CONCLUSION Postoperative QRS widening relative to baseline after CRT is associated with a considerable increased mortality risk during follow-up. Whether QRS narrowing should be achieved to optimize CRT placement, and thereby increase the rate of CRT responders and improve outcome, deserves further research.

KEYWORDS Cardiac resynchronization therapy; Heart failure; Outcome; QRS duration; Electrocardiogram

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Introduction

Cardiac resynchronization therapy (CRT) is currently recommended to improve symptoms, left ventricular (LV) function, and prognosis in patients with moderate to severe heart failure, LV systolic dysfunction, and prolonged QRS duration.¹ Prolonged QRS duration has been associated with LV mechanical dyssynchrony resulting in diminished LV systolic performance. CRT frequently induces QRS narrowing, with subsequent

improvement in cardiac function and heart failure symptoms. However, a number of patients have a postoperative paced QRS duration that is longer than the preoperative duration.^{2–4} This observation may in part explain why 20%–40% of patients fail to improve after CRT despite prolonged QRS duration at baseline.⁵ Consistently, previous reports have suggested that patients with QRS widening immediately after CRT experience less frequently an improvement in functional status and LV reverse remodeling during follow-up.^{2,3,4,6,7}

However, beyond long-term LV reverse remodeling and symptomatic improvement, the impact of QRS widening immediately after CRT device implantation on mortality has not been studied. Hence, we sought to investigate the

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relationship between postoperative QRS widening relative to baseline and mortality in a prospective cohort of patients with heart failure receiving CRT.

Methods

Study population

The present cohort consisted of ambulatory patients with heart failure referred to Hôpital Saint Philibert, Lomme, France, for CRT device implantation between 2011 and 2014. CRT was indicated for patients with LV ejection fraction (LVEF) $\leq 35\%$ who remained in New York Heart Association (NYHA) class II, III, and ambulatory IV despite optimal medical treatment and QRS duration ≥ 120 ms in the case of left bundle branch block (LBBB) morphology or with QRS duration ≥ 150 ms in the case of non-LBBB morphology.¹ Exclusion criteria were as follows: (1) myocardial infarction, acute coronary syndrome, or coronary revascularization during the previous 3 months; (2) primary mitral or aortic valve disease; and (3) uncontrolled rapid atrial fibrillation. Patients received maximally tolerated doses of β -blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and spironolactone, as recommended by current guidelines. Blood was sampled in the supine position for serum creatinine the day before CRT device implantation. B-type natriuretic peptide levels were obtained in a subset of the study population (Triage assay, Beckman, Villepinte, France). The study was approved by the Lille Catholic University ethics committee for non-interventional research. Informed consent was obtained at the time of enrollment from all patients.

CRT device implantation

Boston Scientific (Natick, MA), Medtronic (Minneapolis, MN), St. Jude Medical (St Paul, MN), Sorin (Milan, Italy), and Biotronik (Berlin, Germany) CRT devices were implanted by electrophysiologists targeting a basal lateral, anterolateral, or posterolateral coronary sinus vein for LV lead positioning. Interventricular timing was set at zero. A short-sensed atrioventricular (AV) delay (between 80 and 100 ms) and a paced delay (130 ms) were programmed to promote biventricular pacing. Attention was paid before hospital discharge to verify the absence of fusion or pseudofusion beats on the electrocardiogram (ECG) and continuous monitoring. In patients in ongoing atrial fibrillation, radiofrequency ablation of the AV node was performed if sufficient bradycardia was not obtained despite optimal medical treatment in order to obtain a high percentage of biventricular pacing. In the case of AV node ablation, devices were subsequently programmed in a VVIR mode with a paced heart rate of 70 beats/min.

ECG

Twelve-lead electrocardiography was performed the day before and the day after CRT device implantation. All measurements were performed off-line using millimeter paper by a single investigator (H.B.-B.) blinded to clinical

and outcome data. QRS duration before and after CRT device implantation was measured in the ECG derivation showing the wider QRS. Paced QRS duration was measured from the stimulation spike to the end of the QRS complex. Relative QRS widening ($\Delta\text{QRS}\%$) was the subtraction of the postoperative QRS duration and the preoperative QRS duration related to the preoperative QRS duration. Patients were classified into 2 groups: QRS(+) comprising those with $\Delta\text{QRS}\% > 0$ and QRS(-) comprising those with $\Delta\text{QRS}\% \leq 0$. The interobserver variability of the preoperative and the postoperative QRS duration was tested in a randomly selected set of 40 patients from the study population. Biventricular paced QRS morphology was defined as positive when there was a prominent R wave in lead V₁ (R/S ratio ≥ 1 in lead V₁) and/or a prominent S wave in lead I (R/S ratio ≤ 1 in lead I) on the postprocedural ECG.⁸

Postoperative Chest Radiography

Location of the LV lead was determined using postoperative anteroposterior and lateral chest radiography. The position of the LV lead tip was classified as posterior, lateral, anterolateral, or anterior along the longitudinal axis.⁹ Similarly, the position of the LV lead was categorized as apical and nonapical.⁹

Echocardiography

Echocardiography was performed the day before CRT device implantation and at 9-month follow-up by investigators blinded for the clinical status of the patient using the Vivid E9 ultrasound system (GE Healthcare, Velizy, France). Segments that displayed akinesis or dyskinesis in combination with a disproportionate local wall thinning and hyperreflectivity in comparison with adjacent contractile segments were scored as "scarred." Global longitudinal strain (GLS) was obtained from the 3 apical views¹⁰ change in LV end-systolic volume (ΔLVESV) was defined as the extent of reduction in LVESV between baseline and 9-month follow-up relative to baseline LVESV. Response to CRT was defined as $\Delta\text{LVESV} \geq 15\%$.¹¹⁻¹⁴ ΔLVEF and ΔGLS were defined as the differences between baseline and 9-month follow-up values. The interobserver reproducibilities of ΔLVESV , ΔLVEF , and ΔGLS after CRT in our echocardiography laboratory have been previously reported.¹⁴

Outcomes

During follow-up, patients were monitored by their personal physicians. Events were ascertained by clinical interviews and/or by phone calls to physicians, patients, and (if necessary) next of kin. The end point of the study was overall mortality. Cardiovascular mortality was considered if death was related to heart failure, myocardial infarction, arrhythmia, stroke, or sudden death.

Statistical analysis

Quantitative data are presented as mean \pm SD or median (interquartile range) and were compared using a 2-sided

Table 1 Demographic, clinical, and laboratory data in patients with and without QRS widening [QRS(+) and QRS(-)].

Parameter	Overall (n = 237)	QRS(+) (n = 50)	QRS(-) (n = 187)	P
Demographic and clinical data				
Age (y)	71 ± 11	71 ± 11	68 ± 12	.038
Sex: male	158 (66)	40 (80)	118 (63)	.037
Body mass index (kg/m ²)	28 ± 14	27 ± 4	28 ± 15	.856
Diabetes mellitus	67 (28)	13 (26)	53 (28)	.880
Hyperlipidemia	95 (40)	15 (31)	80 (43)	.167
Coronary artery disease	88 (37)	21 (42)	67 (36)	.524
β-Blockers	210 (89)	46 (92)	164 (88)	.600
ACE inhibitors/ARB	205 (88)	43 (88)	162 (88)	1.000
Atrial fibrillation	58 (25)	16 (32)	42 (23)	.243
NYHA class III or IV	121 (51)	23 (46)	98 (52)	.518
Heart rate (beats/min)	73 ± 14	72 ± 15	72 ± 14	.784
Systolic blood pressure (mm Hg)	122 ± 20	119 ± 22	123 ± 20	.090
Diastolic blood pressure (mm Hg)	69 ± 12	67 ± 11	70 ± 12	.270
QRS width (ms)	164 ± 26	142 ± 19	170 ± 25	<.001
Left bundle branch block	184 (77)	42 (84)	142 (76)	.306
ΔQRS%	-12 ± 15	13 ± 15	-32 ± 19	<.001
Laboratory data				
Creatinine serum level (mg/dL)	13 ± 6	14 ± 6	13 ± 6	.630
Plasma B-type natriuretic peptide level (pg/mL)*	791 ± 1020	950 ± 1240	751 ± 953	.172

Values are presented as mean ± SD or as n (%).

ACE = angiotensin-converting-enzyme; ARB = angiotensin receptor blocker; NYHA = New York Heart Association; ΔQRS% = changes in QRS duration relative to baseline.

*Available in 207 patients.

Student *t* test or Mann-Whitney *U* test, as appropriate. Qualitative data are presented as absolute numbers and percentages and were compared using the χ^2 test or Fisher exact test, as appropriate. Correlations between continuous variables were assessed using Pearson correlation coefficients. The median duration of follow-up was computed using the reverse Kaplan-Meier method. Univariate analysis followed by multivariate Cox regression survival analysis was used to identify the relationship between QRS widening and occurrence of events during follow-up. The proportional hazards assumption was confirmed using statistics and graphs on the basis of Schoenfeld residuals. Penalized smoothing splines were used to illustrate the association of ΔQRS% as a continuous variable and the risk of death. Survival curves were obtained using the Kaplan-Meier method. For both multivariate Cox and linear regression analyses, model building techniques were not used and covariates entered in the model were considered of potential prognostic impact on an epidemiological basis. These covariates were preoperative QRS duration, NYHA functional class III or IV, age, coronary artery disease, serum creatinine serum levels, LV end-diastolic volume (LVEDV), and LVEF. Hazard ratios (HRs) for continuous variables in Cox models were rescaled by the within-study SD. Intraclass correlation coefficient (ICC) and Bland-Altman plots were obtained to assess the interobserver agreement of the preoperative and the postoperative QRS duration. For all tests, a 2-tailed *P* value of $\leq .05$ was considered statistically significant. Statistical analysis was performed with R 3.0.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Two hundred thirty-seven patients with heart failure due to LV systolic dysfunction (mean LVEF 26% ± 5%) were enrolled and received CRT with pacemaker (20%) or CRT with defibrillator (80%). Clinical, ECG, biological, and echocardiographic data are detailed in Table 1. Half of the patients were in NYHA functional class III or IV. Sixty-nine percent of patients had QRS width ≥ 150 ms. Thirty-one patients (13%) had permanent RV pacing at baseline and were subsequently upgraded. Nineteen patients (8%) had a nonspecific intraventricular conduction delay, and 3 patients (0.1%) had right bundle branch block. Overall, 203 patients (86% of the study population) had biventricular paced QRS morphology on the postoperative ECG. One hundred and fourteen LV leads (48%) had a lateral position, 111 (47%) a posterior, 2 (1%) an anterior, and 10 (4%) an anterolateral position. Hence, 225 (95%) had a lateral position. In addition, 199 (84%) had a nonapical position. QRS width decreased from 164 ± 26 to 141 ± 19 ms in the overall study population (median value of ΔQRS% -20% [interquartile range -40% to -10%]). ΔQRS% as a continuous variable did correlate with baseline GLS but not with baseline LVEF, LVESV, and LVEDV (Table 2). Fifty patients (21%) experienced QRS widening after CRT [QRS(+) group]. As compared with QRS(-) patients, QRS(+) patients were older, more frequently of male sex, and had narrower baseline QRS (Table 1) and had greater LV dilatation and more scarred LV segments (Table 3). Of the 50 patients in the QRS(+) group, only 3 (6%) had no biventricular paced morphology on the postoperative ECG. Of the 187 patients in the QRS(-) group, 31 (17%) had no biventricular paced

Table 2 Relationship between Δ QRS% and baseline echocardiographic parameters and their changes between baseline and follow-up

Parameter	Δ QRS%: <i>r</i> (95% CI)	<i>P</i>
LV ejection fraction	0.05 (−0.08 to 0.17)	.471
Change in LV ejection fraction	0.28 (0.15 to 0.40)	<.001
Global longitudinal strain	−0.13 (−0.0006 to −0.26)	.049
Change in LV global longitudinal strain	0.15 (0.01 to 0.29)	.036
LV end-diastolic volume	−0.11 (−0.24 to 0.01)	.076
Change in LV end-diastolic volume	0.15 (0.01 to 0.28)	.033
LV end-systolic volume	−0.12 (−0.24 to 0.007)	.065
Change in LV end-systolic volume—absolute	0.19 (0.05 to 0.32)	.007
Change in LV end-systolic volume—relative	0.27 (0.14 to 0.39)	<.0001

CI = confidence interval; LV = left ventricular; Δ QRS% = changes in QRS duration relative to baseline.

morphology ($P = .095$). Of the 50 patients in the QRS(+) group, 44 (89%) had a lateral position of the LV lead, while 180 patients (96%) from the QRS(−) group had a lateral position of the LV lead ($P = .135$). In addition, in QRS(+) patients, 40 patients (79%) had a nonapical position of the LV lead, while 157 QRS(−) patients (84%) had a nonapical position of the LV lead ($P = .504$). Interobserver agreement for QRS duration was good (ICC of 0.94 for preoperative QRS duration and ICC of 0.86 for postoperative QRS duration). Bland-Altman plots showing interobserver agreement for QRS duration are shown in Figure 1.

Relationship between QRS widening and outcome after CRT

Death status was available in 100% of cases. During a median follow-up of 24 months, 39 patients died. Of the 25 patients who died of cardiovascular causes, 19 died of heart failure (76%), 5 died of sudden cardiac death (21%), and 1 died of stroke. The cause of death remains unknown in 1 patient. At 1 year, 2 years, and 3 years, survival free from death was $91\% \pm 4\%$, $85\% \pm 5\%$, and $76\% \pm 7\%$, respectively.

By Cox univariate analysis, Δ QRS% was associated with increased overall mortality (HR 1.37; 95% confidence interval [CI] 1.01–1.85; $P = .044$). The character of the

relationship between Δ QRS% as a continuous variable and the risk of overall mortality during follow-up was estimated using spline functions for Δ QRS% (Figure 2). There was no increase in overall mortality risk with Δ QRS% in the QRS(−) group (HR 0.82; 95% CI 0.56–1.2 per Δ QRS% decrease; $P = .303$). In contrast, there was a sharp increase in overall mortality risk with increasing Δ QRS% in the QRS(+) group (HR 1.64; 95% CI 1.01–2.68 per Δ QRS% increase; $P = .047$). As represented in Figure 3A, survival free from overall mortality was significantly lower in QRS(+) patients compared with QRS(−) patients (log rank, $P = .029$). QRS(+) patients experienced a 2.07-fold increased risk of mortality as compared with QRS(−) patients (Table 4). After adjustment (Table 4), QRS(+) patients displayed an independent increased risk of overall mortality (adjusted HR 2.67; 95% CI 1.07–6.65; $P = .035$). As depicted in Figure 3B, survival free from cardiovascular mortality was lower in QRS(+) patients than in QRS(−) patients ($P = .002$). In multivariate analysis, QRS widening remained associated with cardiovascular mortality (adjusted HR 3.63; 95% CI 1.13–11.65; $P = .03$) (Table 4). After further adjustment for LBBB and sex, QRS widening remained significantly associated with all-cause mortality and cardiovascular mortality (adjusted HR 2.61; 95% CI 1.05–6.50; $P = .04$ and adjusted HR 3.68; 95% CI 1.14–11.93; $P = .03$, respectively). In addition, QRS widening remained independently associated with both

Table 3 Echocardiographic data at baseline, 9-mo follow-up, and their changes in patients with and without QRS widening [QRS(+) and QRS(−)]

Parameter	Overall (n = 237)	QRS(+) (n = 50)	QRS(−) (n = 187)	<i>P</i>
Baseline LV ejection fraction (%)	26 ± 5	26 ± 5	26 ± 5	.423
9-mo LV ejection fraction (%)	40 ± 12	33 ± 12	41 ± 11	<.001
Change in LV ejection fraction (%)	13 ± 11	7 ± 11	15 ± 10	<.001
Baseline LV end-diastolic volume (mL)	245 ± 70	271 ± 75	238 ± 68	.005
9-mo LV end-diastolic volume (mL)	192 ± 70	234 ± 70	181 ± 66	<.001
Change in LV end-diastolic volume (mL)	55 ± 56	41 ± 70	59 ± 52	.110
Baseline LV end-systolic volume (mL)	183 ± 60	203 ± 68	177 ± 57	.017
9-mo LV end-systolic volume (mL)	122 ± 67	163 ± 69	111 ± 62	<.001
Change in LV end-systolic volume—absolute (mL)	62 ± 53	43 ± 63	67 ± 49	.026
Change in LV end-systolic volume—relative (%)	34 ± 27	17 ± 31	38 ± 24	<.001
Basal global longitudinal strain (%)	−7.8 ± 2.6	−7.2 ± 2.2	−7.9 ± 2.7	.187
9-mo global longitudinal strain (%)	−10.1 ± 4.1	−8.6 ± 4.3	−10.6 ± 3.9	.010
Change in global longitudinal strain (%)	2.1 ± 3.5	1.6 ± 3.6	2.2 ± 3.5	.295
No. of LV scarred segments	0.9 ± 2.4	1.4 ± 2.4	0.8 ± 2.4	.018

Values are presented as mean ± SD.

LV = left ventricular.

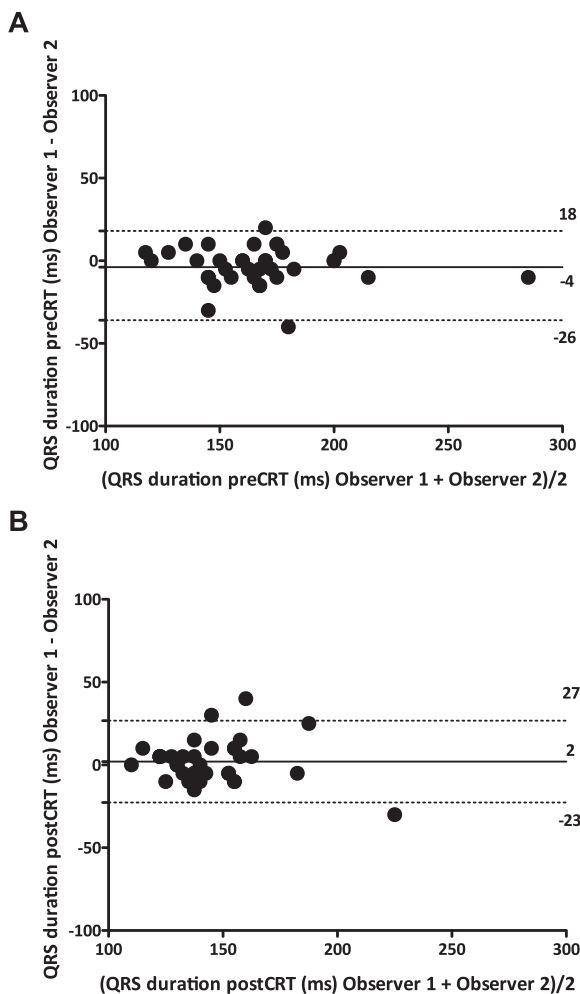


Figure 1 Bland-Altman plots of the differences between 2 observers for preoperative (A) and postoperative (B) QRS duration. CRT = cardiac resynchronization therapy.

mortality and cardiovascular mortality in the subgroup of patients with LBBB (adjusted HR 3.91; 95% CI 1.27–12.05; $P = .018$ and adjusted HR 5.43; 95% CI 1.21–24.30; $P = .027$, respectively). In the subset of 207 patients with available plasma B-type natriuretic peptide levels, QRS widening remained associated with mortality ($P = .05$) and cardiovascular mortality ($P = .026$) after adjustment for baseline plasma B-type natriuretic peptide levels. Figure 4 shows QRS duration and the final LV lead position assessed by radiography of 2 patients from the study population, the first (panel A) with QRS widening after CRT and the second (panel B) without QRS widening after CRT.

Relationship between QRS widening and echocardiographic response to CRT

Echocardiographic data at 9-month follow-up were obtained in 207 patients. As shown in Table 2, Δ QRS% did correlate with Δ LVESV and Δ LVEDV, Δ LVEF, and Δ GLS. The extent of LVESV relative reduction was significantly greater in QRS(–) patients than in QRS(+) patients (Table 3). Similarly, the improvement in LVEF and GLS was greater in QRS(–) patients than in QRS(+) patients (Table 3). After

adjustment, QRS widening remained significantly associated with Δ LVESV, Δ LVEF, and Δ GLS ($P < .001$ for all). Of note, QRS(+) patients were less frequent responders to CRT than were QRS(–) patients (20 [47%] vs 136 [83%]; $P < .0001$).

Discussion

The present study is the first to demonstrate that QRS widening after CRT is associated with a nearly 3-fold increase in mortality during follow-up. The relationship between postimplantation QRS widening after CRT and mortality remained significant even after adjustment for important prognostic confounders. Hence, QRS widening after CRT identifies a high-risk group of heart failure patients.

CRT is firmly indicated in patients with reduced LVEF $\leq 35\%$ and wide QRS complex to produce reverse LV remodeling and thereby improve outcome.^{15–18} QRS duration reflects the necessary time for the entire myocardial depolarization and is thus probably the best measurement to assess myocardial dyssynchrony, as baseline QRS duration is the only criterion that has been consistently found to predict CRT response in terms of clinical outcome.¹⁵ In addition, CRT corrects myocardial dyssynchrony by reducing QRS duration. Nevertheless, 30%–40% of patients with enlarged baseline QRS fail to improve after CRT.⁵ Interestingly, some patients may experience a postoperative paced QRS duration after CRT that is more prolonged than the preoperative QRS duration. Molohek et al³ reported in a cohort of 61 patients with severe heart failure receiving CRT that 36% of patients had an increased QRS duration or decreased QRS duration of <10 ms. A similar proportion of postoperative QRS widening was observed in recent CRT studies.^{6,7} Accordingly, we found in the present report a 21% proportion of QRS widening relative to baseline after CRT.

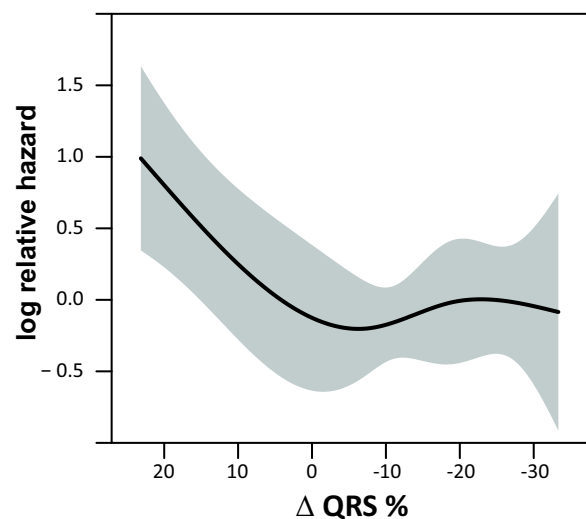


Figure 2 Penalized smoothing splines illustrating the association between Δ QRS% and the risk of death. Δ QRS% = changes in QRS duration relative to baseline.

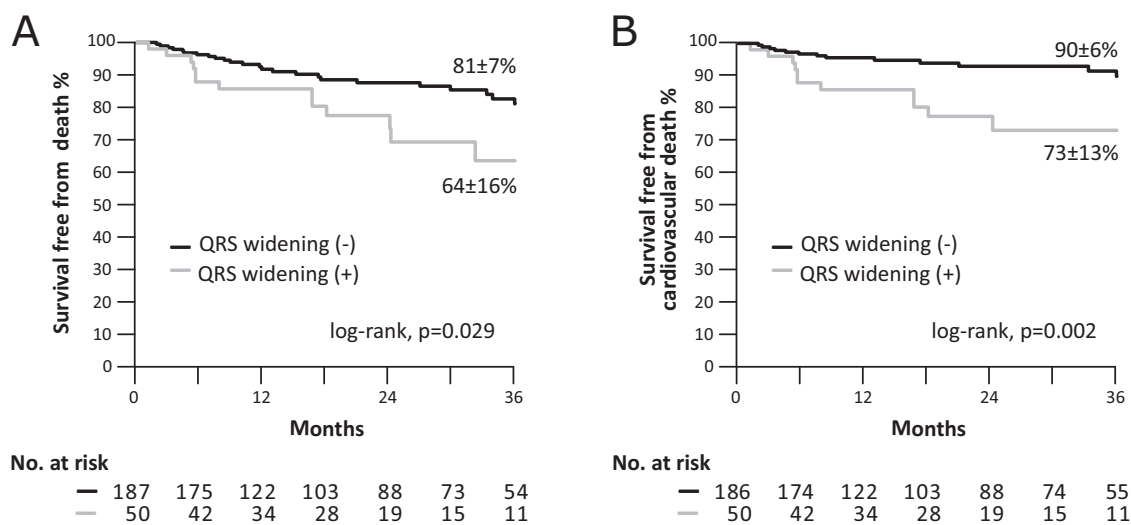


Figure 3 Kaplan-Meier event-free survival for mortality (**A**) and cardiovascular mortality (**B**) according to QRS(+) and QRS(-). QRS(+) = patients with QRS widening; QRS(-) = patients without QRS widening.

Previous reports have consistently demonstrated a relationship between reduction in QRS duration after CRT and echocardiographic response to CRT. Compared with non-responders, responders to CRT have greater QRS narrowing as measured by Δ QRS%.^{6,7,19} In addition, in an ECG substudy of the PROSPECT study⁴ the difference between postimplantation and preimplantation QRS width predicted quality-of-life improvement. Consistently, a strong relationship was observed in the present report between reduction in QRS duration and LV reverse remodeling.

It has been suggested that a narrower LV paced QRS duration would imply electrically viable tissue and a wider LV paced QRS duration would imply proximity to a region of scar where electric signals conduct slowly and resynchronization is less likely to occur.⁴ In the present report, QRS (+) patients had more LV scarred segments than did QRS(-) patients. Whether extensive fibrosis is more frequent in QRS (+) patients cannot, however, be precisely ascertained from the present data, as cardiovascular magnetic resonance

imaging was not systematically performed in the present report.

In a subanalysis of the CARE-HF trial,²⁰ QRS duration at 3 months was associated in univariate analysis with favorable outcome after CRT. The present study builds on previous reports by showing that patients with immediate QRS widening after CRT had a considerable increased risk of both all-cause and cardiovascular mortality during follow-up. Hence, these data suggest that the measurement of LV paced QRS duration immediately after CRT identifies a subgroup of high-risk patients with a nearly 3-fold increase in mortality. In addition, QRS widening easily permits an immediate postoperative evaluation of the dyssynchrony substrate correction. Further research would be useful to determine whether improvement in CRT devices (eg, optimized epicardial or LV endocardial lead positioning, or triple-site or multipoint pacing) can decrease the number of patients with QRS widening by lowering the global necessary time for entire myocardial depolarization.²¹

Table 4 Univariate and multivariate Cox regression analyses of the relationship between QRS widening and all-cause mortality and cardiovascular mortality

Analysis	Parameter	All-cause mortality		Cardiovascular mortality	
		HR (95% CI)	P	HR (95% CI)	P
Univariate	QRS(+)	2.07 (1.06–4.03)	.033	3.19 (1.45–7.04)	.004
Multivariate	QRS(+)	2.67 (1.07–6.65)	.035	3.63 (1.13–11.65)	.030
	Baseline QRS width	1.00 (0.68–1.47)	.989	0.80 (0.45–1.41)	.437
	NYHA class III or IV	3.13 (1.37–7.16)	.007	3.18 (1.13–8.96)	.029
	Age	2.07 (1.27–3.37)	.003	3.1 (1.55–6.21)	.001
	Coronary artery disease	0.81 (0.40–1.62)	.548	0.54 (0.21–1.35)	.188
	Creatinine serum level	1.26 (1.02–1.54)	.029	1.26 (0.97–1.65)	.086
	LV ejection fraction	0.66 (0.45–0.95)	.027	0.57 (0.35–0.93)	.024
	LV end-diastolic volume	1.27 (0.85–1.89)	.247	1.46 (0.89–2.38)	.135

CI = confidence interval; HR = hazard ratio; LV = left ventricular; NYHA = New York Heart Association.

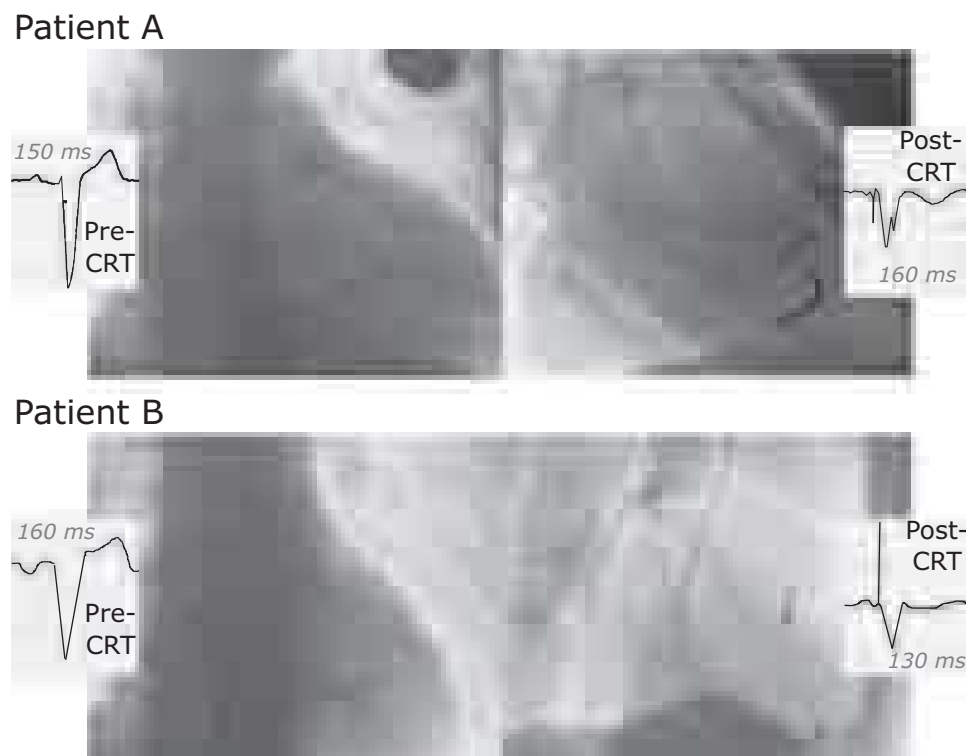


Figure 4 Electrocardiogram and the final left ventricular lead position assessed by radiography of 2 patients from the study population, the first (A) with QRS widening after CRT who died 11 months after CRT and the second (B) without QRS widening after CRT who still remained alive during follow-up. CRT = cardiac resynchronization therapy.

Study Limitations

This single-center study included a relatively small number of patients. In addition, the findings of the present report may reflect the practice of our center and may not be generalizable to everyday clinical practice. However, clinical and echocardiographic data were prospectively collected with off-line analysis and patient follow-up was prospectively planned. In addition, QRS width assessment was performed by a cardiologist blinded to clinical, echocardiographic, and outcome data. CRT pacing settings were commonly not changed or adjusted during the time period of the study. However, a meta-analysis of 12 trials comparing AV and/or interventricular delay optimization and conventional CRT device programming found that AV and/or interventricular delay optimization had a neutral effect on clinical and echocardiographic outcomes.²²

Conclusion

QRS widening relative to baseline after CRT is associated with a considerable increased risk of mortality during follow-up and allows identifying a high-risk group of heart failure patients. Further research would be useful to determine whether QRS narrowing should be achieved to optimize CRT lead placement and thereby increase the rate of CRT responders and improve outcome.

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6 Signification clinique des patterns de déformation septale chez les patients insuffisants cardiaques bénéficiant d'un traitement par resynchronisation cardiaque.*

* Menet A, Bernard A, Tribouilloy C, Leclercq C, Gevaert C, Guyomar Y, et al. Clinical significance of septal deformation patterns in heart failure patients receiving cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging. 29 déc 2016;(132)

6.1 Introduction

Le faible coût de l'échocardiographie et sa grande disponibilité nous poussent à évaluer cet outil comme prédicteur de la réponse au TRC en quantifiant l'asynchronisme myocardique. Cependant, malgré des résultats initiaux encourageants, une étude multicentrique (PROSPECT) n'a pas réussi à démontrer l'utilité des paramètres classiques de désynchronisation échographique comme des prédicteurs de la réponse au TRC pour l'amélioration des symptômes d'insuffisance cardiaque et le remodelage ventriculaire. Dans l'insuffisance cardiaque à FEVG basse, il existe une désynchronisation mécanique sans substrat électrique qui ne représente pas une bonne cible pour le TRC. Cet asynchronisme est une des explications de la difficulté pour les paramètres échocardiographiques à prédire la réponse au TRC. De nouveaux paramètres de désynchronisation ont vu le jour ayant pour objectif d'être spécifiques du substrat électrique de la désynchronisation et donc de la réponse au TRC.

Certains de ces paramètres se veulent même spécifiques du BBG. Dans le vrai BBG, l'activation commence du ventricule droit et traverse le septum en 40-50 ms avant d'atteindre l'endocarde du VG. 50ms sont nécessaires pour pénétrer le réseau de Purkinje et pour se propager à l'endocarde de la paroi latérale du VG. Enfin 50 ms sont nécessaires pour activer l'ensemble de la paroi postéro-latérale. Le QRS induit mesure 140 à 150 ms. La paroi latérale n'étant pas activée durant la protosystole, la pression intra-VG ne monte pas. Le septum peut facilement se contracter car il n'a qu'une post-charge basse puis est refoulé vers le VD à cause de la contraction de la paroi latérale du VG. Ce mouvement est appelé flash septal et est identifiable de manière visuelle, en mode TM ou en doppler tissulaire. La contraction tardive de la paroi latérale du VG induit une contraction post-systolique après la fermeture de la valve aortique.

Pour décrire cette désynchronisation électromécanique, certains auteurs se sont attachés à l'aspect de contraction du septum ou de la pointe : septal flash, apical rocking, pattern de contraction septal en strain. D'autres ont regardé le mouvement septal et de la paroi postéro-latérale : en strain

longitudinal, en strain radial. Enfin certains ont essayé de quantifier l'amplitude de manière automatique : systolic stretch index.

L'ensemble de ces paramètres ont été évalués pour des patients ayant un TRC, afin de relier les indices au pronostic des patients implantés. Sans étude randomisée, nous ne pouvons pas répondre de manière formelle à deux questions : le pronostic des patients n'ayant pas reçu de TRC en fonction de ces paramètres de désynchronisation et par la même de l'utilité de ces paramètres dans la sélection des patients à resynchroniser.

6.1.1 Flash et apical rocking

Le flash septal est le mouvement caractéristique du septum en présence d'un BBG avec une contraction précoce durant la phase pré et protosystolique puis un recul vers le VD. Il est mis en évidence de manière visuelle en parasternal grand axe, petit axe ou 4 cavités et s'aidant éventuellement du mode TM et TM couleur. Ce mouvement est associé avec un remodelage inverse après TRC chez les patients ayant une IC FEb.(133,134) Il permet d'améliorer un score de prédiction clinique et électrocardiographique de prédiction de la réponse.(135) Il est également prédictif de la survie et des hospitalisations pour insuffisance cardiaque dans l'étude PREDICT-CRT.(11)

L'apical rocking qui est un mouvement horaire de la pointe du VG (figure 12) est fortement associé à l'étiologie non ischémique de la cardiopathie hypokinétique puisque les patients avec une cardiopathie ischémique peuvent ne pas avoir d'apical rocking ou même un mouvement antihoraire de la pointe du VG.(136) L'amplitude de l'apical rocking est influencé par le volume télédiastolique du VG et par la largeur du QRS.(136) Il est associé à une diminution des événements cardiaques majeurs et à une super réponse après un TRC en analyse multivariée.(137,138) Il est également prédictif de la survie et des hospitalisations pour insuffisance cardiaque dans l'étude PREDICT-CRT.(11)

Le coefficient Kappa de corrélation inter-juge est malheureusement à 0.71 ce qui en fait un paramètre difficilement utilisable en pratique quotidienne.(11)

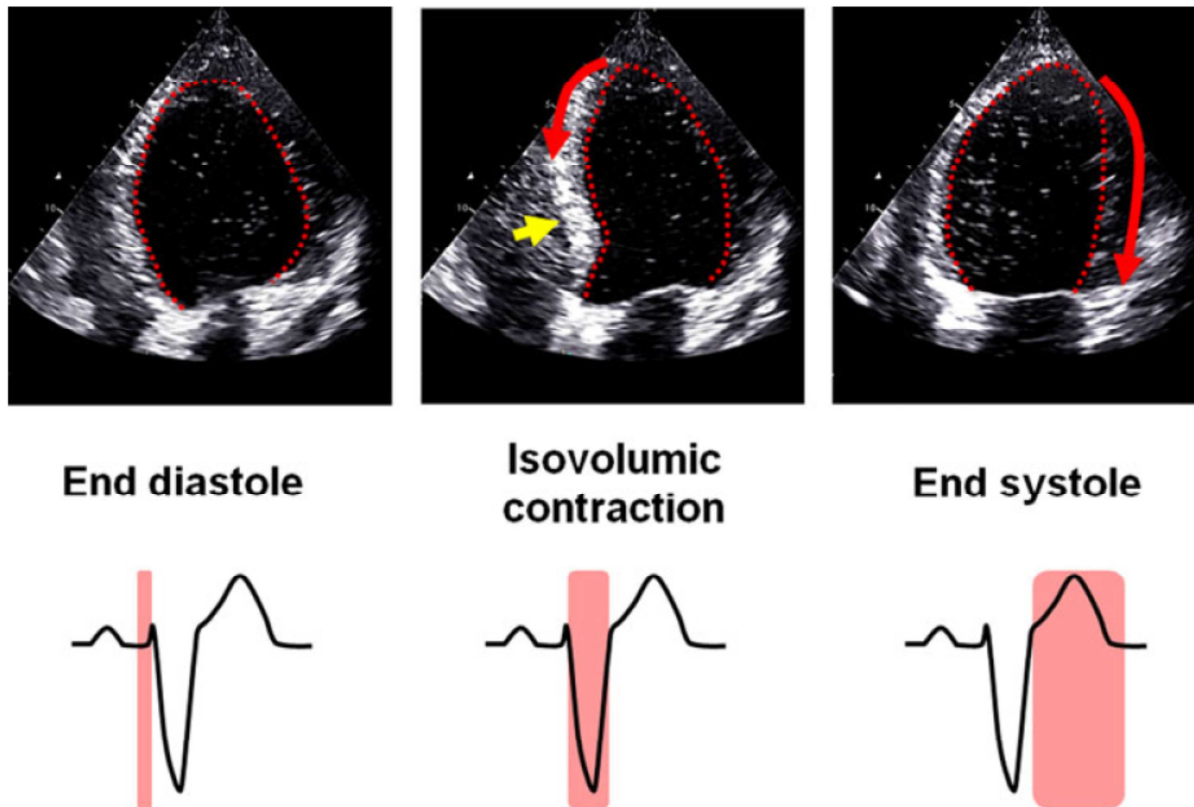


Figure 12. Séquence typique des évènements électriques (en bas) et mécanique (en haut) dans un BBG. L'activation électrique du septum donne une contraction septale précoce qui attire l'apex vers le septum tandis que le septum bouge vers le VG. (flèche jaune = flash septal). L'activation retardée de la paroi latérale tire ensuite l'apex vers la paroi latérale VG pendant la phase d'éjection tandis que le septum est étiré. Cette séquence typique de mouvement septal-latéral de l'apex est décrite comme l' « Apical-rocking ». Le mouvement du septum est quant à lui appelé « septal flash ».(11)

6.1.2 Strain longitudinal et radial

6.1.2.1 Radial strain : délai septo-latéral.

Le délai entre l'activation précoce du septum et l'activation tardive de la paroi postéro-latérale peut être calculé avec la technique du strain. L'équipe de Lumens a démontré à l'aide du modèle CircAdapt® que la simulation d'un BBG avec un délai croissant entre l'activation du septum et de la paroi latérale entraînait une augmentation des délais mesurés entre le septum et la paroi postéro-latérale en strain. L'identification d'un délai important entre ces parois en strain radial pourrait aider à différencier l'asynchronisme électromécanique de l'asynchronisme mécanique.(39) Il existe cependant un problème lié à la reproductibilité du strain radial lié au mouvement longitudinal du cœur entraînant une sortie du plan des speckles (marqueurs utilisés pour traquer l'imagerie et obtenir des données de déformation myocardique).(139)

6.1.2.2 Strain longitudinal : pattern de contraction classique longitudinal du BBG

En comparaison au strain radial, le strain longitudinal est très reproductible et largement accepté par la communauté des échocardiographistes dans la plupart des situations cliniques.(140)

Risum et al. ont décrit 3 critères permettant de reconnaître la contraction classique du BBG parmi les patients présentant un BBG à l'ECG : (1) raccourcissement précoce d'au moins un segment basal ou mid-ventriculaire de la paroi septale et étirement d'au moins un segment basal ou mid-ventriculaire de la paroi latérale. (2) pic de contraction septale précoce (dans les premiers 70% de la phase d'éjection). (3) pic de contraction de la paroi latérale après la fermeture aortique.(141) Ces trois critères sont nécessaires à la description d'une contraction classique du BBG (Figure 13)

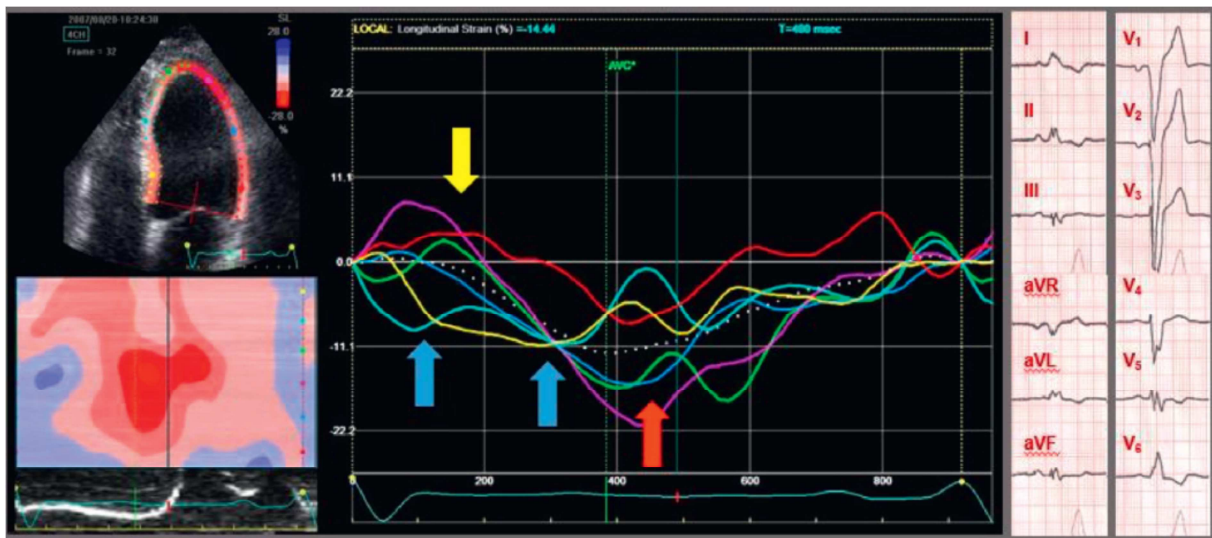


Figure 13. Illustration de la contraction classique du BBG. Flèches bleues : contraction septale précoce basale et mid-ventriculaire puis deuxième raccourcissement durant la phase d'éjection. Flèche jaune : étirement des segments latéraux. Flèche rouge : pic de contraction de la paroi latérale après la fermeture aortique. (12)

Ce pattern de contraction a été retrouvé de façon plus fréquente chez les patients ayant un BBG avec des critères diagnostics stricts. (142) Ce pattern de contraction a été plus retrouvé chez des patients ayant un QRS ≥ 150 ms(12) et très fortement corrélé à la réponse au TRC.(141) L'absence de ce pattern de contraction est associée avec un moins bon pronostic au long cours, y compris chez les patients avec des QRS intermédiaires (120-150 ms)(12) et chez les patients avec une stimulation VD (chez qui l'apex est souvent le premier segment activé)(143). Ce paramètre était très reproductible dans l'étude de Risum et al. Toutefois, dans notre expérience, l'identification du pattern BBG dépend beaucoup de l'expérience. Un cardiologue avec une forte expérience en échocardiographie de resynchronisation sera plus sensible pour détecter ces patterns qu'un novice et le sera même parfois trop.

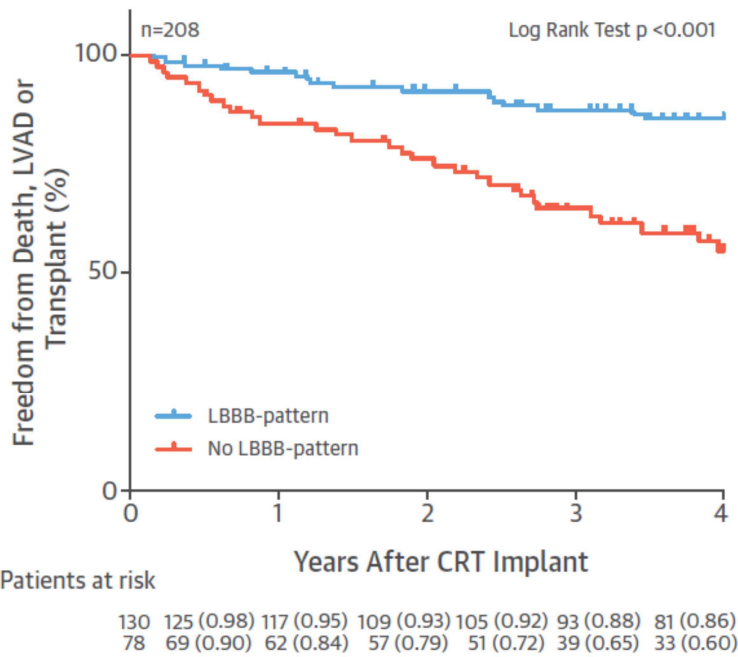


Figure 13 bis. Courbes de survie en fonction de la présence ou de l'absence du pattern de contraction typique du BBG. CRT= traitement par resynchronisation cardiaque. LVAD= assistance ventriculaire gauche

6.1.3 Indice d'étirement systolique (IES).

Lumens et al. ont utilisé un modèle informatique à partir du strain radial qui est sensible au substrat de désynchronisation électromécanique et peu sensible au substrat de désynchronisation mécanique pur. Ce nouvel index appelé indice d'étirement systolique (IES) est la somme de l'étirement systolique de la paroi postéro-latérale et de l'étirement systolique du septum qui caractérisent tous deux le substrat électromécanique de réponse au TRC. Il a été validé dans une cohorte de 191 patients. Les patients ayant un IES $\geq 9.7\%$ ont moins d'hospitalisations et de mortalité 2 ans après un TRC (hazard ratio ,0.32 : intervalle de confiance à 95%, 0.19-0.53) et moins de mortalité, transplantation cardiaque ou assistance ventriculaire gauche (hazard ratio, 0.28, intervalle de confiance à 95%, 0.15-0.55). Cet indice restait indépendamment associé à ces end-points chez les patients avec un QRS intermédiaire (120-150 ms) et chez les patients ayant une morphologie de QRS non BBG à l'ECG.(13)

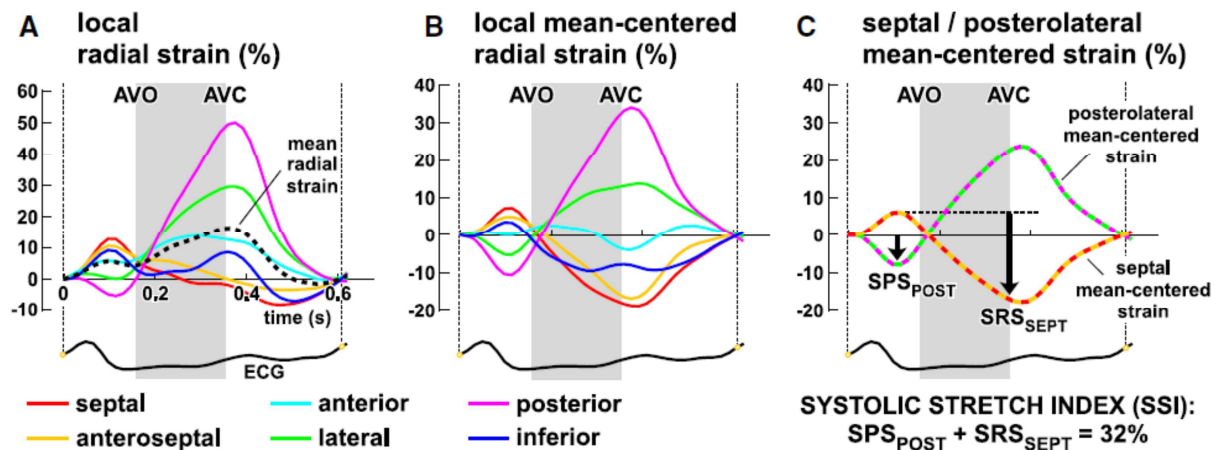


Figure 13 ter. Calcul de l'indice d'étirement systolique (IES). Données de strain radial d'un patient ayant un QRS de 168 ms et un BBG. Les lignes pointillées verticales indiquent le début du QRS. L'IES est obtenu en (A) calculant la moyenne du strain radial du VG (ligne en tiret) (B) calculant la moyenne-centrée régionale des strain radiaux (soustraction de la moyenne du strain radial des strains régionaux) (C) calculant et additionnant l'étirement systolique postéro-latéral (SPS_{POST}) et l'étirement septal systolique (SRS_{SEPT}). ((13))

6.1.4 Patterns de contraction septale

Leenders et al. sont les premiers à avoir décrit les patterns de contraction septale chez les patients ayant un BBG.(14) Il s'agit en d'autres termes de s'aider du strain myocardique pour visualiser le flash septal dont l'analyse visuelle simple n'est parfois pas aisée et peu reproductible d'un observateur à l'autre. Il définit trois patterns de contraction septale du BBG en fonction de la contractilité des parois du VG (Figure 14). Ces patterns de contraction ont été modélisés à l'aide du logiciel de simulation CircAdapt®. Leur valeur clinique a été évaluée dans une cohorte de 132 patients. Il démontre dans cette cohorte que ces patterns sont prédictifs de l'amélioration des volumes ventriculaires gauches, de la FEVG et de la réduction de la fuite mitrale dans le suivi.

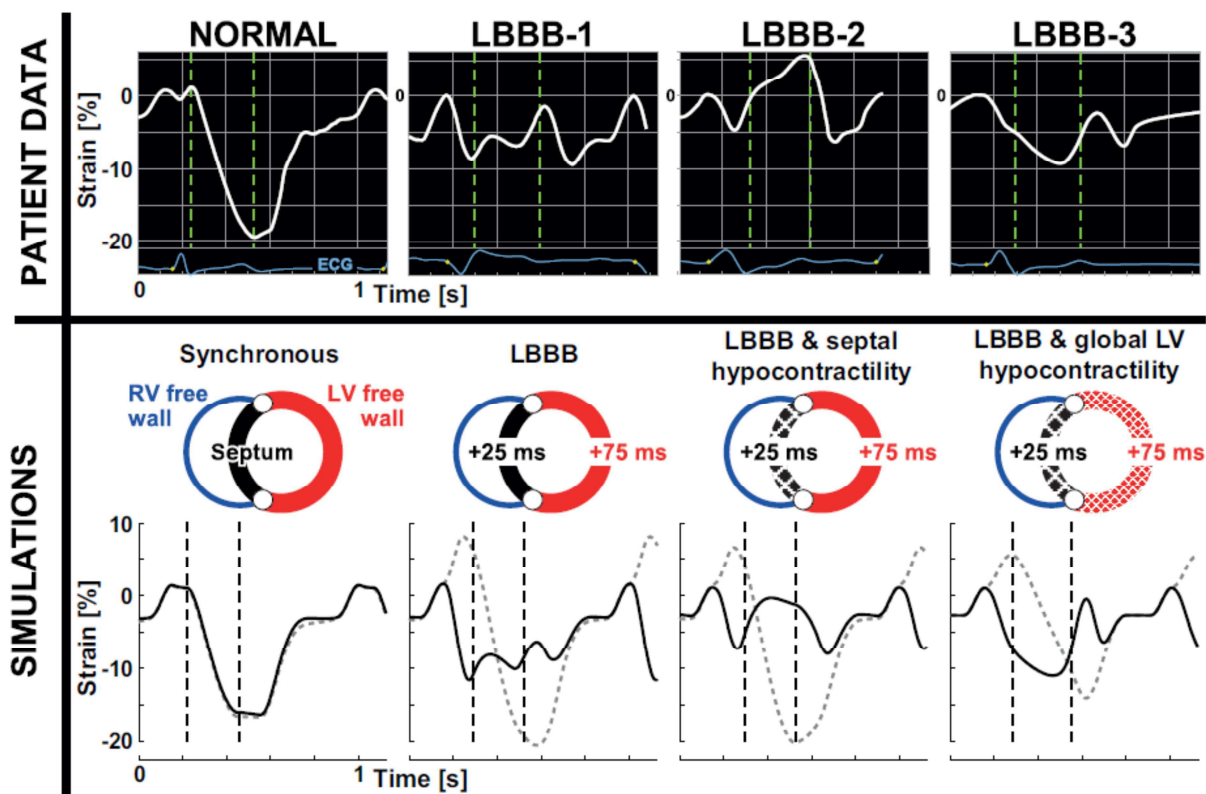


Figure 14. Comparaison entre les patterns déformation septale mesurés chez des patients (en haut) et simulés par ordinateur (en bas). Chez un sujet normal sans comorbidité (NORMAL) et 3 sous-groupes de contraction septale chez les patients avec un BBG (LBBB-1, LBBB-2 et LBBB-3).

La paroi septale est représentée en ligne pleine et la paroi latérale en pointillé. La première ligne verticale pointillée représente l'ouverture de la valve aortique et la deuxième sa fermeture. Le BBG classique (LBBB) a un délai de 25 ms seconde pour le septum et 75 ms pour la paroi latérale). Si la contractilité est normale, on retrouve un aspect LBBB-1, si la contractilité est diminuée au niveau du septum retrouve un aspect LBBB-2 et si la contractilité est diminuée de façon globale, on retrouve un aspect LBBB-3.(14)

Nous avons pu mettre en évidence une relation entre patterns et réponse au TRC dans une cohorte de 101 patients. 92% des patients ayant un pattern 1 ou 2 étaient répondeurs au TRC contre 59% des patients ayant un pattern 3. Les améliorations de volume télésystolique (77 ± 40 mL vs 39 ± 39 mL), de SLG (2.7 ± 3.2 vs 0.2 ± 2.4) et de FEVG (17 ± 10 vs 8 ± 11 %) étaient meilleur dans le groupe des patterns 1 et 2 que pour les patterns 3. Les patients ayant des patterns 1 ou 2 étaient plus souvent des femmes, avaient moins souvent une cardiopathie ischémique et avaient un BNP moins élevés que les patients ayant un pattern 3. (15)

Dans ce travail, nous nous sommes attachés à donner la valeur pronostique des patterns de contraction septaux sur la mortalité, la mortalité cardiovasculaire et les hospitalisations pour insuffisance cardiaque.

6.2 Résultats

Nous avons constitué une cohorte bicentrique (Centre hospitalier de Saint Philibert et CHU de Rennes) de 284 patients implantés d'un TRC pour insuffisance cardiaque à fraction d'éjection basse $\leq 35\%$, NYHA 2 à 4 et des QRS ≥ 120 ms. Un strain septal longitudinal en coupe 4 cavités a été réalisé sur une station de travail sur les échographies précédant l'implantation de TRC. En comparaison avec les patterns de contraction septale 1 et 2, les patterns 3 (Figure 13) avaient une mortalité totale (HR ajusté = 3.78, IC à 95%: 1.85–7.75, $P < 0.001$) une mortalité cardiovasculaire (HR ajusté = 3.84, IC à 95%: 1.45–10.16, $P = 0.007$) et un taux d'hospitalisation (HR ajusté = 4.41, 95% CI: 2.18–8.90, $P < 0.001$) pour insuffisance cardiaque plus élevé. Par ailleurs le taux de patients répondeurs en volume était de 47% pour les patterns 3 et de 89% et 92 % pour les patterns 1 et 2. Dans le sous-groupe de patients ayant un QRS entre 120 et 150 ms qui posent problème quand à la probabilité de réponse, ces résultats étaient consistants avec pour les patterns 3 : une surmortalité totale (HR ajusté = 3.04, IC à 95% 1.37-6.74, $p=0.006$) une surmortalité cardiovasculaire (HR ajusté = 5.50, IC à 95% 1.63-18.50, $p=0.006$) et une augmentation des hospitalisations pour insuffisance cardiaque (HR ajusté= 5.03, IC à 95% 2.09- -12.1, $p<0.001$). Nous avons également comparé l'analyse de ces patterns de contraction septale analysés en strain longitudinal à l'analyse visuelle de la contraction septale (le flash septal) en les ajoutant de manière séparés dans les modèles multivariés de prédiction du risque. Nous avons pu montrer que les patterns septaux en strain améliorent de manière significative la prédiction du risque et sa discrimination tandis que le flash septal ne les améliore pas.

L'identification des patterns septaux en strain longitudinal donne donc une information pronostique importante chez les candidats au TRC en plus des informations cliniques, électrocardiographiques (notamment BBG et largeur du QRS initial) et échocardiographiques. Ce paramètre sera particulièrement utile en pratique clinique pour les patients avec des QRS intermédiaires chez qui le bénéfice du TRC reste incertain.



Clinical significance of septal deformation patterns in heart failure patients receiving cardiac resynchronization therapy

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Aims

Specific septal motion related to dyssynchrony is strongly linked to reverse remodelling, in patients with systolic heart failure (HF) receiving cardiac resynchronization therapy (CRT). We aimed to investigate the relationship between septal deformation patterns studied by longitudinal speckle tracking and clinical outcome following CRT.

Methods and results

A total of 284 CRT candidates from two centres (HF NYHA classes II–IV, ejection fraction < 35%, QRS \geq 120 ms) were prospectively included. Longitudinal strain of the septum in the apical four-chamber view determined three patterns of septal contraction. The endpoints were overall mortality, cardiovascular mortality, and hospitalization for HF. Compared with patterns 1 or 2, pattern 3 was associated with an increased risk for both overall and cardiovascular mortality [hazard ratio (HR) = 3.78, 95% confidence interval (CI): 1.85–7.75, $P < 0.001$ and HR = 3.84, 95% CI: 1.45–10.16, $P = 0.007$, respectively] and HF hospitalization (HR = 4.41, 95% CI: 2.18–8.90, $P < 0.001$). Addition of septal patterns to multivariable models, including baseline QRS width and presence of left bundle branch block, improved risk prediction, and discrimination. In patients with intermediate QRS duration (120–150 ms), pattern 3 remained associated with a worse outcome than pattern 1 or 2 ($P < 0.05$ for all endpoints).

Conclusion

The identification of septal deformation patterns provides important prognostic information in CRT candidates in addition to ordinary clinical, electrocardiographic, and echocardiographic predictors of outcome in HF patients. This parameter may be particularly useful in patients with intermediate QRS duration in whom the benefit of CRT remains uncertain.

Keywords

cardiac resynchronization therapy • heart failure • outcome • speckle tracking • echocardiography

Introduction

Cardiac resynchronization therapy (CRT) is indicated (class I) in patients with left ventricular ejection fraction (LVEF) < 35%, left bundle branch block (LBBB), or QRS duration of 150 ms or more. In contrast, the benefit of CRT in patients with intermediate QRS duration (120–150 ms) or with a non-LBBB morphology remains unclear.¹

In addition, around 30% of patients fail to improve and may even deteriorate after CRT.² Despite initial encouraging results, a multicentre report failed to demonstrate any benefit from the use of echocardiography-based mechanical dyssynchrony in predicting heart failure (HF) symptom improvement or reverse remodelling after CRT.³ Furthermore, important concerns were raised regarding feasibility and reproducibility of echocardiographic parameters in

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routine clinical settings.³ Hence, current guidelines do not recommend echocardiographic assessment of dyssynchrony to improve patient selection for CRT.

In patients with LBBB, the inter-ventricular septum has a specific motion, characterized by short-lived early events, followed by paradoxical septal motion.⁴ The so-called 'septal flash' (SF) has been associated with favourable LV reverse remodelling and better outcome following CRT.^{5,6} Longitudinal speckle tracking strain echocardiography has been recently used for the assessment of septal motion, by demonstrating various septal deformation patterns, among HF patients with LBBB,⁷ with two patterns (1 and 2) sturdily linked to LV reverse remodelling following CRT.⁸ However, their clinical significance has not been thoroughly investigated. Hence, the present report aims at (i) demonstrating that septal deformation patterns would be independent predictors of clinical outcomes beyond current clinical, electrocardiographic, and echocardiographic predictors in HF patients receiving CRT; (ii) evaluating the prognostic impact of septal deformation patterns in patients with intermediate QRS duration (120–150 ms); and (iii) evaluating whether assessment of the septal motion by septal deformation patterns provides a better predictive value than classical assessment of the SF.

Methods

Study population

Clinical, electrocardiogram, and Doppler-echocardiographic data were collected in patients referred for CRT implantation in the context of two registries from two hospitals (Lille and Rennes). Data of both centres were pooled together. The present study is a retrospective analysis of the pooled data of these two registries. CRT was indicated for patients with LVEF \leq 35% who remained in NYHA functional class II, III, and ambulatory IV, despite optimal medical treatment and QRS duration \geq 120 ms in the event of LBBB morphology or with QRS duration \geq 150 ms in the event of non-LBBB morphology.^{9,10} Exclusion criteria were (i) myocardial infarction, acute coronary syndrome, or coronary revascularization in the past 3 months; (ii) primary mitral or aortic valve disease; and (iii) uncontrolled rapid atrial fibrillation. Patients received a maximum tolerated dose of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and spironolactone. Blood was sampled in the supine position for serum creatinine before CRT device implantation. Brain natriuretic peptide (BNP) levels were available in a subset of the study population (Triage assay; Beckman, Villepinte, France). Local ethics committee of each centre approved this study.

Echocardiography

Echocardiography was performed the day before CRT implantation, and at 6- to 9-month follow-up, in most patients, with a GE Vivid E9 or 7 ultrasound system (General Electric healthcare, Velizy, France). Longitudinal two-dimensional speckle-tracking strain curves were analysed offline using a dedicated workstation (EchoPAC PC release BT12; GE Vingmed Ultrasound AS). Global longitudinal strain was the average of segmental peak systolic longitudinal strains from the three apical views.¹¹ Speckle-tracking software was used to derive septal deformation from the single-wall recordings. The region of interest was set along the endocardial border from base to apex, excluding the apical cap and adapted to match wall thickness. Global wall deformation was used for analysis. Septal deformation patterns (Figure 1) were classified on the basis

of the septal shortening and stretching sequence.⁷ Pattern 1 was considered in case of double peaked systolic shortening, pattern 2 in case of early shortening peak, followed by prominent systolic stretching, and pattern 3 in case of pseudo-normal shortening with a late systolic shortening peak and/or if pattern 1 and 2 criteria were not met.⁷ If amplitude of the peaks were within 150% relative range of each other, more than one systolic peak and pattern 1 were adjudicated.⁷ Early septal thickening/thinning within the isovolumic contraction period defined the SF. The SF could be visualized on the short- or long-axis parasternal views either by using gray scale or tissue Doppler colour M-mode. Basal, mid, and apical segments of the septum were checked for SF presence.^{5,6} Septal strain tracing associated with pattern recognition and identification of the SF were independently performed offline in a centralized core laboratory in Lille by two trained independent investigators (A.M. and C.G.) blinded to the patients' clinical status and follow-up data. Reproducibility of septal deformation patterns was tested offline in the entire cohort by another trained investigator (S.M.). To evaluate inter-observer agreement of septal deformation patterns, all acquired grey-scale 2D images obtained from the apical four-chamber view were available to the second observer. Strain analysis of the interventricular septum was independently performed by the second observer, and pattern recognition was performed on the basis of this independent analysis. Change in LV end-systolic volume (Δ LVESV) was defined as the extent of reduction in LVESV between baseline and 6–9 months follow-up relative to baseline LVESV. Response to CRT was defined as a relative decrease in LV end-systolic volume \geq 15%, between baseline and 6–9 months follow-up.¹² Δ LVEDV, Δ LVEF, and Δ GLS were defined as the differences between baseline and 6–9 months follow-up values.

Outcomes

During follow-up, patients were monitored by their own private physicians. Events were recorded by clinical interviews and/or by phone calls to physicians, patients, and (if necessary) next of kin. The primary endpoint of the study was overall mortality and secondary endpoints were cardiovascular mortality and hospitalization for HF. Cardiovascular mortality was considered if death was related to HF, myocardial infarction, arrhythmia, or sudden death.

Statistical analysis

Quantitative data are presented as mean \pm standard deviation or median [25th–75th percentile]. Qualitative data are presented as absolute numbers and percentages. Comparison of the means was carried out using a paired two-sided Student's *t*-test or Mann–Whitney *U* test. Continuous variables for the three groups of septal deformation patterns were compared using one-way analysis of variance or Kruskal–Wallis test. Comparison of categorical variables was carried out using a chi-square test or a Fisher exact test as appropriate. The duration of follow-up was computed for each endpoint using the reverse Kaplan–Meier method. Survival curves were obtained using the Kaplan–Meier method. Univariate followed by multivariate Cox regression survival analyses were used to identify the relationship between septal deformation patterns, SF, and occurrence of events during follow-up. For both multivariate Cox analyses, model building techniques were not used and covariates entered in the model were considered for potential prognostic impact, on an epidemiological basis. These covariates included QRS duration, NYHA functional classes III–IV, age, coronary artery disease, serum creatinine levels, LBBB, and LVEF. The overall performance of the multivariable models was assessed using Bayesian information criteria. The increased discriminative values of septal deformation patterns and SF were investigated by estimating the C statistics. The integrated discrimination improvement and the net reclassification improvement were

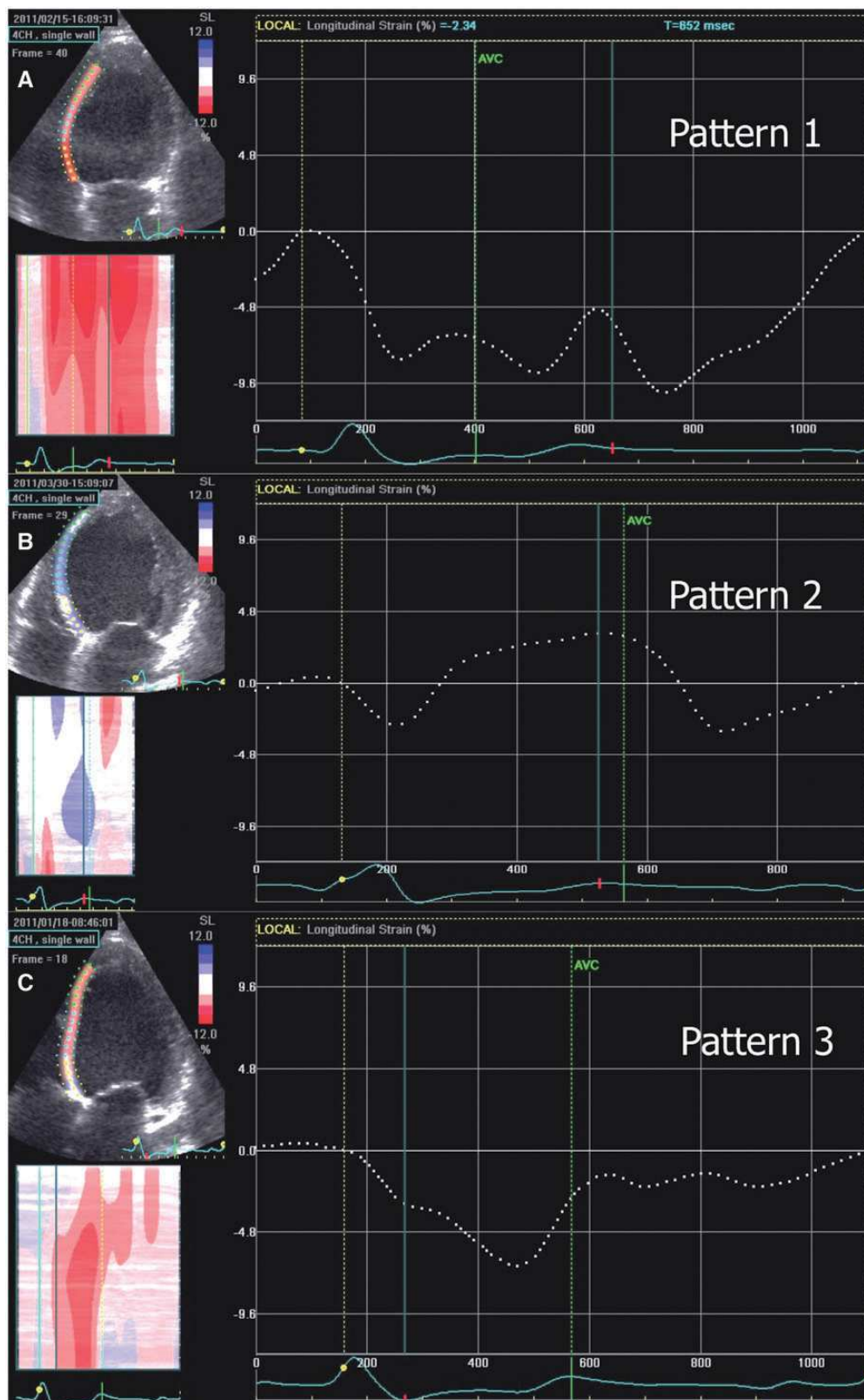


Figure 1 Septal longitudinal deformation patterns. Pattern 1 (A) was considered in case of a double-peaked systolic shortening, pattern 2 (B) in case of an early shortening peak followed by prominent systolic stretching, and pattern 3 (C) in case of if pseudo-normal shortening with a late systolic shortening peak. AVO, aortic valve opening; AVC, aortic valve closure.

Table 1 Demographic, clinical, and laboratory data in the study population and according to septal deformation patterns

	All N = 284	Septal pattern 1 N = 104	Septal pattern 2 N = 64	Septal pattern 3 N = 116	P-value
Demographic and clinical data					
Age (years)	70.2 ± 11.3	71 ± 11	67 ± 13	72 ± 11	0.024
Male gender, n (%)	194 (68)	68 (65)	36 (56)	90 (78)	0.009
BMI (kg/m ²)	27 ± 5	27 ± 5	27 ± 5	28 ± 5	0.022
Diabetes, n (%)	73 (26)	29 (28)	15 (23)	29 (25)	0.796
Dyslipidaemia, n (%)	118 (42)	44 (43)	23 (36)	51 (44)	0.562
Coronary artery disease, n (%)	100 (35)	32 (31)	16 (25)	52 (45)	0.014
Atrial fibrillation, n (%)	64 (23)	17 (17)	13 (20)	34 (30)	0.057
NYHA functional class III-IV	156 (55)	63 (61)	28 (44)	65 (56)	0.099
Heart rate (b.p.m.)	72 ± 14	70 ± 13	79 ± 15	70 ± 14	<0.001
Systolic blood pressure (mmHg)	123 ± 20	124 ± 19	122 ± 21	122 ± 21	0.855
Diastolic blood pressure (mmHg)	69 ± 12	68 ± 12	72 ± 12	68 ± 11	0.144
QRS width (ms)	164 ± 26	168 ± 25	166 ± 22	160 ± 28	0.089
QRS width < 150 ms, n (%)	61 (22)	19 (18)	8 (13)	34 (29)	0.019
LBBB, n (%)	213 (75)	78 (75)	57 (89)	78 (67)	0.005
RV pacing, n (%)	35 (12)	18 (17)	3 (5)	14 (12)	0.054
Beta blockers, n (%)	253 (90)	94 (90)	55 (86)	104 (92)	0.424
ACE inhibitors/ARB, n (%)	250 (89)	92 (89)	56 (88)	102 (90)	0.835
Biological data					
Creatinine (mg/dL)	13 ± 5	12.8 ± 6.8	11.4 ± 3.7	13.4 ± 4.7	0.060
BNP (pg/mL)*	428 [166;924]	294 [96;723]	419 [144;724]	566 [302;1154]	0.004
Echocardiography data					
LV Ejection Fraction (%)	27 ± 5	28 ± 4	24 ± 6	27 ± 6	<0.001
Myocardial scar, n (%)	45 (18)	12 (14)	8 (13)	25 (25)	0.064
Global Longitudinal Strain (%)	-8.0 ± 2.9	-8.5 ± 2.6	-6.5 ± 2.1	-7.9 ± 2.6	<0.001
LV end-diastolic diameter (mm)	66 ± 8	65 ± 8	70 ± 9	66 ± 8	0.001
SF, n (%)	224 (79)	96 (92)	60 (94)	68 (59)	<0.001

Data available in *204 patients.

determined, to further describe the added utility of both parameters when added to the multivariable model. Hazard ratios (HRs) for continuous variables in Cox models were rescaled by the within-study standard deviation. Cohen's kappa for two raters was obtained to assess inter-observer agreement of septal wall deformation patterns. Adjusted Cohen's kappa bootstrap confidence interval was obtained using 1000 samples (boot library in R). For all tests, a two-tailed *P*-value ≤ 0.05 was considered statistically significant. Statistical analysis was performed with R 3.0.3 (Youngstown, OH, USA).

Results

Baseline characteristics

Two hundred and eighty-four HF patients eligible for CRT were enrolled in the present study. Patient's characteristics are detailed in Table 1. Two hundred and thirteen patients (75%) had a LBBB, 30 (11%) had a non-specific intra-ventricular conduction delay, 6 had a RBBB (2%), and 35 had permanent right ventricular pacing (12%). Patterns 1 and 2 were observed in 104 (37%) and 64 (22%) patients, respectively (Table 1). More patients with pattern 3 (*n* = 116, 41%)

were male and LBBB was found less often; they also had shorter QRS duration, had ischemic heart disease, LV myocardial scarring, and atrial fibrillation compared with patients with pattern 1 or 2. The septal deformation patterns repartition did not differ between patients in NYHA functional class IV compared with those in NYHA functional classes II–III (29 vs. 37% of septal pattern 1, 24 vs. 23% of septal pattern 2 and 47 vs. 40% of septal pattern 3, *P* = 0.810). However, in the 203 patients with plasma BNP available, plasma BNP values were higher in patients with a septal pattern 3 compared with those with a septal pattern 1 or 2 (294[96;723] pg/mL in septal pattern 1, 419[144;724] pg/mL in septal pattern 2, and 566[302;1154] pg/mL in septal pattern 3, overall *P*-value = 0.004).

Septal deformation strain pattern and outcome following CRT

Death status was available for all participants. During a median 24-month follow-up, 41 patients died. Twenty-four patients died of cardiovascular causes, and cause of death remained unknown for three patients. Forty-seven patients were hospitalized for HF during follow-up.

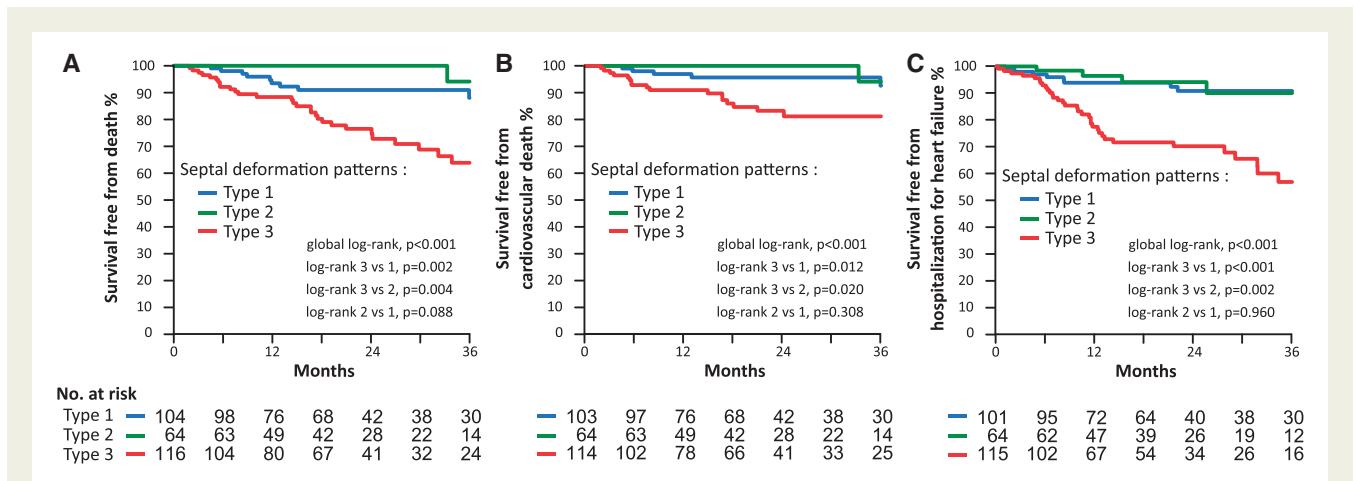


Figure 2 Kaplan–Meier event-free survival for mortality (A) cardiovascular mortality (B) and hospitalization for HF (C) according to septal deformation patterns.

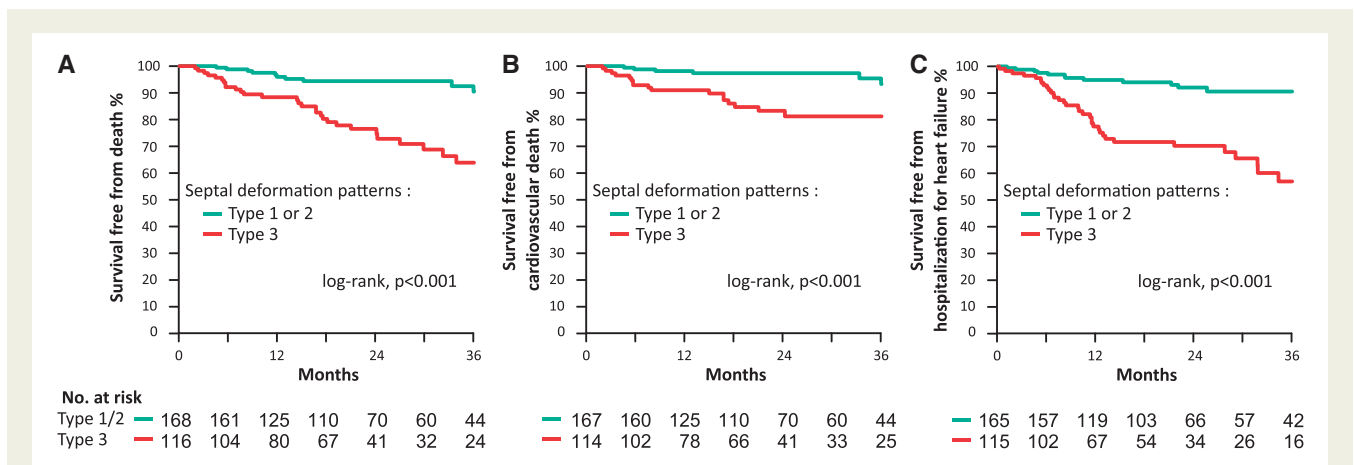


Figure 3 Kaplan–Meier event-free survival for mortality (A) cardiovascular mortality (B) and hospitalization for HF (C) according to septal deformation patterns.

Survival from all-cause mortality at 1 year, 2 years, and 3 years was, respectively, $95 \pm 5\%$, $91 \pm 6\%$, and $88 \pm 8\%$ in patients with pattern 1; 100%, 100%, and $94 \pm 6\%$ in patients with pattern 2; and $88 \pm 6\%$, $76 \pm 8\%$, and $61 \pm 11\%$ in patients with pattern 3 (Figure 2). All-cause mortality was higher in patients with pattern 3, compared with patients with either pattern 1 ($P = 0.002$) or pattern 2 ($P = 0.004$). Similarly, cardiovascular mortality and HF hospitalization rates were higher in patients with pattern 3 than for patients with either pattern 1 ($P = 0.012$ and $P < 0.001$, respectively) or pattern 2 ($P = 0.020$ and $P = 0.002$, respectively). Survival free from all-cause mortality, cardiovascular mortality, and hospitalization for HF was similar between patients with patterns 1 and 2 ($P > 0.05$ for all comparisons). Survival from overall mortality, cardiovascular mortality, and hospitalization for HF in patients with a septal pattern 1 or 2 compared with patients with a septal pattern 3 is represented in Figure 3.

Using Cox univariate analysis (Table 2), pattern 3 was associated with a significantly increased risk of all-cause mortality [HR = 4.41, 95% confidence interval (CI): 2.21–8.80, $P < 0.001$], cardiovascular mortality (HR = 4.82, 95% CI: 1.91–12.14, $P < 0.001$), and HF hospitalization (HR = 4.48, 95% CI: 2.36–8.49, $P < 0.001$) compared with patients with pattern 1 or 2. After adjustment, patients with pattern 3 still displayed an independent increased risk of overall mortality, cardiovascular mortality, and HF hospitalization compared with patients with pattern 1 or 2 (Table 2).

A follow-up echocardiogram was performed in 256 patients at 6–9 months follow-up. Twelve patients did not attempt their echocardiographic examination and 14 died before the second echocardiogram. Echocardiographic data and their changes during the follow-up are presented in Table 3. Δ LVESV, Δ LVEDV, Δ LVEF, and Δ GLS significantly differed in patients with a septal deformation pattern 3 compared with those with a septal deformation pattern 1 or 2.

Table 2 Relationship between septal deformation patterns 3 vs. 1–2 and all-cause mortality, cardiovascular mortality, and HF hospitalization by Cox analysis

	All-cause mortality		Cardiovascular mortality		HF hospitalization	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Univariate analysis						
Septal deformation pattern 3 vs. 1–2	4.41 (2.21–8.80)	<0.001	4.82 (1.91–12.14)	<0.001	4.48 (2.36–8.49)	<0.001
Multivariate analysis	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Septal deformation pattern 3 vs. 1–2	3.78 (1.85–7.75)	<0.001	3.84 (1.45–10.16)	0.007	4.41 (2.18–8.90)	<0.001
QRS width	0.96 (0.73–1.28)	0.803	0.73 (0.47–1.15)	0.173	0.82 (0.62–1.10)	0.18
NYHA functional class III or IV	2.41 (1.13–5.15)	0.024	2.14 (0.82–5.56)	0.118	1.30 (0.70–2.41)	0.408
Age	1.69 (1.10–2.59)	0.016	2.44 (1.29–4.60)	0.006	0.86 (0.62–1.19)	0.349
Coronary artery disease	0.85 (0.44–1.63)	0.629	0.71 (0.30–1.70)	0.445	0.99 (0.53–1.85)	0.971
Creatinine serum	1.34 (1.09–1.65)	0.006	1.36 (1.03–1.78)	0.029	1.44 (1.16–1.79)	<0.001
LV ejection fraction	0.62 (0.45–0.84)	0.002	0.55 (0.37–0.83)	0.005	0.72 (0.54–0.98)	0.034
LBBB	0.89 (0.44–1.80)	0.753	0.94 (0.35–2.52)	0.897	0.93 (0.47–1.85)	0.831

Table 3 Baseline and follow-up echocardiographic data according to the septal deformation patterns

Variable	[ALL] N = 284	Septal pattern 1 N = 104	Septal pattern 2 N = 64	Septal pattern 3 N = 116	P-value
LV ejection fraction					
Baseline LV ejection fraction (%)	27 ± 5	28 ± 4	24 ± 6	27 ± 6	0.002
9-month LV ejection fraction (%) ^a	39 ± 11	44 ± 10	41 ± 11	34 ± 11	<0.001
Δ LV ejection fraction ^a	13 ± 11	16 ± 9	16 ± 10	7 ± 11	<0.001
LV end-diastolic volume					
Baseline LV end-diastolic volume (mL)	242 ± 70	231 ± 65	265 ± 81	239 ± 66	0.018
9-month LV end-diastolic volume (mL) ^a	194 ± 72	172 ± 60	188 ± 84	216 ± 69	<0.001
Δ LV end-diastolic volume (mL) ^a	50 ± 55	60 ± 49	75 ± 64	25 ± 45	<0.001
LV end-systolic volume					
Baseline LV end-systolic volume (mL)	179 ± 60	167 ± 52	202 ± 70	178 ± 57	0.004
9-month LV end-systolic volume (mL) ^a	124 ± 68	101 ± 52	119 ± 80	147 ± 65	<0.001
Δ LV end-systolic volume (mL) ^a	57 ± 52	68 ± 41	82 ± 61	31 ± 44	<0.001
CRT responders (%) ^a	187 (73)	81 (89)	58 (92)	48 (47)	<0.001
Global longitudinal strain					
Basal global longitudinal strain (%)	-8.0 ± 2.9	-8.7 ± 2.9	-6.5 ± 2.3	-8.2 ± 2.9	<0.001
9-month global longitudinal strain (%) ^a	-10.1 ± 4.0	-11.8 ± 3.8	-10.3 ± 3.9	-8.6 ± 3.8	<0.001
Δ global longitudinal strain (%) ^a	-2.1 ± 3.5	-2.9 ± 3.5	-3.7 ± 3.6	-0.4 ± 2.8	<0.001

LV, left ventricle.

^aData available in 256 patients.

Septal deformation strain pattern and outcome in patients with 120–150 ms QRS duration

Characteristics of the 61 patients with QRS duration 120–150 ms, compared with patients with a QRS duration \geq 150 ms are detailed in Supplementary data online, Table S1. Frequency of septal patterns 1–2 was lower in this subgroup of patients compared with patients with QRS width $>$ 150 ms (44 vs. 63%, $P=0.01$). Survival free from all-cause mortality, cardiovascular mortality, and from HF hospitalization was lower in patients with a pattern 3 compared with those with a patterns 1–2 ($P=0.005$, $P=0.013$, and $P=0.019$, respectively, Figure 4).

Comparison with the SF

All-cause mortality, cardiovascular mortality, and HF hospitalization were lower by univariate analysis in patients with a SF than in those without (all log rank P -value <0.05 , Figure 5, see Supplementary data online, Table S2). The addition of septal deformation pattern to the multivariate model improved risk prediction and discrimination (Table 4). In contrast, adding the absence of SF to the same multivariate models did not improve risk prediction and discrimination (Table 4). In Figure 6, survival free from mortality, cardiovascular mortality, and HF hospitalizations, respectively, according to presence of the SF and/or septal patterns are shown.

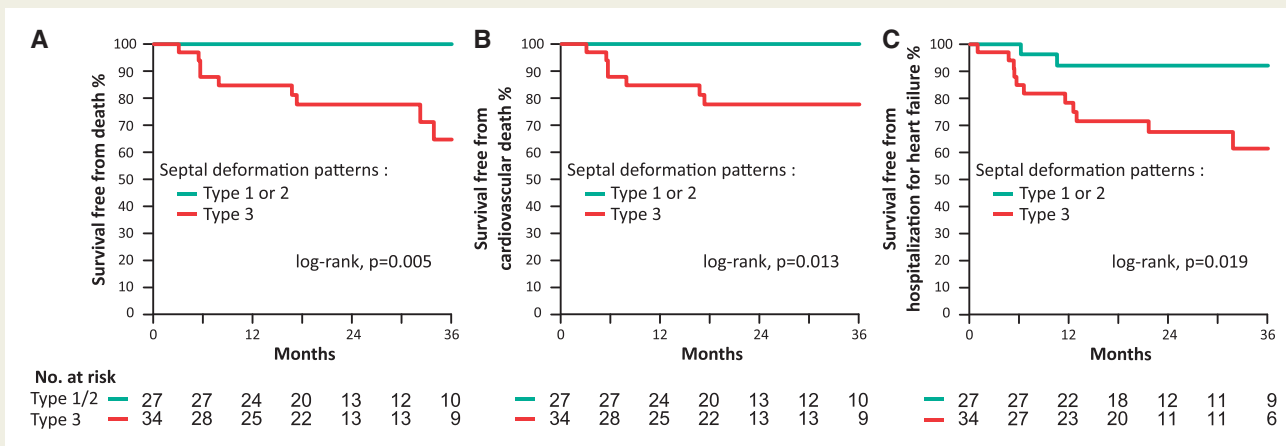


Figure 4 Kaplan–Meier event-free survival for mortality (A) cardiovascular mortality (B) and hospitalization for HF (C) according to septal deformation patterns in the patients with a QRS duration between 120 and 150 ms.

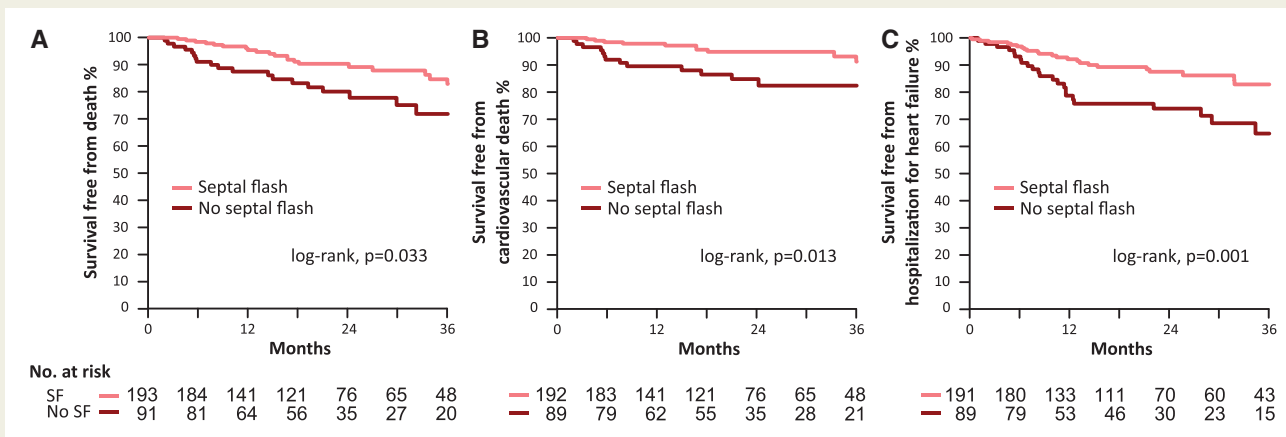


Figure 5 Kaplan–Meier event-free survival for mortality (A) cardiovascular mortality (B) and hospitalization for HF (C) according to the presence or absence of an SF.

Reproducibility

A suitable inter-observer agreement was found for septal deformation patterns in three categories as indicated by a kappa value at 0.82 (95% CI: 0.75–0.88).

Discussion

This study indicates that (i) septal deformation patterns are powerful independent predictors of clinical outcomes in addition to current predictors of outcome in CRT candidates; (ii) the prognostic value of septal deformation patterns remains unaltered in patients with intermediate QRS duration (120–150 ms); and (iii) the value of septal deformation patterns in terms of risk prediction and discrimination is significantly higher than the value of the SF.

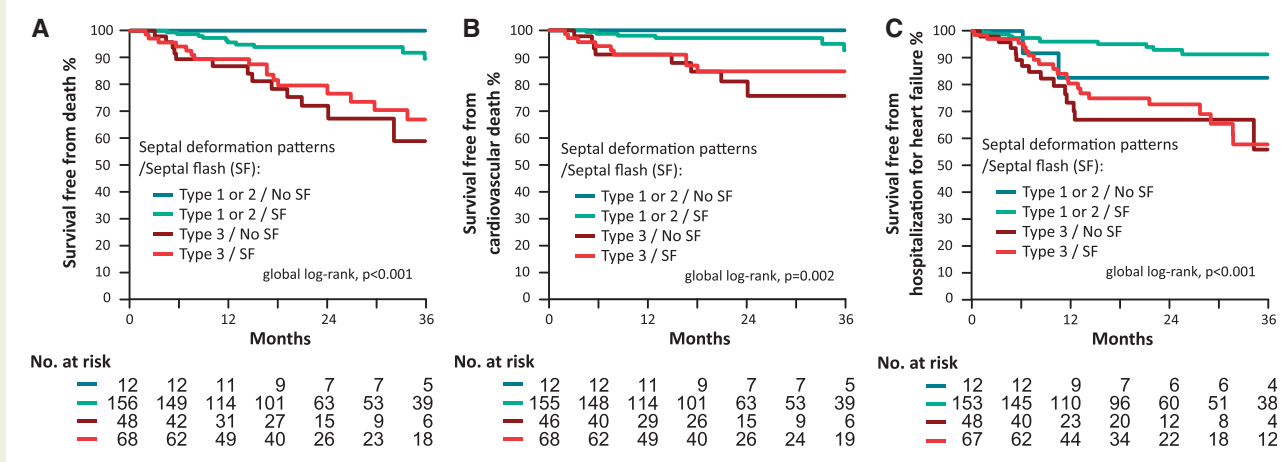
The LBBB is identified by an early deformation of the septum due to contraction of the right ventricle free wall (the SF, identified

visually or using M-mode, and/or tissue Doppler imaging), which is unopposed as contraction of the LV free wall is delayed due to the conduction delay.⁴ Presence of the SF is associated with reverse remodelling following CRT.⁵ The SF has, however, some disadvantages, such as limited value at rest.^{5,13} In contrast, dobutamine stress echocardiography may enhance the identification of SF to better predict LV reverse remodelling following CRT.¹³ Echocardiographic identification of SF was recently included in a multiparametric predictive score of LV reverse remodelling.¹⁴ In the recent PREDICT-CRT trial, both the absence and unsuccessful correction of SF were associated with both a high risk for non-response after CRT and unfavourable long-term survival.⁶ Importantly, inter-observer agreement for SF was only moderate here, with a kappa value of 0.71. In agreement with previous reports, a relationship was found in this present report, between SF and outcomes in univariate analysis. However, the relationship was weakened after adjustment for classical predictors of outcome in HF, thereby indicating the possibility

Table 4 Cox multivariate models: predictive value, discrimination, and reclassification with either septal deformation pattern 3 vs. 1–2 or absence of an SF

		Multivariable model	Multivariable model + absence of SF	Multivariable model + septal deformation pattern 3 vs. 1–2	
All-cause mortality	Prediction	Adjusted HR (95% CI), P	1.67(0.88–3.13), P = 0.121	3.78 (1.85–7.75), P < 0.001	
	Discrimination	BIC	417	420	407
		Harell's C statistic	0.745	0.747	0.799
		IDI	Reference	0.010(-0.006 to 0.066), P = 0.326	0.081(0.002–0.181), P = 0.047
		c-NRI	Reference	0.116(-0.163 to 0.345), P = 0.326	0.392(0.072–0.552), P = 0.033
Cardiovascular mortality	Prediction	Adjusted HR (95% CI), P	2.22(0.96–5.26), P = 0.063	3.84(1.45–10.16), P = 0.007	
	Discrimination	BIC	252	255	250
		Harell's C statistic	0.794	0.798	0.827
		IDI	Reference	0.021(-0.022 to 0.102), P = 0.405	0.049(-0.020 to 0.152), P = 0.219
		c-NRI	Reference	0.157(-0.352 to 0.401), P = 0.319	0.309(-0.018 to 0.542), P = 0.073
Hospitalization for HF	Prediction	Adjusted HR (95% CI), P	2.22(1.23–4.00), P = 0.008	4.41(2.18–8.90), P < 0.001	
	Discrimination	BIC	492	491	478
		Harell's C statistic	0.666	0.695	0.735
		IDI	Reference	0.024(-0.007 to 0.094), P = 0.179	0.121(0.038–0.227), P < 0.001
		c-NRI	Reference	0.217(-0.066 to 0.415), P = 0.126	0.483(0.182–0.661), P < 0.001

BIC, Bayesian information criteria; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

**Figure 6** Kaplan–Meier event-free survival for mortality (A) cardiovascular mortality (B) and hospitalization for HF (C) according to both the presence or the absence of the SF and septal deformation patterns 1–2 or 3.

for other indices of dyssynchrony to be amenable to CRT in clinical practice.

Septal motion can also be evaluated using speckle tracking longitudinal strain. Leenders *et al.*⁷ used computer-based simulation in humans, to report that the septal deformation pattern integrates the effects of dyssynchronous activation of the heart and differences in septal and LV free wall contractility, hence providing integrated information on two key determinants of CRT response. Pattern 1 was obtained by simulating typical LBBB dyssynchrony of ventricular activation with preserved septal and LV free wall contractility. Therefore, after the initial shortening, a second motion toward the

LV was observed after equalization of the wall stress between the septum and free wall, during the ejection phase (Figure 1). Pattern 2 was obtained by additionally imposing septal hypocontractility to the activation delay, hence resulting in a dyssynchronous motion of the septum within the whole systole because it cannot counterbalance the increase in LV pressure owing to the preserved LV free wall contraction (Figure 1). Lastly, deterioration in LV free wall contractility resulted in pattern 3; in this case, septal contraction is prolonged, because the free wall cannot generate wall stress against the septum to stop septal inward motion and push back toward the right ventricle (Figure 1). In addition, the presence of extensive LV fibrosis may be

associated with a type 3 pattern, as Leenders *et al.*⁷ demonstrated more scarred segments by echocardiography in patients with pattern 3 when compared with types 1 and 2, as is the case in the present report. However, magnetic resonance imaging studies are not available in the present cohort of patients. Further research may be conducted to establish the potential link between septal deformation patterns and the presence and extent of diffuse myocardial fibrosis with the use of the T1 mapping technique by cardiac magnetic resonance imaging (cMRI).

We previously demonstrated in a prospective pilot study involving patients with LBBB receiving CRT that patterns 1 and 2 were highly predictive of CRT response after CRT.⁸ The present prospective study builds on previous reports showing that septal deformation patterns are strong predictors of a poor outcome over classical prognostic factors in HF, including baseline QRS width and presence of a LBBB, in a larger cohort of patients receiving CRT. Patients with a pattern 1 or 2 have an excellent outcome following CRT compared with patients with a pattern 3. This finding is consistent with Risum *et al.*,¹⁵ showing that the identification of an activation delay between septal and lateral LV walls by longitudinal speckle tracking strain echocardiography may be more predictive of outcome than strict LBBB criteria on electrocardiogram in CRT recipients. Importantly, the proportion of patients with pattern 1 or 2 is lower in patients with intermediate QRS duration (120–150 ms) compared with patients with wide QRS (44 vs. 63%, $P=0.01$). Consistently, we previously reported that pattern 1 or 2 was very rare in HF patients with reduced LVEF and narrow QRS (QRS duration <120 ms).¹⁶ In a meta-analysis of five CRT randomized control trials, the benefit of CRT in terms of outcome was greater in patients with wide QRS (QRS > 150 ms), compared with those with a QRS duration between 120 and 150 ms who seemed to not gain any benefit from CRT.¹ Findings of the present study may be of importance, as patients with septal deformation patterns 1 or 2 identified among patients with intermediate QRS duration, are associated with an excellent outcome after CRT.

Patients with a pattern 3 may have a poor outcome and response rate to CRT because of more advanced HF, as indicated by an older age, a high proportion of male patients, a high frequency of CAD, a narrower QRS duration, and a lower frequency of LBBB. However, the prognostic value of septal deformation patterns persists even after adjustment on these factors linked to outcome and to the absence of response to CRT in HF patients. In addition, among patients with an indication for CRT, septal deformation patterns identify those with an excellent outcome (1–2 patients) when compared with others (3). Unfortunately, the natural history of patients with LV dysfunction and enlarged QRS according to septal deformation patterns cannot be assessed, as CRT is firmly recommended in these patients.

Limitations

Septal deformation patterns were not studied during the follow-up; further research is needed to describe a classification of these patterns during biventricular pacing. Patients with pattern 2 have a better outcome despite having higher LV volumes and lower LV ejection fraction and GLS than other patients as previously reported.⁷ These patients have probably a less advanced stage of the disease than type 3 patients and derive more benefit of CRT as pattern 1 patients. Besides the SF and septal deformation patterns, recent reports

highlighted the value of new echocardiography indices of electromechanical dyssynchrony based on the contractile consequences of the intra-LV activation delay to predict LV response and outcome after CRT.¹⁷ These indices include the LBBB—typical pattern by longitudinal strain,¹⁵ presence of apical rocking,⁶ and the systolic stretch index by radial strain.¹⁸ To our knowledge, only one study compared the reproducibility and the predictive value of SF and apical rocking.⁶ The predictive value of SF and apical rocking in terms of outcome was similar. Importantly, the inter-observer agreement for apical rocking was only moderate and similar to the SF, with a Kappa value of 0.71 for both. However, as indicated by Mada *et al.*,¹⁹ the reproducibility of the SF and/or apical rocking assessment is high for expert readers (Kappa = 0.90) but is poor for novice readers (Kappa = 0.25–0.53). In contrast, an automatic speckle tracking-based pattern analysis based on two indices of dyssynchrony responsive to CRT, yielded similar results in terms of reproducibility for both experts and novices (Kappa = 0.83, 0.85 and Kappa = 0.76, 0.88, respectively). Consistently, the visual septal deformation pattern recognition, which is in principle very comparable to the automatic speckle tracking based pattern analysis, had a similar reproducibility in the present report (Kappa = 0.82). Further large multicentre studies are needed to evaluate the reproducibility and the comparative predictive value of these indices of dyssynchrony responsive to CRT. The higher plasma BNP levels observed in patients with a pattern 3 compared with other patients suggest that the hemodynamic status of the patients may influence the septal patterns. This hypothesis deserves however specific longitudinal studies.

Conclusions

The identification of septal deformation patterns in CRT candidates provides important prognostic information in addition to current clinical, electrocardiographic and echocardiographic predictors of outcome in HF patients. This reproducible parameter may be particularly useful in patients with intermediate QRS duration in whom the benefit of CRT remains uncertain.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of interest: None declared.

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7 Facteurs déterminants de l'élargissement du QRS

7.1 Introduction

Nous avons pu montrer que l'élargissement du QRS est prédicteur de la mortalité totale et de la mortalité cardiovasculaire avec un sur risque multiplié par presque 3. Ce résultat est vérifié après ajustement sur les variables confondantes ce qui fait de ces patients un groupe à haut risque. Ces patients sont principalement des patients non répondeurs (53%) alors qu'il n'existe que 27% de non répondeurs chez les patients qui affinent leur QRS après TRC.

Nous pouvons alors nous poser la question des paramètres associés à l'élargissement du QRS : le traitement est-il mal administré ? (mauvaise position de sonde, mauvais paramètres de resynchronisation), ou existe-t-il un substrat de réponse à la resynchronisation ? (la largeur du QRS en base n'est pas lié à un trouble conducteur d'une branche et notamment de la branche gauche, en échocardiographie présence du substrat de la réponse au TRC).

Pour répondre à cette question, nous avons réalisé des analyses complémentaires qui ont été l'objet de la thèse d'exercice de cardiologie de Ludovic APPERT et sont actuellement en cours de publication.

7.2 Résultats

Une analyse en régression logistique visant à expliquer l'élargissement du QRS retrouve la largeur du QRS de base comme étant le facteur prédictif le plus important (OR 0.15 , IC 95 % 0.07 - 0.28, $p < 0.001$) suivi du diamètre télédiastolique du VG (OR 2.1, IC à 95% (1.22 - 3.8), $p = 0.010$) et de la positivité du QRS dans la dérivation D1 (OR 4.59, IC 95% (1.07 - 27.07), $p = 0.06$) qui est un marqueur de la qualité technique de la resynchronisation. Un QRS systématiquement élargi par un TRC alors que la technique et les paramètres de resynchronisation sont adaptés doit faire poser la question d'un mauvais substrat électrique de la désynchronisation (ex : élargissement du QRS lié à une hypertrophie VG avec éventuellement un trouble de conduction au niveau du Purkinje).

Un point intéressant est que la largeur du QRS de base explique en grande partie la variation de largeur du QRS après resynchronisation mais lorsque l'on s'intéresse à la mortalité, la variation de la largeur du QRS après resynchronisation (HR 2.67, IC 95% (1.07–6.65), $p = 0.035$) prend le pas en analyse de cox sur la largeur du QRS de base (HR= 1.00, IC 95% (0.68–1.47), $p = 0.989$).

Si l'on analyse maintenant les déterminants de la réponse en volume en régression logistique (diminution du volume télédiastolique du VG de plus de 15%), l'élargissement du QRS (OR=0.29, IC 95% (0.1 - 0.84), p=0.022) prend également le pas sur la largeur du QRS de base (OR= 1.21, IC 95% (0.76 - 2.03), p=0.432). Par ailleurs, l'impact du pattern de contraction septal en strain (type 3 vs 1 ou 2) est également majeur (OR=0.13, IC 95% (0.05 - 0.3), p<0.001).

Si l'on associe le pattern de contraction septale en échographie pré-TRC à l'élargissement du QRS, nous mettons en évidence un sous-groupe de patient dont le taux de non réponse est de 77% (Figure 14). Il sera donc particulièrement important en clinique d'identifier ces patients afin de discuter dès l'implantation d'un meilleur placement de la sonde VG, un réglage affiné des paramètres de resynchronisation (avec une aide possible de l'échographie), une stimulation multipoints ou encore un arrêt complet de la resynchronisation qui aurait un effet délétère.

Cet effet délétère de l'élargissement des QRS peut se voir dès les premiers jours. Une analyse systématique de l'Echographie précoce avec TRC montre que les patients qui élargissent leur QRS ont une moins bonne amélioration de la FEVG (5±8 vs 0.6±6 %, p<0.001) et une moins bonne amélioration du volume ventriculaire télésystolique (12±19 vs 1±19, p=0.001) que ceux dont le QRS est affiné.

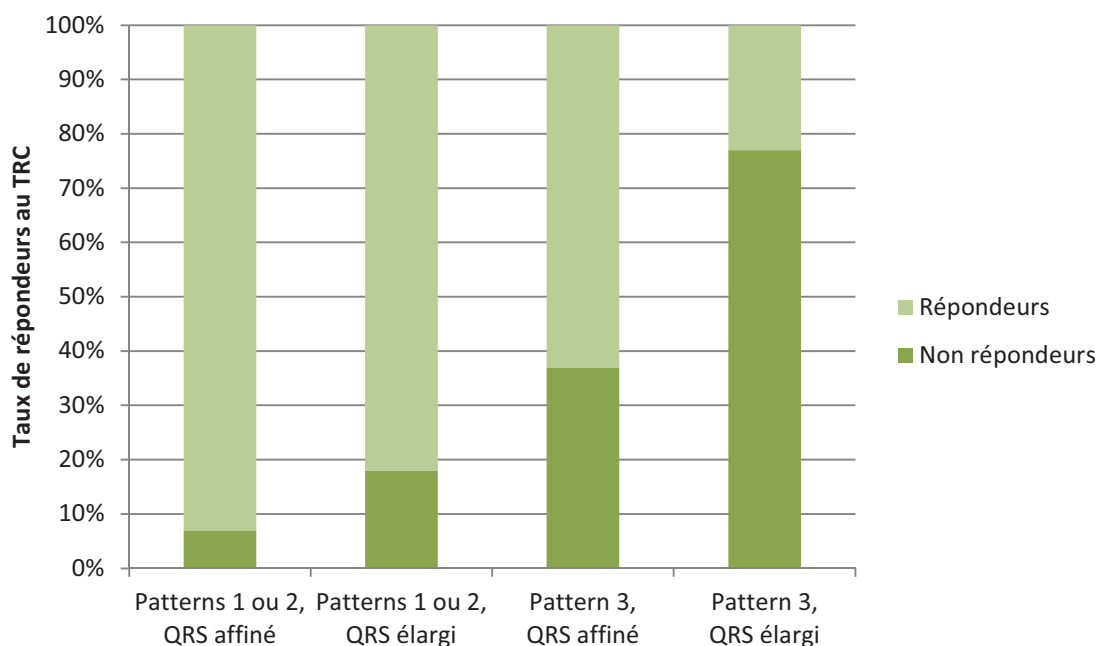


Figure 14. Taux de répondeurs (Δ VTSVG>15%) au TRC selon 4 groupes associant le pattern de contraction septal et l'élargissement du QRS après TRC. S'il existe un pattern 1 ou 2, le taux de réponse reste excellent (93 % si le QRS s'affine et 82 % si le QRS ne s'élargit). Si il existe un pattern 3 mais que le QRS est affiné après TRC, le taux de réponse reste correct à 63%. Par contre si il existe un pattern 3 et que le QRS s'élargit le taux de réponse s'effondre à 23%.

8 Rôle de l'échographie avant une resynchronisation cardiaque : nouvelles avancées et développements en cours.*

* Marechaux S, Menet A, Guyomar Y, Ennezat P-V, Guerbaai RA, Graux P, et al. Role of echocardiography before cardiac resynchronization therapy: new advances and current developments. *Echocardiogr Mt Kisco N.* nov 2016;33(11):1745-52.(144)

8.1 Introduction

Les nouveaux paramètres de désynchronisations qui ont vu le jour et les nombreuses heures passées à étudier la littérature et les ETT des patients avant un TRC nous ont progressivement amené à la certitude que l'analyse de ces paramètres ne peut pas être inutile dans la sélection des patients pour un TRC. C'est dans ce contexte qu'il nous a semblé nécessaire de proposer une nouvelle revue de la littérature de ce domaine.

8.2 Résumé

Le rôle de l'ETT pour améliorer la sélection des patients qui vont bénéficier d'un TRC reste débattu. Même si des études pionnières avaient rapporté le lien entre désynchronisation mécanique (évaluée par les délais de contraction entre les parois du ventricule gauche) et la réponse au TRC, la valeur prédictive de ces paramètres n'a pas été confirmée dans les études multicentriques. Cependant, de récentes études ont démontré que l'évaluation classique de l'asynchronisme mécanique du VG utilisant les délais entre paroi en ETT ne dépend pas uniquement d'un délai d'activation électrique (asynchronisme électrique) mais aussi d'anomalies de de contraction régionales et/ou de conditions de charge qui ne représentent pas une cible appropriée au TRC. De récentes études mettent en évidence de nouveaux indices de désynchronisation électromécaniques mesurés en ETT pour prédire la réponse et le pronostic après une TRC. Ces indices sont le flash septal, le pattern de contraction typique du BBG en strain longitudinal, le rocking apical, les patterns de strain septal et l'index d'étirement systolique. Ces indices permettent une approche mécanistique basée sur des séquences de contraction liées à un asynchronisme électrique. Ces indices sont rarement retrouvés chez les patients ayant des QRS fins (<120 ms) tandis que leur fréquence augmente chez les patients ayant une durée de QRS >120 ms. Ces indices devraient permettre d'améliorer la sélection des patients étant de bons candidats pour le TRC en pratique clinique, surtout ceux chez qui le bénéfice du TRC reste

incertain, par exemple les patients avec un QRS intermédiaire entre 120 et 150 ms ou une morphologie de QRS non BBG.

Role of echocardiography before cardiac resynchronization therapy: new advances and current developments

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The role of echocardiography in improving the selection of patients who will benefit from cardiac resynchronization therapy (CRT) remains a source of debate. Although previous landmark reports have demonstrated a link between mechanical dyssynchrony, assessed by delays between left ventricle (LV) walls and response to CRT, the predictive value of these findings has not yet been confirmed in multicenter trials. Indeed, recent studies demonstrated that the classical assessment of LV mechanical dyssynchrony using delay between walls by echocardiography depends not only on LV electrical activation delay (electrical dyssynchrony), but also on abnormalities in regional contractility of the LV and/or loading conditions, which do not represent an appropriate target for CRT. Recent reports highlighted the value of new indices of electromechanical dyssynchrony obtained by echocardiography, to predict LV response and outcome after CRT including septal flash, left bundle branch block—typical pattern by longitudinal strain, apical rocking, septal strain patterns, and systolic stretch index. This was achieved using a mechanistic approach, based on the contractile consequences of electrical dyssynchrony. These indices are rarely found in patients with narrow QRS (<120 ms), whereas their frequency rises in patients with an increase in QRS duration (>120 ms). These indices should improve candidate selection for CRT in clinical practice, especially for patients in whom the benefit of CRT remains uncertain, for example, patients with intermediate QRS width (120–150 ms).

KEYWORDS

cardiac resynchronization therapy, echocardiography, EKG, heart failure, outcome, speckle tracking

Cardiac resynchronization therapy (CRT) represents one of the major advances in the past two decades, for patients with heart failure and reduced left ventricular (LV) ejection fraction (HFrEF).¹ Besides coordinating contraction of LV segmental walls, CRT improves LV performance, LV filling function, reverses LV remodeling, and also reduces the amount of mitral regurgitation.^{2,3} CRT improves both quality of life and symptoms in HFrEF patients having electrical dyssynchrony (prolonged QRS duration).^{4,5} Also, CRT is correlated with a reduction in mortality in both symptomatic (NYHA functional class III–IV) and

minimally symptomatic (class I–II) patients.^{6,7} However, CRT is an invasive and costly procedure; thus appropriate patient selection is particularly important. Indeed, 20% to 40% of patients fail to improve after CRT, despite having baseline electrical dyssynchrony.⁵ Due to the low cost and wide availability of echocardiography, it can be considered as an adequate tool to detect CRT indications, by assessing LV myocardial mechanical dyssynchrony. However, despite initial encouraging results, a multicenter report failed to demonstrate benefit of echocardiographic assessment of mechanical dyssynchrony, in predicting

successful outcome after CRT, for improvement in heart failure symptoms or reverse remodeling.⁸ The present review aims to describe recent developments in the assessment of myocardial dyssynchrony, using echocardiography in HFrEF patients, to improve the selection of those who may derive benefit from CRT.

1 | ECHOCARDIOGRAPHY TO PREDICT RESPONSE TO CRT: THE CLASSICAL APPROACH

Response to CRT is commonly evaluated in terms of LV reverse remodeling. In clinical practice, a relative reduction of 15% or more in LV end-systolic volume compared to baseline defines LV reverse remodeling and has been associated with better long-term outcome after CRT.^{9–11} Other echocardiographic surrogates including improvement in LV ejection fraction and LV global longitudinal strain are also used in clinical practice.¹¹ Landmark reports from the early 2000s, describe the ability of echocardiographic indices to predict CRT response in HFrEF patients with electrical dyssynchrony (prolonged QRS duration >120 ms). Classically, mechanical dyssynchrony is evaluated in terms of atrioventricular dyssynchrony, interventricular dyssynchrony, and intraventricular dyssynchrony (Fig. 1). Intraventricular dyssynchrony was frequently evaluated by tissue Doppler imaging (TDI) (Fig. 1). Some TDI indices were developed including the basal septal to basal lateral delay in time-to-peak myocardial systolic velocity during the ejection phase, with reference to the onset of the QRS complex (Ts) (Fig. 1) or the standard deviation of Ts from 12 LV segments. These indices were highly predictive of CRT response in monocenter trials.^{12–15} However, despite these initial promising results, echocardiographic assessment of mechanical dyssynchrony was not predictive of CRT response in the multicenter PROSPECT trial.⁸ Moreover, reproducibility of echocardiographic indices, especially for TDI-derived indices was of concern, in this trial.⁸ Consequently, the 2010 ESC guidelines did not recommend the use of echocardiography and TDI-based indices of mechanical synchrony in patient selection.¹⁶

2 | ELECTRICAL VS MECHANICAL DYSSYNCHRONY

In patients without electrical dyssynchrony (narrow QRS duration <120–130 ms), CRT failed to consistently improve heart failure

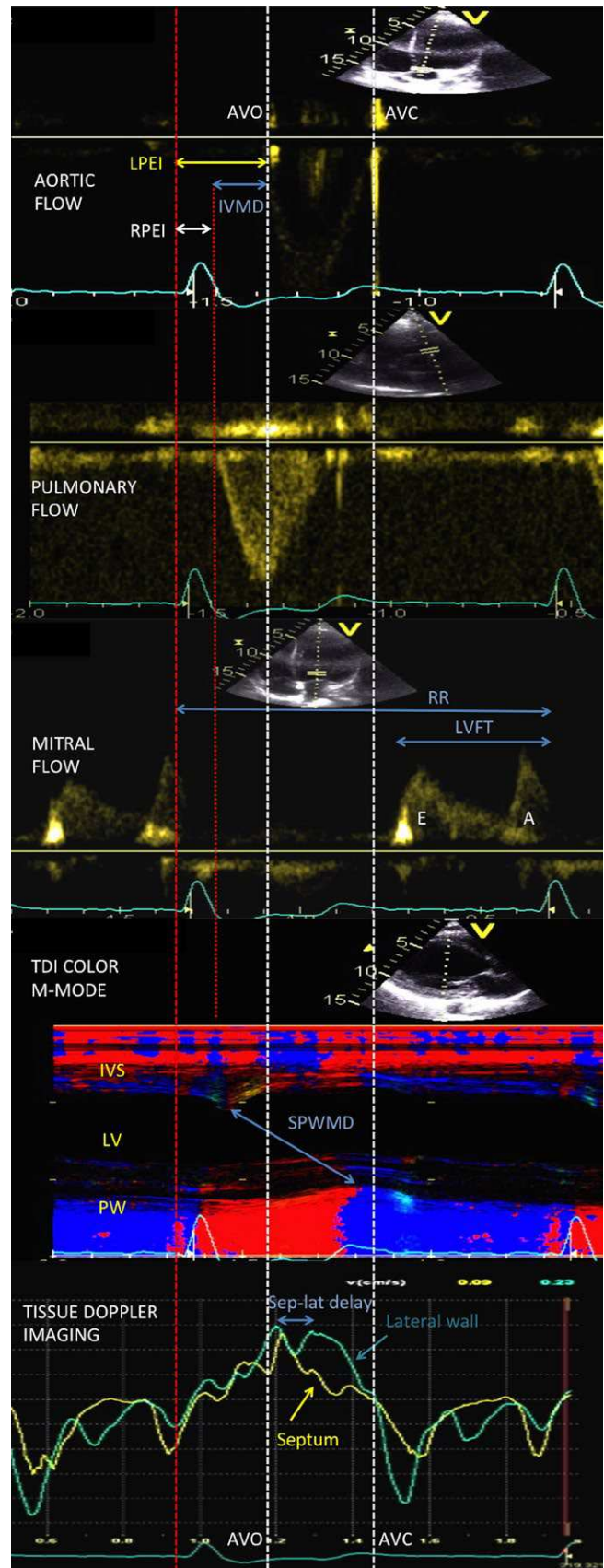


FIGURE 1 Classical echocardiographic indices of dyssynchrony obtained by blood flow Doppler, M-mode imaging, and pulsed-wave tissue Doppler imaging. LPEI = left ventricular preejection interval; RPEI = right ventricular preejection interval; IVMD = interventricular mechanical delay; LVFT = left ventricular filling time; IVS = interventricular septum; PP = posterior wall; LV = left ventricle; SPWMD = septal-to-posterior wall-motion delay; Sep-Lat delay: septal-to-lateral delay by tissue Doppler imaging; AVO = aortic valve opening; AVC = aortic valve closure

symptoms, functional capacity and outcome in clinical studies.^{17–21} The recent randomized controlled EchoCRT trial aimed to evaluate whether the identification of mechanical dyssynchrony using

TDI (septal-to-lateral wall delay >80 ms) and radial strain by speckle tracking (septal-to-posterior delay >130 ms) improved the outcome of HFrEF patients with narrow QRS (QRS duration <130 ms).²² In this trial, patients randomized to the CRT-On group displayed a significantly increased risk of overall mortality compared with those in the CRT-Off group.¹⁵ In addition, 76% of patients enrolled in this trial had persistent or worsened mechanical dyssynchrony 6 months after CRT, which translated into an unfavorable outcome in a post hoc analysis. Furthermore, a similar persistence or worsening of mechanical dyssynchrony in both CRT-Off and CRT-On groups was observed.²³ These findings clearly demonstrate that echocardiographic mechanical dyssynchrony without electrical dyssynchrony is frequently observed in HFrEF patients and is not affected by CRT, and thus do not represent an appropriate target for this therapy.

Lumens et al. used the computer-based Circ-Adapt model to demonstrate that besides electrical dyssynchrony, changes in regional LV function influence delays between LV walls in the event of LV systolic dysfunction.²⁴ Using speckle tracking radial strain, a simulated decrease in LV free wall contraction was associated with increased

delays between walls (Fig. 2B). Similarly, LV free wall scarring generated increased intraventricular delays (Fig. 2C). Accordingly, patients with ischemic cardiomyopathy and posterolateral myocardial scarring have been previously identified as poor responders to CRT.²⁵ Impact of LV loading conditions on LV mechanical dyssynchrony has also been documented using speckle tracking radial strain, in patients with nonischemic dilated cardiomyopathy and mainly narrow QRS.²⁶ Increasing afterload results in greater mechanical dyssynchrony, whereas decreasing afterload reduces mechanical dyssynchrony. Mechanical dyssynchrony in patients with HFrEF without electrical dyssynchrony is primarily related to changes in LV regional function and loading conditions and does not represent an appropriate target for CRT.

In randomized control studies testing the effect of CRT on outcome, patients had electrical dyssynchrony with a majority also having a left bundle branch block (LBBB). It has been suggested that only patients with LBBB benefit from CRT, compared to those with right bundle branch block or nonspecific intraventricular conduction delay. In addition, patients with a "true" LBBB (QRS duration ≥ 140 ms for men and ≥ 130 ms for women, along with mid-QRS notching or slurring in ≥ 2 contiguous leads) experienced more frequently reverse remodeling following CRT, compared to patients with a "false" LBBB (left ventricular hypertrophy and left anterior fascicular block).²⁷ Consistently, in a meta-analysis of five randomized control trials which included around 80% of patients with a LBBB, CRT was associated with an improved outcome when QRS duration was of 150 ms or more, while the benefit of CRT in patients with QRS duration of less than 150 ms remained unclear.²⁸

In normal conduction, activation begins within the LV and right ventricular endocardium. In a true LBBB, activation begins in the right ventricle and proceeds across the septum for 40 to 50 ms before reaching the LV endocardium and requires another 50 ms for reentry into the LV Purkinje network, to propagate to the endocardium of the posterolateral wall. Finally, another 50 ms is required to activate the posterolateral wall, producing a total QRS duration of 140 to 150 ms.²⁹ The first activation site of the LV endocardium is called the breakthrough site, which is a single site located in the mid-to-apical septum. Hence, the first notching/slurring on the EKG surface reflects the activation of the endocardial left ventricular septum, whereas the second represents the activation of the epicardial posterolateral wall. As the LV free wall is still not activated in LBBB during early systole, LV pressure does not rapidly increase. Thus, the septum can easily contract due to the reduced afterload, producing the distinctive, early rapid movement of the interventricular septum at the breakthrough site. This early movement is followed by a subsequent counter wall motion toward the right ventricle, mainly caused by the increasing LV pressure.³⁰ This movement has been called the "septal flash" or "septal beaking" and can be identified visually or using M-mode and/or TDI (Fig. 3, movie clips S1 and S2). As the septal wall cannot generate wall stress against the increased LV pressure, the septal wall is pushed back toward the right ventricle, resembling dyskinesia, even if the septal wall continues to contract. Late activation of

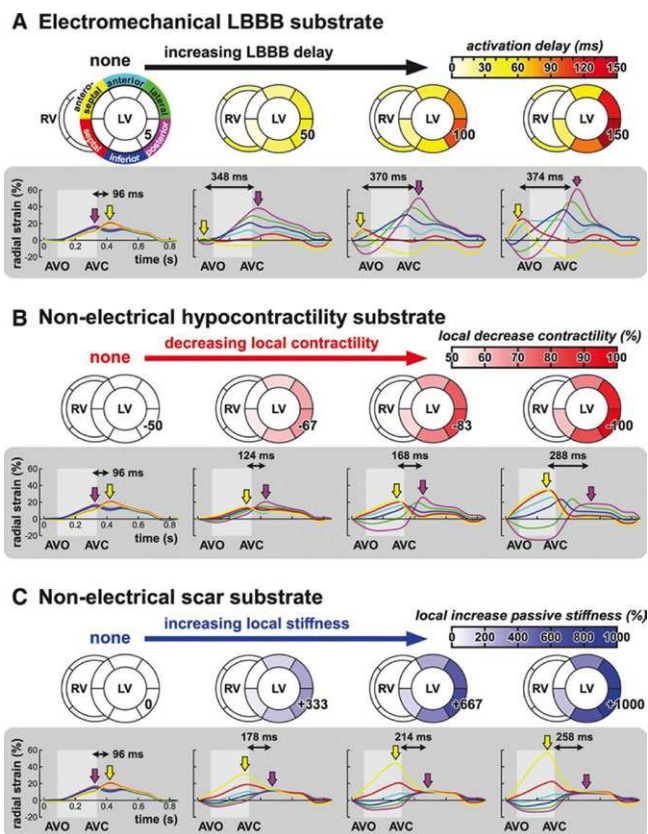
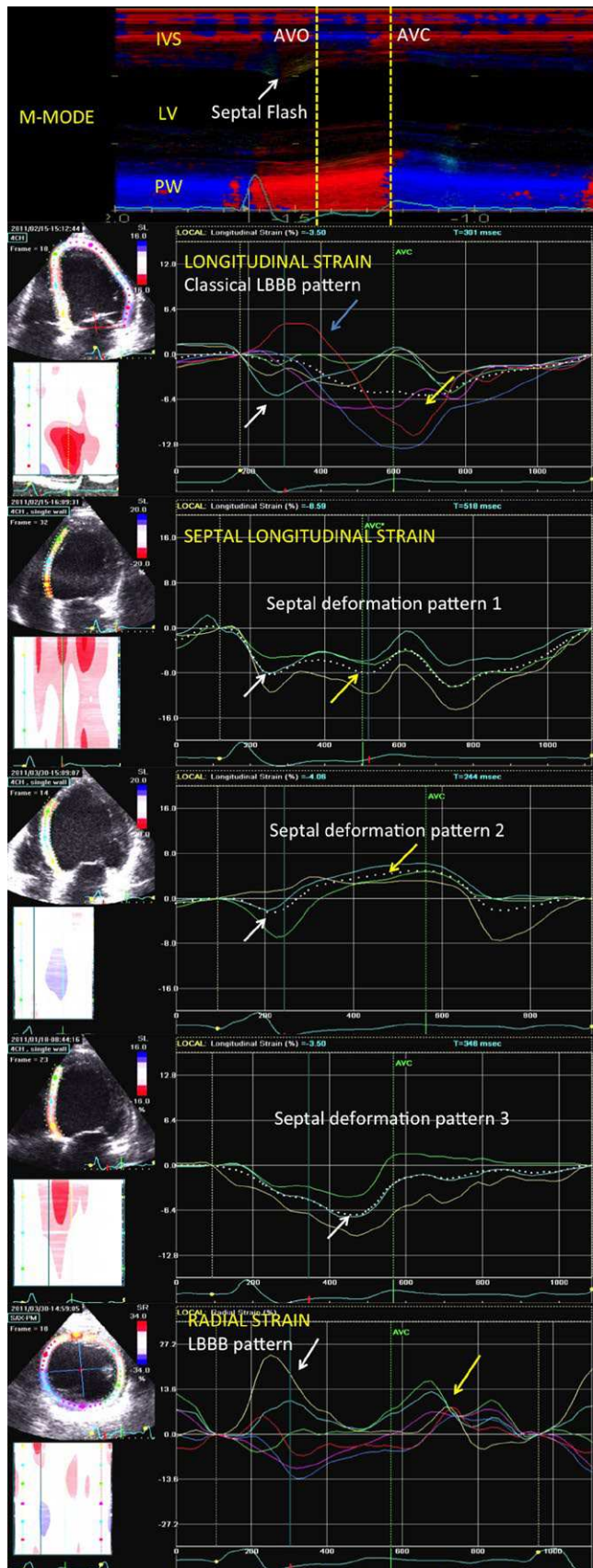


FIGURE 2 Simulated substrates of mechanical dyssynchrony. **A.** electromechanical dyssynchrony induced by a LBBB; **B.** mechanical dyssynchrony induced by a more pronounced deterioration in LV free wall contractility compared with the LV septal wall; **C.** mechanical dyssynchrony induced by increased stiffness of LV walls with a LV septal-to-lateral gradient. Reproduced from Lumens et al.,²⁴ with permission



the epicardial posterolateral wall is consequently identified by a late postsystolic contraction occurring after aortic valve closure (Fig. 3).

FIGURE 3 Indices of electromechanical dyssynchrony responsive to CRT by M-mode imaging, speckle tracking longitudinal and radial strain. AVO= aortic valve opening; AVC= aortic valve closure; IVS= interventricular septum; PP= posterior wall; LV= left ventricle. The septal flash (SF) corresponds to an early terminated posterior movement of the interventricular septum toward the left ventricle. The classical longitudinal LBBB pattern is defined as (1) early shortening of at least one basal or mid-ventricular segment in the septal wall (white arrow) and early stretching in at least one basal or mid-ventricular segment in the lateral wall (blue arrow); (2) early septal peak shortening (within the first 70% of the ejection phase); and (3) lateral wall peak shortening after aortic valve closure (yellow arrow). Septal deformation patterns were classified on the basis of the septal shortening and stretching sequence (dotted curves). Pattern 1 was considered in case of a double-peaked systolic shortening (white and yellow arrows). Pattern 2 was considered in case of an early shortening peak followed by prominent systolic stretching (white arrow). Pattern 3 was considered if pseudo-normal shortening with a late systolic shortening peak (white arrow). The radial LBBB pattern is characterized by an early deformation of the anteroseptal wall (white arrow) and a late postsystolic deformation of the posterolateral wall (yellow arrow)

3 | IDENTIFICATION OF ELECTROMECHANICAL DYSSYNCHRONY BY ECHOCARDIOGRAPHY

3.1 | Septal flash and apical rocking

Previous reports demonstrated that the presence of a septal flash is associated with reverse remodeling following CRT in HFrEF patients.^{31,32} Inclusion of the septal flash recorded by echocardiography in a multiparametric predictive score of LV reverse remodeling resulted in significant improvement of the predictive value of the score, over clinical and electrocardiographic data.³³ However, it has been suggested that performing a dobutamine stress echocardiography, compared with a resting examination, may enhance the identification of the septal flash to help predict CRT response.³¹ Apical rocking, identified in apical four-chamber view, is characterized by a short septal motion of the apex due to early contraction of the septum in systole and a subsequent long motion to the lateral side during ejection, due to the late lateral contraction caused by the LBBB. This rocking movement results in a clockwise motion of the LV apical myocardium perpendicular to the LV long axis (movie clip S3). Clockwise apical rocking is strongly linked to the etiology of LV dysfunction (dilated cardiomyopathy) as patients with ischemic heart disease may have a counter clockwise rotation or no rotation of the LV apex.³⁴ The magnitude of the apical rocking is proportional to LV end-diastolic volume in dilated cardiomyopathy and is not influenced by QRS duration.³⁴ Apical rocking in multivariable analyses has been associated with fewer major adverse cardiac events in patients receiving CRT.³⁵ In the recent PREDICT-CRT trial, absence of apical rocking and unsuccessful correction of the septal flash were associated with a high risk for CRT failure and unfavorable long-term survival.³⁶ Unfortunately, inter-observer agreement for both apical rocking and septal flash was only moderate, with a Kappa value of 0.71,³⁶ indicating that

the assessment of these parameters may not be sufficient in routine practice.

Delay between the early activated septum and the late activated posterolateral wall can also be identified using speckle tracking strain echocardiography. Lumens and colleagues used the Circ-Adapt model to show that simulating a progressive increase in LBBB-mediated LV activation delays resulted in increasing delays between septal and posterolateral walls, assessed by radial strain speckle tracking imaging (Figs 2A and 3). Identification of a large delay between an early septal flash and a postsystolic delayed posterior wall contraction, obtained from standard M-mode recordings or from radial strain time-dependent curves, may help to differentiate patients with electromechanical dyssynchrony responsive to CRT from those with mechanical dyssynchrony.^{37,38} However, reproducibility issues may occur with radial strain by speckle tracking and may be highly sensitive to the out-of-plane motion of the speckles owing to the longitudinal movement of the heart.³⁹

3.2 | Classical LBBB longitudinal strain pattern

Longitudinal strain obtained by speckle tracking is highly reproducible and has been widely accepted when compared with radial strain, in most clinical situations.⁴⁰ Among patients with a LBBB, some have a typical LBBB longitudinal deformation pattern, including all three following criteria: (1) early shortening of at least one basal or mid-ventricular segment in the septal wall and early stretching in at least one basal or mid-ventricular segment in the lateral wall; (2) early septal peak shortening (within the first 70% of the ejection phase); and (3) lateral wall peak shortening after aortic valve closure (Fig. 3).⁴¹ This typical pattern was more frequently found in patients with strict LBBB criteria.⁴² This was additionally observed in patients with QRS width duration of 150 ms or more⁴³ and was strongly associated with effective CRT response.⁴¹ In a recent bicenter report, absence of a typical LBBB pattern was strongly associated with poor outcome in patients receiving CRT, even in the subgroup of patients with intermediate QRS width (duration from 120 to 150 ms) (Fig. 4).⁴³ This approach was highly reproducible. Poor prognosis of the absence of this typical pattern was also found in RV-paced patients upgraded to CRT, the apex being more often the first activated segment in this latter case.⁴⁴

3.3 | Septal deformation patterns

The septal motion associated with LBBB can also be evaluated using speckle tracking longitudinal strain. The amount of stretching following prematurely terminated preejection septal shortening has been associated with LV reverse remodeling and determines outcome following CRT.⁴⁵ Leenders et al., using computer-based simulation in humans, reported that the septal deformation pattern integrates the effects of dyssynchronous activation of the heart and differences in septal and LV free wall contractility, providing integrated information on two key determinants of CRT response.⁴⁶ Pattern 1 was obtained by simulating typical LBBB dyssynchrony of ventricular activation

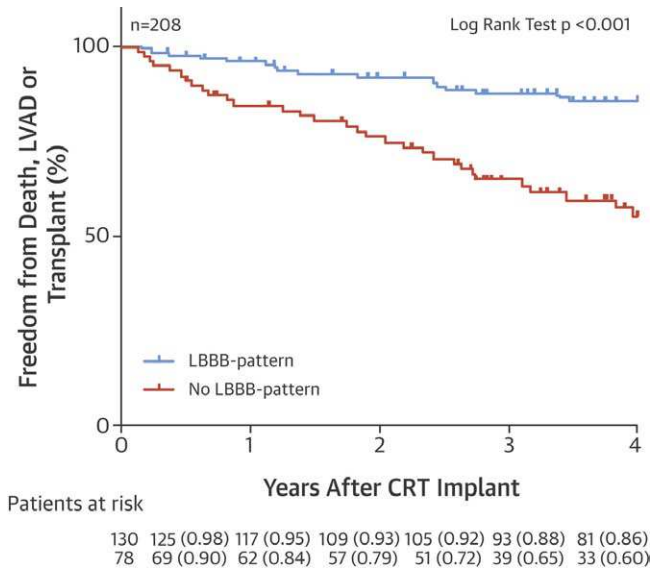


FIGURE 4 Kaplan–Meier curves showing freedom from death, left ventricular assist device, or heart transplant after CRT according to the presence of a typical LBBB longitudinal pattern. Reproduced from Risum et al.,⁴³ with permission

with preserved septal and LV free wall contractility. Hence, after the initial shortening, a second motion toward the left ventricle was observed after equalization of the wall stress between the septum and free wall, during the ejection phase (Fig. 3). Pattern 2 was obtained by additionally imposing septal hypocontractility to the activation delay, resulting in a dyskinetic motion of the septum within the whole systole, as it cannot counterbalance the increase in LV pressure owing to the preserved LV free wall contraction (Fig. 3). Lastly, deterioration in LV free wall contractility resulted in pattern 3. In this case, septal contraction is prolonged, as the free wall cannot generate wall stress against the septum to stop septal inward motion and push back toward the right ventricle (Fig. 3). Importantly, the mechanisms responsible for the septal flash and the amount of septal stretching (septal rebound stretch) seem to differ. Indeed, the mechanism driving the septal flash is early contraction of the right ventricular free wall, which exerts force on the septum and pulls it leftwards when unopposed by contraction of the left ventricular free wall. In contrast, septal rebound stretch depends on early shortening of the septum being terminated by late contraction of the left ventricular free wall.⁴⁷

We previously demonstrated in a prospective study that patterns 1 and 2, present in 62% of patients with LBBB receiving CRT, were highly predictive of LV reverse remodeling after CRT (91% positive predictive value).⁴⁸ Patients with pattern 3 experienced LV reverse remodeling in only 59% of cases and had an increased risk of death or hospitalization for heart failure after CRT, compared to those with patterns 1 or 2. The kappa value for inter-reader variability for characterization of septal deformation pattern was excellent at 0.84. Larger studies are needed to identify predictors of “nonresponse” in patients with pattern 3 and to further explore the prognostic value of these patterns.

3.4 | Systolic stretch index (SSI)

Lumens et al., using computer-based simulations, designed a radial strain-based index, sensitive to the electromechanical substrates responsive to CRT and relatively insensitive to nonelectrical substrates.²⁴ This novel index, called SSI, was defined as the sum of posterolateral systolic prestretch and septal systolic rebound stretch, which characterized the electromechanical substrate responsive to CRT. Importantly, in a validation cohort of 191 patients receiving CRT, the authors observed that patients with $SSI \geq 9.7\%$ had significantly less heart failure hospitalizations or deaths 2 years after CRT (hazard ratio, 0.32; 95% confidence interval, 0.19–0.53) and less deaths, transplants, or LV assist devices (hazard ratio, 0.28; 95% confidence interval, 0.15–0.55). Consistently, $SSI \geq 9.7\%$ remained independently associated with significantly less heart failure hospitalizations or deaths (hazard ratio, 0.41; 95% confidence interval, 0.23–0.79; $P=.004$) and less deaths, transplants, or LV assist devices (hazard ratio, 0.27; 95% confidence interval, 0.12–0.60; $P=.001$) in patients with intermediate QRS duration or a non-LBBB morphology on the EKG.

3.5 | Relationship between electromechanical dyssynchrony and electrical dyssynchrony

In a recent report, we investigated classical mechanical dyssynchrony indices and electromechanical indices amenable to CRT in four groups of patients: patients with HFrEF, a prolonged QRS duration and an indication for CRT (group 1); patients with HFrEF and a narrow QRS (group 2); patients with heart failure and preserved ejection fraction (group 3); and patients with hypertension, without any history of heart failure (group 4).⁴⁹ Importantly, tissue Doppler-based indices of mechanical dyssynchrony were grossly similar among these four groups. In contrast, indices of electromechanical dyssynchrony (septal flash, typical LBBB longitudinal pattern, and septal deformation pattern 1 or 2) were highly prevalent in patients with HFrEF and prolonged QRS duration and very rare in other patients, including patients with HFrEF and narrow QRS.⁴⁹ Using a principal component analysis approach, we demonstrated that these indices of electromechanical dyssynchrony were mostly found in patients having HFrEF and prolonged QRS duration awaiting CRT. In contrast, patients with HFrEF and narrow QRS, and hypertensive or HFpEF patients were similar in terms of mechanical dyssynchrony. Hence, these findings demonstrate that electrical dyssynchrony on EKG is strongly related to echocardiographic indices of electromechanical dyssynchrony responsive to CRT.

4 | FUTURE DEVELOPMENTS AND POTENTIAL ROLE OF ECHOCARDIOGRAPHY IN THE SELECTION OF PATIENTS BEFORE CRT

None of the previously reported studies were randomized; therefore, the relationship between echocardiographic indices of

electromechanical dyssynchrony responsible to CRT and outcome of patients who did not undergo CRT remains unknown. As patients with a very prolonged QRS duration (≥ 150 ms) derive maximal benefit from CRT in randomized controlled studies, excluding these patients from CRT would be unethical. In contrast, identification of reliable electromechanical indices of dyssynchrony by echocardiography in patients with QRS of 120–149 ms is of particular interest, as this subgroup of patients does not seem to derive benefit from CRT in a recent meta-analysis.²⁸ Accordingly, randomized controlled trials using electromechanical dyssynchrony may be considered in this subgroup of patients with intermediate QRS duration. Factors other than dyssynchrony may primarily negatively impact on outcome after CRT, including extent of LV myocardial scarring, identified by cardiac MRI and importance of LV diastolic and right systolic ventricular dysfunction. In addition, LV lead position optimization or technological advances in CRT devices as multipoint pacing, may improve cardiac resynchronization and consequently patient outcome. In the near future, a multimodal approach including echocardiography, cardiac CT and electro-anatomical mappings should improve patient selection for CRT.⁵⁰

5 | CONCLUSION

Classical assessment of LV mechanical dyssynchrony using delay between walls by echocardiography depends not only on electrical dyssynchrony, but also on abnormalities in regional contractility of the LV and on loading conditions; therefore, it may not represent an appropriate tool to select appropriate patients for CRT. In contrast, the echocardiographic identification of electromechanical dyssynchrony based on a mechanistic approach using septal flash, apical rocking, typical LBBB longitudinal pattern, septal deformation patterns, and systolic stretch index may be a more effective approach, especially for patients with intermediate QRS width, for whom the benefit of CRT remains uncertain.

FUNDING

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Movie clip S1. Parasternal long axis view illustrating the septal flash (arrow); LV: left ventricle; LA: left atrium.

Movie clip S2. Apical 4-chamber view illustrating the septal flash (arrow); LV: left ventricle; LA: left atrium.

Movie clip S3. Apical 4-chamber view illustrating apical rocking (arrows); LV: left ventricle; LA: left atrium.

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9 Evolution de la regurgitation mitrale secondaire chez des patients insuffisants cardiaques après resynchronization biventriculaire: impact sur le pronostic à long-terme au-delà du remodelage inverse*

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9.1 Introduction

La fuite mitrale secondaire est fréquente chez les patients ayant une insuffisance cardiaque avec FEVG basse et elle est prédictive d'un mauvais pronostic.(145,146) La fuite mitrale secondaire est la résultante d'un déséquilibre entre une diminution des forces de fermeture mitrales et une augmentation des forces de tension sur les cordages mitraux dues à la diminution et/ou incoordination de la contraction du VG. Le TRC entraîne une diminution de la fuite mitrale secondaire à court et à long terme.(147–150) A court terme, le mécanisme évoqué de diminution de la fuite mitrale secondaire est une amélioration des forces de fermeture de la valve mitrale, résultant eux même d'une meilleure coordination des muscles papillaires et d'une amélioration de la fonction VG. A long terme, le mécanisme est surtout attribué au remodelage inverse du VG.(151,152) La réduction de la fuite mitrale secondaire après TRC a été associée à un meilleur pronostic.(153) Cependant, à notre connaissance, la valeur pronostique de l'insuffisance mitrale secondaire en base vs à court et long terme après TRC au-delà du remodelage ventriculaire gauche n'a pas été évaluée. L'objectif de cette étude est d'évaluer dans une large cohorte de patients insuffisants cardiaques recevant un TRC 1/ l'évolution de l'insuffisance mitrale secondaire en base, en post TRC précoce et tardif 2/la relation entre l'insuffisance mitrale significative à chaque étape, le remodelage inverse du VG dans le suivi et les évènements cardiovasculaire majeurs au long cours et 3/la valeur pronostique de la présence d'une insuffisance mitrale secondaire tardive après TRC sur les évènements cardiaques majeurs indépendamment du remodelage VG inverse.

9.2 Résultats

Nous avons pu mesurer l'insuffisance mitrale en pré et en post implantation immédiate de TRC chez 198 patients de notre cohorte. Une échocardiographie tardive à 9 mois du TRC a pu être effectuée chez 172 patients. Nous avons regardé l'impact d'une insuffisance mitrale secondaire significative (fuite au moins modérée) sur la mortalité totale, la mortalité cardiovasculaire et les hospitalisations pour insuffisance cardiaque à chaque étape. La fréquence des fuites mitrales secondaires significatives a baissé de 23% (n=45) à 8% (n=16) immédiatement après le TRC. Parmi les 172 patients qui ont bénéficié d'une échocardiographie à 9 mois, 17 patients (10%) avaient une insuffisance mitrale secondaire significative. Durant une durée médiane de suivi de 48mois, 49 patients sont morts et 36 patients ont été hospitalisés pour insuffisance cardiaque. Les patients ayant une insuffisance mitrale secondaire significative après un TRC (qu'elle soit précoce ou tardive) avaient un risque de décès total, de décès cardiovasculaire et d'hospitalisations pour insuffisance cardiaque plus élevé que les autres patients. En ajustant sur le remodelage inverse dans le suivi, la fuite mitrale secondaire significative restait associée à un sur-risque de mortalité totale (HR ajusté 3.77, p=0.014), de mortalité cardiovasculaire (HR ajusté 5.36, p=0.037) et d'hospitalisations pour insuffisance cardiaque (HR ajusté 7.33, p=0.001). L'insuffisance mitrale secondaire significative persistante malgré un TRC est un facteur pronostic important en sus du remodelage du VG. Des études sont nécessaires pour évaluer l'impact des nouvelles procédures percutanées de réparation mitrale pour améliorer le pronostic de ces patients à très haut risque.

The time course of secondary mitral regurgitation in heart failure patients receiving cardiac resynchronization therapy: impact on long-term outcome beyond left ventricular reverse remodeling.

Evolution de la regurgitation mitrale secondaire chez des patients insuffisants cardiaques après resynchronization biventriculaire: impact sur le pronostic à long-terme au-delà du remodelage inverse

Running title: *Secondary MR and CRT*

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ABSTRACT

Background- The aim of the present study is to evaluate the clinical significance of secondary mitral regurgitation (MR) prior or early and late after cardiac resynchronization therapy (CRT) in a large cohort of patients with heart failure and reduced ejection fraction.

Methods and results- 198 patients prospectively recruited underwent baseline and early post-CRT echocardiography. Late post-CRT echocardiography was performed 9-months after CRT implantation in 172 patients. The impact of significant secondary MR (\geq moderate) on overall and cardiovascular mortality, and on hospitalization for heart failure (HF) was studied, at each stage. The frequency of significant secondary MR decreased from 23% (n=45) to 8% (n= 16) immediately after CRT. Among the 172 patients who underwent late echocardiography follow up, 17 patients (10%) had significant secondary MR. During a median follow up of 48 months, 49 patients died and 36 were hospitalized for HF. Patients with either early or late post-CRT significant secondary MR, displayed an increased risk of death, cardiovascular death and heart failure hospitalizations during follow up ($p<0.05$ for all endpoints). After adjustment on LV reverse remodeling, late post-CRT significant secondary MR, remained associated with an increased risk of overall mortality (adjusted HR 3.77, $p=0.014$), cardiovascular mortality (adjusted HR 5.36, $p=0.037$), and HF hospitalizations (adjusted HR 7.33, $p=0.001$).

Conclusions- Significant secondary MR in spite of CRT portends important prognostic information beyond LV reverse remodeling. Further studies are needed to evaluate the role of new percutaneous procedures of mitral valve repair in order to improve the outcome of these very high-risk patients.

Keywords: Cardiac resynchronization therapy; heart failure; outcome; secondary mitral regurgitation; echocardiography.

RESUME

Contexte- Le but de cette étude était d'évaluer la signification clinique de l'insuffisance mitrale secondaire avant, précocement et tardivement après resynchronisation biventriculaire dans une large cohorte de patients insuffisants cardiaques par dysfonction systolique du ventricule gauche.

Méthodes et résultats- 198 patients recrutés prospectivement ont bénéficié d'une échocardiographie avant et juste après l'implantation d'un stimulateur cardiaque en resynchronisation biventriculaire. Une échocardiographie tardive était réalisée 9 mois après l'implantation chez 172 patients. L'impact de l'insuffisance mitrale secondaire significative (\geq grade 2) sur la mortalité totale et cardiovasculaire et sur les hospitalisations pour insuffisance cardiaque était étudié à chaque stade. La fréquence de l'insuffisance mitrale secondaire significative diminuait de 23% (n=45) en pré-implantation à 8% (n= 16) immédiatement après l'implantation. Parmi les 172 patients qui ont bénéficié d'une échocardiographie tardive, 17 patients (10%) avaient une insuffisance mitrale secondaire significative. Pendant un suivi médian de 48 mois, 49 patients sont décédés et 36 ont été hospitalisés pour insuffisance cardiaque. Les patients avec une insuffisance mitrale secondaire significative précocement ou tardivement après resynchronisation biventriculaire présentaient un risque accru de mortalité, de mortalité cardiovasculaire et d'hospitalisation pour insuffisance cardiaque dans le suivi ($p < 0.05$ pour tous les critères de jugement) Après ajustement sur la survenue d'un remodelage inverse dans le suivi, l'insuffisance mitrale secondaire tardivement après resynchronisation biventriculaire restait associée avec un risque accru de mortalité (HR ajusté 3.77, $p=0.014$), de mortalité cardiovasculaire (HR ajusté 5.36, $p=0.037$) et d'hospitalisation pour insuffisance cardiaque dans le suivi (HR ajusté 7.33, $p=0.001$).

Conclusions- La présence d'une insuffisance mitrale secondaire significative malgré une resynchronisation biventriculaire apporte une information pronostique importante au-delà du remodelage inverse post-resynchronisation. D'autres études seront nécessaires pour évaluer le rôle des nouvelles procédures percutanées de réparation valvulaire mitrale pour améliorer le pronostic de ces patients à haut risque.

Mots clés : resynchronisation biventriculaire ; insuffisance cardiaque ; pronostic ; insuffisance mitrale secondaire ; échocardiographie.

Introduction:

Secondary mitral regurgitation (MR) is common in patients with heart failure and reduced LV ejection fraction (HFrEF) and predicts a poor outcome.[1, 2] Secondary MR results from an imbalance, between decreased mitral closing forces and increased tethering forces owing to reduced and/or dyscoordinated LV function, and global and local remodeling resulting in mitral valve tenting. Cardiac resynchronization therapy (CRT) induces immediate/short- and long- term secondary MR reduction.[3-6] While immediate/short-term reduction in secondary MR, following CRT seems to result from the improvement of LV mitral closing forces, as a result of a better coordination of papillary muscles and improved LV systolic function, long-term reduction in secondary MR, is mainly attributed to the chronic reduction in LV end-systolic size induced by CRT, ie LV reverse remodeling.[7, 8] Left ventricular reverse remodeling following CRT strongly predicts outcome in HFrEF patients in terms of mortality and HF hospitalizations, and is commonly used in clinical practice as a surrogate of clinical outcome to identify CRT responders.[9] While secondary MR at baseline may not be associated with outcome in HFrEF patients receiving CRT, the reduction in secondary MR following CRT has been associated with better clinical outcomes.[6, 10] However, to our knowledge, the prognostic value of baseline versus early and late post-CRT secondary MR beyond left ventricular reverse remodeling remains uninvestigated. Hence, the aim of the present prospective study is to evaluate in a large cohort of HFrEF patients receiving CRT 1) the time course of secondary MR at baseline, early and late after CRT 2) the relationship between presence of significant secondary MR at each stage, LV reverse remodeling during follow up and adverse long-term clinical outcomes and 3) whether late post-CRT significant secondary MR, portends independent prognostic information beyond LV reverse remodeling.

METHODS

Study population.

Clinical, ECG and Doppler-echocardiographic data were prospectively collected in a cohort of patients receiving CRT. As recommended by guidelines, CRT was indicated for patients with left ventricular ejection fraction (LVEF) \leq 35% who remained in NYHA functional class II, III and ambulatory IV, despite optimal medical treatment and QRS duration \geq 120 ms in the event of left bundle branch block (LBBB) morphology, or with QRS duration \geq 150 ms in the event of non-LBBB morphology. Exclusion criteria were: *i*) myocardial infarction, acute coronary syndrome, or coronary revascularization in the past three months; *ii*) primary mitral or aortic valve disease; *iii*) uncontrolled rapid atrial fibrillation. Patients received a maximum tolerated dose of beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers and spironolactone. Local ethics committee of the Groupement des Hôpitaux de l'Institut Catholique de Lille approved this study.

Echocardiography

Echocardiography was performed the day before CRT implantation with a GE Vivid E9 ultrasound system (General Electric healthcare, Velizy, France). Early post CRT studies were performed on the day of hospital discharge. Late post CRT studies were obtained at 9-months follow up. Three cardiac cycles were stored for each measurement for subsequent off line analysis by a blinded investigator to the clinical status of the patient (EchoPAC PC release BT12; GE Vingmed Ultrasound AS). Measurements were made over 3 cardiac cycles and the average value calculated. LVEF was measured by the Simpson biplane method. LV end-diastolic and end-systolic dimensions were obtained with the use of M-mode recordings acquired at a sweep speed of 100 mm/s. Pulsed-wave Doppler was performed in the apical 4-chamber view at end-expiration with a 3-mm sample volume, to obtain mitral inflow velocities (E and A waves). Left atrial (LA) volume was obtained according to current guidelines. Mitral regurgitant orifice area (effective regurgitant orifice [ERO]) was measured by the proximal flow convergence technique. Depth, size, and sector settings were optimized for optimal color Doppler resolution. The Doppler color flow zero baseline was shifted downward to obtain satisfactory hemispheric proximal iso-velocity surface area. The proximal flow convergence was imaged and expanded in the apical 4-chamber view. The aliasing velocity (V_r) was carefully adjusted (20-40 cm/s). The midsystole radius of the proximal flow convergence region (r) was measured from the point of aliasing to

the leaflet tips. Maximum mitral regurgitant velocity and the regurgitant time-velocity integral were obtained from continuous-wave Doppler recordings. The regurgitant flow was measured as $2 \times \Pi \times r^2 \times V_r$ and mitral ERO was obtained. MR severity was classified as mild ($ERO < 10 \text{ mm}^2$), moderate ($10 \text{ mm}^2 \leq ERO < 20 \text{ mm}^2$) or severe ($ERO \geq 20 \text{ mm}^2$). Secondary MR was considered significant in case of mitral $ERO \geq 10 \text{ mm}^2$. LV reverse remodeling was defined as a relative decrease in LV end-systolic volume $\geq 15\%$, between baseline and 9-months after CRT implantation, as previously reported.[9]

CRT Device Implantation

Boston Scientific (Natick, MA), Medtronic (Minneapolis, MN), St Jude (St Paul, MN), Sorin (Milan, Italy), and Biotronik (Berlin, Germany) CRT devices were implanted by electrophysiologists targeting a basal-lateral, antero-lateral or postero-lateral coronary sinus vein for LV lead positioning. Interventricular timing was set to zero. A short sensed AV delay (between 80 and 100 ms) and paced delay (130 ms) was programmed to promote biventricular pacing. Particular attention before hospital discharge was made, to verify the absence of fusion or pseudo-fusion beats on the ECG and continuous monitoring. For patients with ongoing atrial fibrillation, radiofrequency ablation of the atrioventricular node, was performed in order to obtain a high percentage of biventricular pacing, if sufficient bradycardia was not obtained despite optimal medical treatment. In case of atrioventricular node ablation, devices were subsequently programmed in a VVIR mode with a paced heart rate of 70 bpm.

Outcomes

During follow-up, patients were monitored by their own private physician. Events were recorded by means of clinical interviews and/or by phone calls to physicians, patients, and (if necessary) next of kin. The primary endpoint of the study was overall mortality and secondary endpoints were cardiovascular mortality and hospitalization for HF. Cardiovascular mortality was considered if death was related to HF, myocardial infarction, arrhythmia, or sudden death.

Statistical analysis

Quantitative data are presented as mean \pm standard deviation or median [25th–75th percentile]. Qualitative data are presented as absolute numbers and percentages. Comparison of the means was carried out using a two-sided

Student's t-test or a Mann–Whitney U test for comparison between 2 groups if the sample size of one of the 2 groups was less than 30.

The median duration of follow-up was computed using the reverse Kaplan-Meier method. Survival curves were obtained using the Kaplan-Meier method and compared using the log rank test. Univariate followed by multivariate Cox regression survival analyses were used to identify the relationship between the presence of significant secondary MR at baseline immediately after CRT and at 9 months follow up, and the occurrence of events during follow-up. For multivariate Cox analyses, model-building techniques were not used and covariates entered in the model were considered for potential prognostic impact, on an epidemiological basis. These covariates included: QRS duration, NYHA functional class III-IV, age, coronary artery disease, atrial fibrillation, LBBB, LVEF and left ventricular end-systolic volume (LVESV) at baseline. LV reverse remodeling was also entered in the models aiming at studying the

Frequency of significant secondary MR decreased from 23% at baseline (45/198) to 8% immediately after CRT implantation (16/198, 13 patients with mitral $10 \leq \text{ERO} < 20 \text{ mm}^2$ and 3 patients with mitral $\text{ERO} \geq 20 \text{ mm}^2$) whereas 182 patients had no (n=141) or mild (n=41) MR.

The comparison of clinical data between patients with and without significant secondary MR at baseline, and early after CRT is depicted in **table 1**. Patients with significant secondary MR at baseline and early after CRT were more often in NYHA functional class III-IV.

Mitral regurgitation late after CRT

Late echocardiographic follow up was available in 172 patients (87%), as 14 patients died before their echocardiographic examination (7%), and 12 (6%) did not attend their echocardiographic examination. Seventeen patients (17/172, 10%) had significant secondary MR late after CRT (12 patients with mitral $10 \leq \text{ERO} < 20 \text{ mm}^2$ and 5 patients with mitral $\text{ERO} \geq 20 \text{ mm}^2$). One hundred and fifty five patients had no (n=129) or only mild (n=26) MR. As shown in **table 1**, patients with significant secondary MR late after CRT were more often in baseline NYHA functional III-IV, and had shorter baseline QRS duration.

Relationship between significant MR and echocardiographic parameters at baseline, early and late after CRT

The comparison of echocardiographic data between patients with and without significant secondary MR at baseline, early and late after CRT is presented in **table 2**.

Patients with significant secondary MR at baseline had larger LV size, lower LV ejection fraction and larger LA volumes (**Table 2**). Mitral valve tenting and systolic artery pulmonary pressure (sPAP) were significantly higher, and parameters of RV systolic function were depressed in significant secondary MR patients compared with others. Similar results were found for patients with significant secondary MR early and late after CRT, except for global longitudinal strain (GLS) that significantly differed between patients with and without significant secondary MR only at the 9-month echocardiography examination.

Changes in secondary MR severity degree over time

Changes in secondary MR degree in the early phase after CRT was studied in 198 patients, and assessed from early to

9-months post CRT studies in 172 patients. These changes are detailed in **figure 2A and 2B**. All patients with no baseline MR or mild MR had either no or mild MR early after CRT. Seventeen patients had significant secondary MR at late follow up. Among these 17 patients, 6 (35%) had either no baseline or mild MR and 8 (47%) had significant secondary MR early after CRT. As shown in **figure 3 (A, B and C)**, acute changes in LV size or ejection fraction were similar between patients with and without significant secondary MR early after CRT. In contrast, patients with significant secondary MR at late follow up, had a poorer improvement in LVEF and a lower decrease in both LV end-diastolic and end-systolic volumes from baseline to the 9-month echocardiography examination (**figure 3D, E and F**, all $p < 0.01$). Early/late changes in mitral tenting area or LA volume did not differ early and late after CRT between patients with and without significant secondary MR (all $p = \text{NS}$).

Relationship between baseline and post-CRT MR and LV reverse remodeling

The proportion of CRT responders (as defined by a relative reduction in LV ESV relative to baseline $\geq 15\%$) was similar between patients with and without significant secondary MR at baseline (30/41 (73%) versus 102/135 (75%), $p = 0.76$). Similarly, LV ESV decreased and LVEF increased comparably, from baseline to the 9 month follow up in patients with and without significant secondary MR at baseline (-64 ± 57 versus -60 ± 50 mL, $p = 0.78$ and $+12 \pm 12$ versus $+13 \pm 11$ %, $p = 0.41$ respectively). The proportion of CRT responders was also similar between patients with and without significant secondary MR early after CRT (9/14 (64%) versus 123/162 (76%), $p = 0.36$). In contrast, the proportion of CRT responders was significantly lower in patients with significant secondary MR at late echocardiography examination follow up compared with other patients (7/17 (41%) versus 123/155 (79%), $p = 0.001$).

Impact of baseline and post-CRT secondary MR on outcome

During a median follow up of 48 ± 2 months, 49 patients died including 27 from cardiovascular causes and 36 patients were hospitalized for decompensated HF.

The survival free of death from any cause, cardiovascular death and heart failure hospitalizations in patients with and without significant secondary MR at baseline is depicted in **figure 4 A, B and C respectively**. As compared with patients without significant MR at baseline, patients with baseline significant secondary MR, displayed an increased risk of HF hospitalizations (HR 2.71 (1.33-5.48), $p = 0.006$), and cardiovascular death (HR 2.61 (1.21-5.63), $p =$

0.015) and a trend towards an increased risk of death from any cause (HR 1.78 (0.97-3.28), $p = 0.063$). After adjustment, only a trend towards an increased risk of HF hospitalizations was observed in patients with significant secondary MR at baseline (**table 3**).

The survival free of death from any cause, cardiovascular death and heart failure hospitalizations in patients with and without significant secondary MR, early after CRT is depicted in **figure 5 A, B and C**. Patients with significant secondary MR early after CRT displayed during follow-up a significant increased risk of death from any cause (HR 3.27 (1.58-6.77), $p = 0.001$), of death from cardiovascular causes (HR 4.69 (1.98-11.13), $p < 0.0001$) and of HF hospitalizations (HR 5.98 (2.75-12.98), $p < 0.0001$). Similar results were found after adjustment (**table 3**).

The survival free of death from any cause, cardiovascular death and HF hospitalizations in patients with and without significant secondary MR late post-CRT is depicted in **figure 6 A, B and C**. Patients with significant secondary MR late after CRT displayed a significant increased risk of death from any cause (HR 3.34 (1.42-7.82), $p = 0.006$), of death from cardiovascular causes (HR 5.25 (1.79-15.38), $p = 0.003$) and of HF hospitalizations (HR 7.78 (3.39-17.86), $p < 0.0001$). After adjustment on predefined covariates including LV reverse remodeling, patients with significant secondary MR late after CRT displayed an independent increased risk of death from any cause (adjusted HR 3.77 (1.30-10.92), $p=0.014$), death from cardiovascular causes (adjusted HR 5.36 (1.11-25.96), $p=0.037$) and HF hospitalizations (adjusted HR 7.33 (2.21-24.29), $p=0.001$) (**table 3**). Both LV reverse remodeling and significant secondary MR late after CRT were independent predictors of long-term outcome (**table 3**).

DISCUSSION

While significant secondary MR prior to CRT did not add independent prognostic information, both early- and late-post CRT significant secondary MR, did portend important prognostic information in terms of mortality and heart failure hospitalizations. In addition, late post-CRT significant secondary MR provided independent prognostic information beyond LV reverse remodeling, during long-term follow-up.

Secondary MR is a common condition in HF patients and is a predictor for poor prognosis. Progressive distortion of global or local LV architecture leads to apical and lateral displacement of papillary muscles, thus causing tethering and restrictive motion of the mitral leaflets.[11, 12] Moreover, the decrease in LV ejection phase efficiency produced

by LV dyssynchrony in patients with enlarged QRS reduces mitral closing forces. Conversely, CRT, by increasing LV closure forces resulting from improved myocardial contractility, and by restoring papillary muscle coordination, acutely reduces secondary MR. In agreement with previous studies, this occurred in two thirds of our HF patients, with baseline secondary MR.[13, 14]

Clinical significance of MR prior CRT

Patients with significant secondary MR at baseline, had indices of more advanced heart failure, including larger LV and LA size, higher pulmonary pressures, and depressed RV function. However after CRT, baseline MR did not predict outcome after adjustment on classical prognostic factors in HF. Consistently, LV reverse remodeling during follow up did not differ in both patients with or without baseline significant secondary MR. These findings suggest that CRT may largely improve poor prognosis of HF patients including those with secondary MR. These findings differ slightly from Verhaert and co-workers' earlier report,[6] as in their study, patients with severe MR before CRT experienced a larger LVESVi decrease. However, similarly to our findings, baseline MR severity was not associated with adverse events. Hence, these results suggest that baseline MR should not be considered as a predictor for poor outcomes, in patients with a CRT indication. Baseline secondary MR is not likely to be in itself an appropriate therapeutic target in this clinical setting, as suggested by current ESC guidelines on valvular heart diseases. Improving LV function is the primary therapeutic strategy to reduce MR [15]

Clinical significance of MR following CRT

Few studies have reported temporal changes in secondary MR after CRT. Half of patients with significant secondary MR at late follow up had no or only mild MR early after CRT, thus demonstrating that the amount of MR widely varies from the early to the late post-CRT period.

Early post-CRT significant secondary MR was an independent predictor of clinical outcome, even after adjustment on classical prognostic factors in heart failure. However early post-CRT MR was not related to acute changes in LV function and size, as previously reported.[6] In contrast, CRT failure in reversing LV remodeling and in improving LV function did correlate with late post-CRT significant secondary MR. This data confirms the hypothesis that secondary MR mirrors in part LV remodeling status. Indeed, LV reverse remodeling induced by CRT reduces LV

dilation and sphericity, thus minimizing tethering forces on MV apparatus, and thereby reducing the amount of MR.[8] However, both LV remodeling and late-post CRT MR were independent predictors of long-term outcomes in the present study.

Identification of ‘responders’ and ‘non-responders’ to CRT has attracted considerable attention as 20% to 40% of patients fail to respond to CRT.[16] Left ventricular reverse remodeling (defined as LVESV reduction $\geq 15\%$) is a strong and reproducible predictor of outcome following CRT.[9] Yu et al also found higher long-term mortality and heart failure events in CRT patients, with a lack of reduction in LVESV of 9.5% or more,[17] and mortality was more than 4-fold higher in the 25% of the REVERSE patient cohort with further LV remodeling, despite CRT. Given the results of the present study, response to CRT should not only rely on changes in LVESV at 6 to 9 months follow-up, but also on the assessment of secondary MR at the same time point. Indeed, patients without LV reverse remodeling and significant secondary MR at 9-months follow-up were at very high-risk in this study, and may derive benefit from specific therapeutic management, targeting the secondary MR. Ongoing trials are evaluating the efficacy of new percutaneous procedures of mitral valve repair such as MitraClip. Pilot studies have concluded that the treatment is safe, and results in an improvement in NYHA functional class, with evidence of reverse LV remodeling.[18, 19]

Limitations

Limitations of this study are inherent to observational studies. This single-center study included a relatively small number of patients. However, clinical and echocardiographic data were prospectively collected with off-line analysis and patient follow-up was prospectively planned. Secondary MR is a dynamic and progressive complex disease; it does not only depend on LV disease parameters but also on external conditions such as therapeutic compliance and daily salt intake. Changes in secondary MR observed in the present study indeed reflect those occurring in routine practice.

Conclusions

Significant secondary MR early and late after CRT portends important long-term prognostic information. Significant secondary MR late after CRT provides independent detrimental prognostic information beyond LV reverse remodeling. Patients with significant secondary MR late after CRT have a considerable increased risk of mortality

during long-term follow up. Hence, the present data reinforces the potential role of alternative therapies, as well as new percutaneous procedures of mitral valve repair, in order to improve the outcome of these very high-risk patients.

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Figure legends

Figure 1: Flow chart of the study patients.

Figure 2: Course of secondary MR degree after CRT. Changes in degree of secondary MR early after CRT was studied in 198 patients (A) and late (9-months) changes in secondary MR were studied in 172 patients (B).

Figure 3. Acute (A, B, C) and chronic (D, E, F) changes in left ventricular ejection fraction (LVEF), left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV) according to the presence of significant secondary MR (MR (+)) early (A, B, C) and late (D, E, F) after CRT respectively.

Figure 4: Kaplan Meier event-free survival according to the presence of significant secondary MR (MR (+)) at baseline (mortality (A) cardiovascular mortality (B) and hospitalization for heart failure (C)).

Figure 5: Kaplan Meier event-free survival according to the presence of significant secondary MR (MR (+)) early after CRT (mortality (D) cardiovascular mortality (E) and hospitalization for heart failure (F)).

Figure 6: Kaplan Meier event-free survival according to the presence of significant secondary MR (MR (+)) late after CRT (mortality (H) cardiovascular mortality (I) and hospitalization for heart failure (J)).

Figure 1

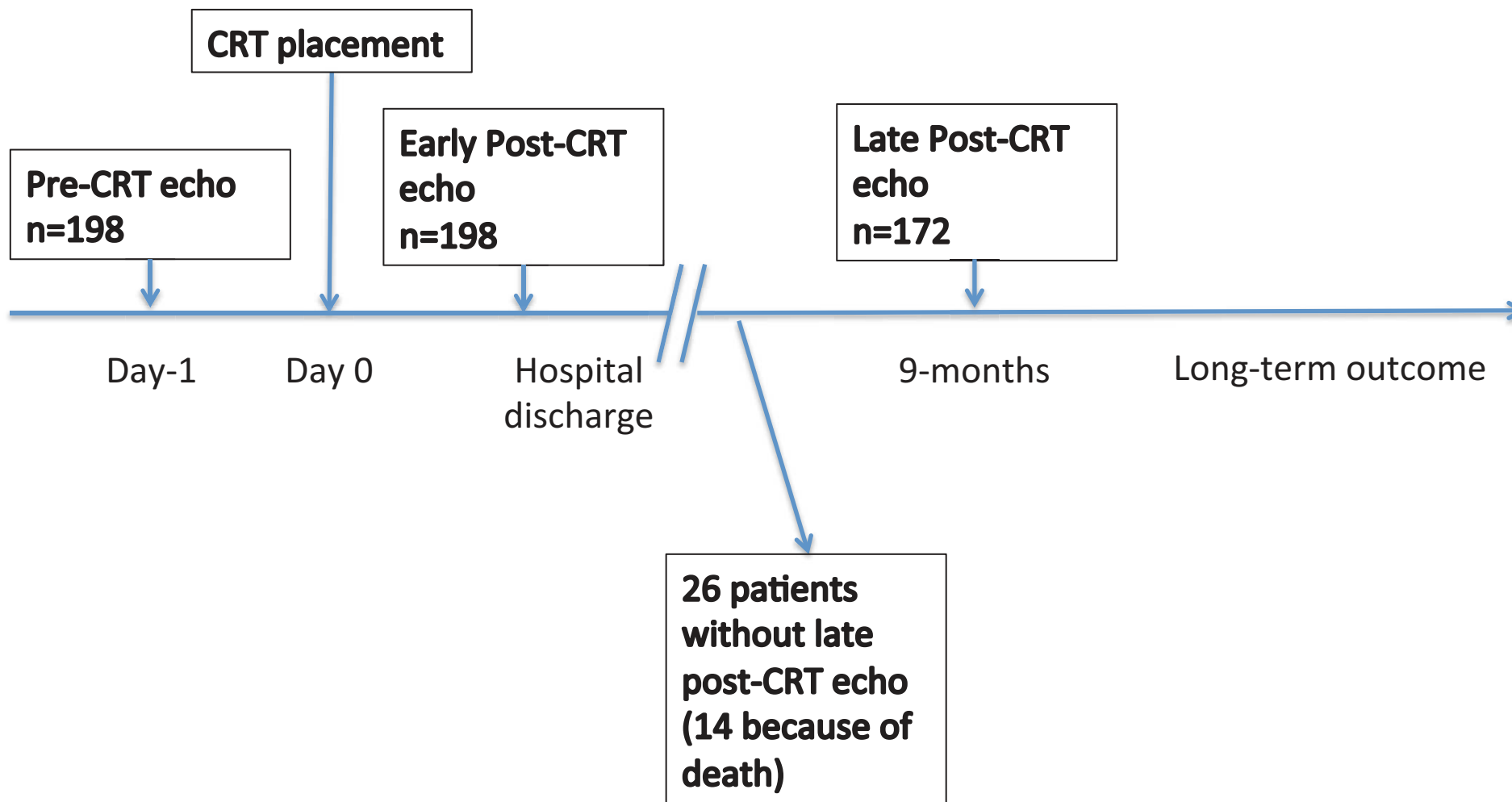


Figure 2A

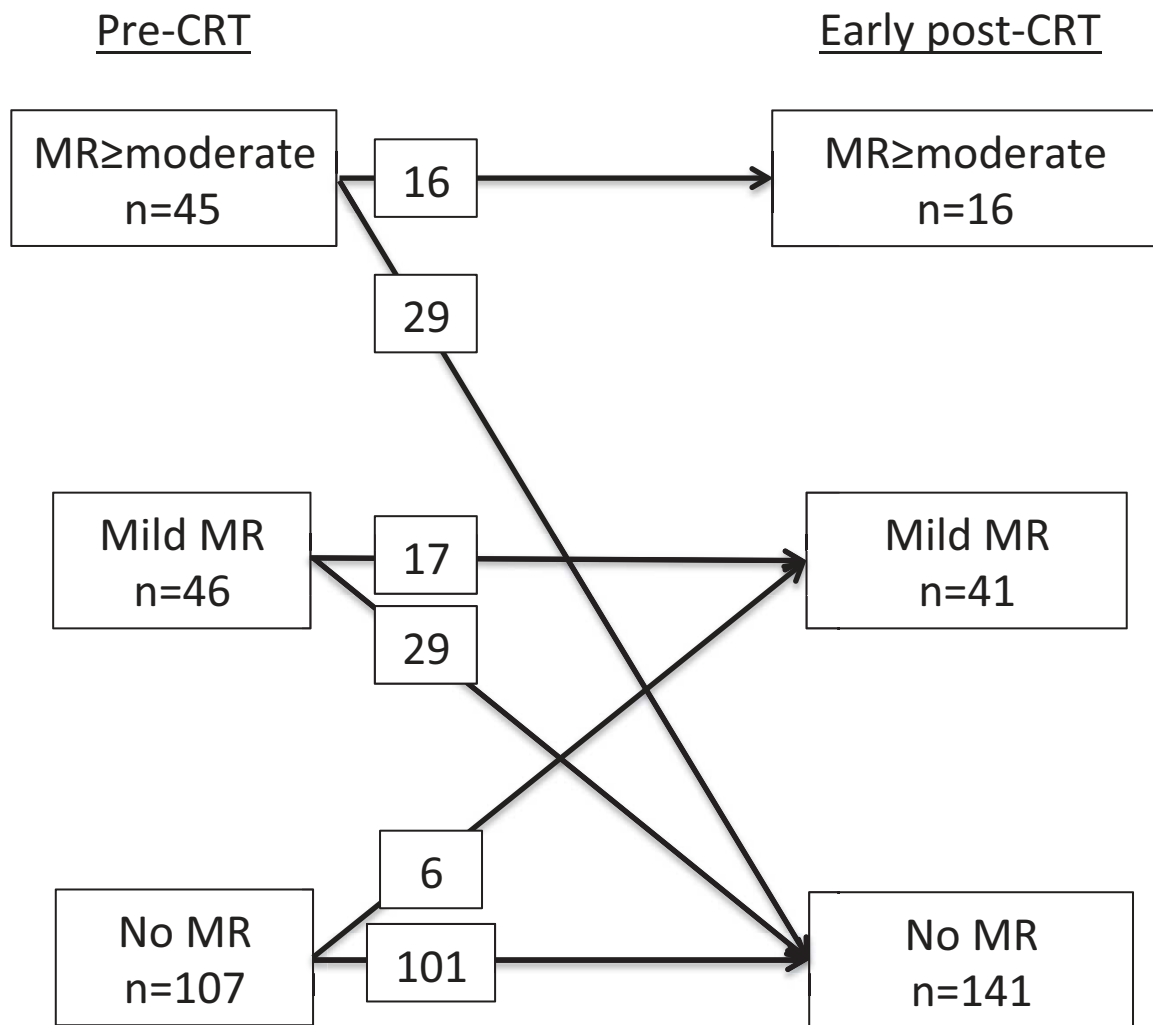


Figure 2B

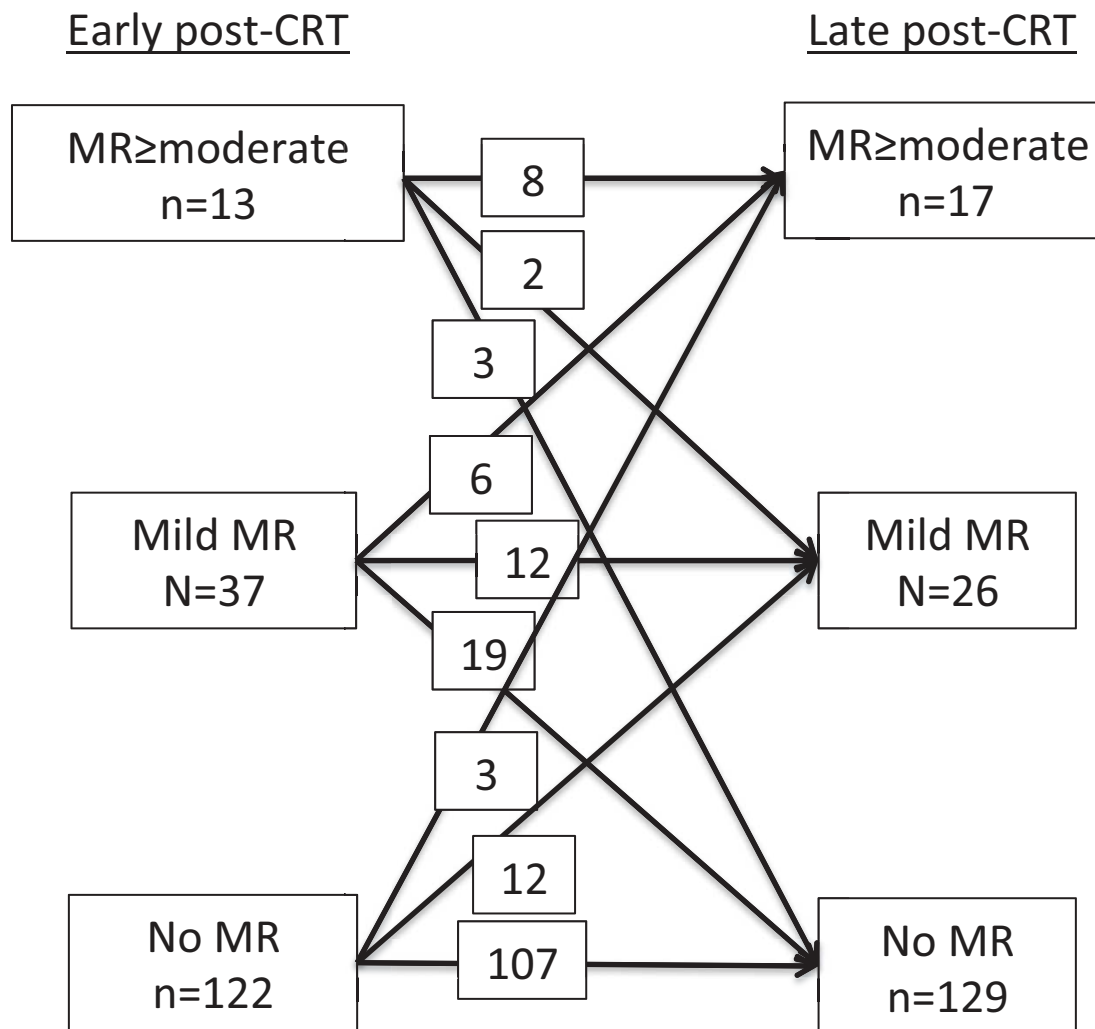
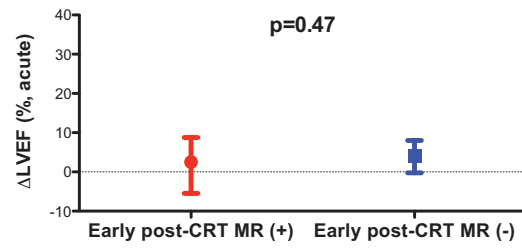
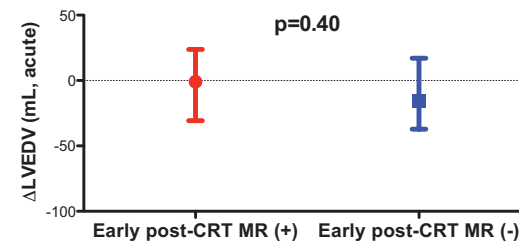


Figure 3

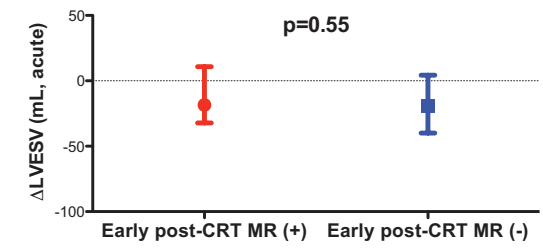
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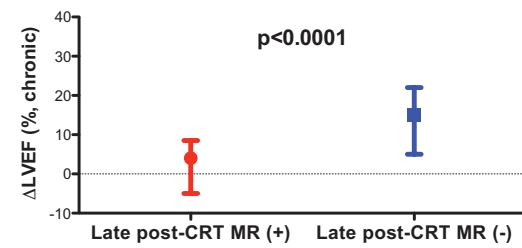
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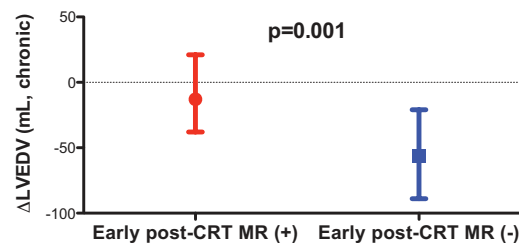
C



D



E



F

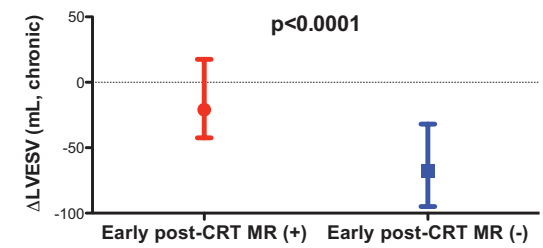
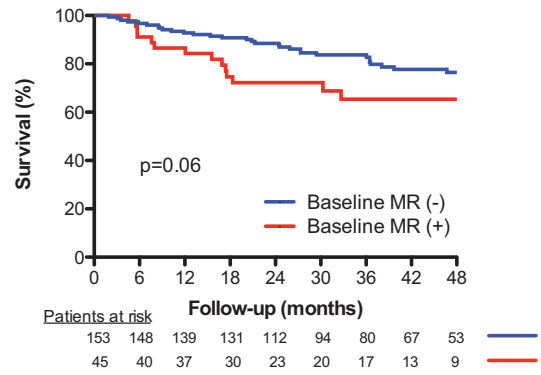
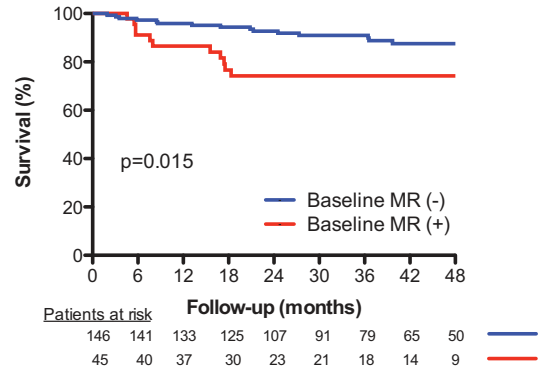


Figure 4

A



B



C

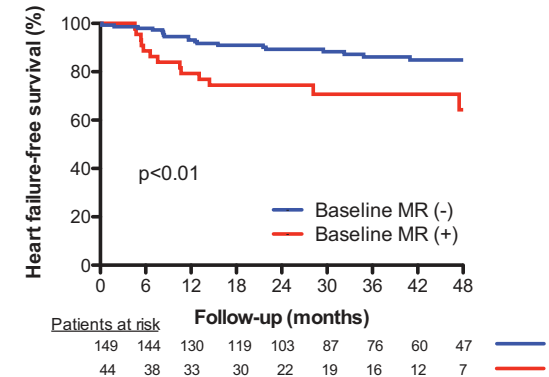
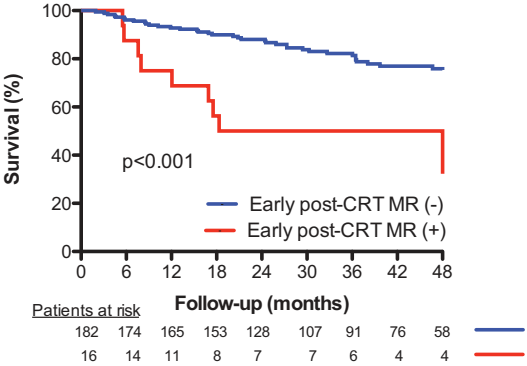
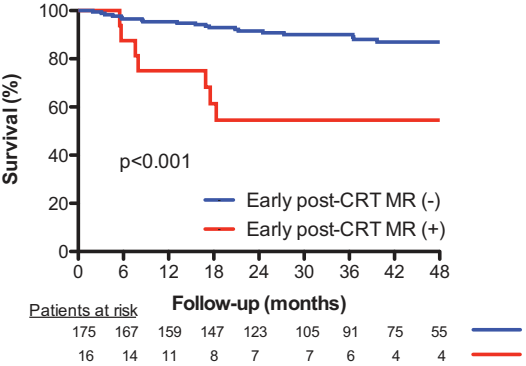


Figure 5

A



B



C

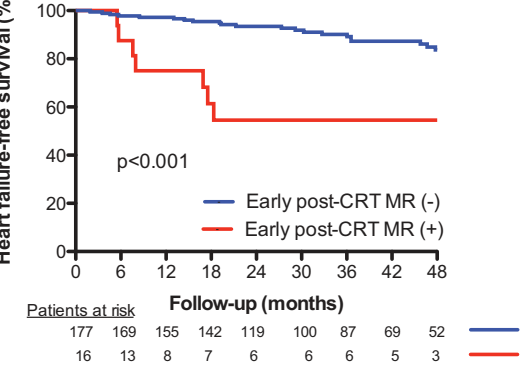
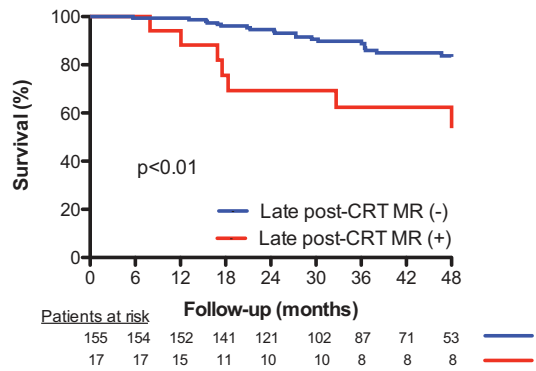
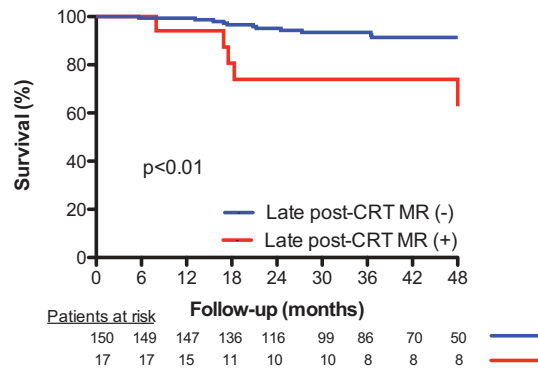


Figure 6

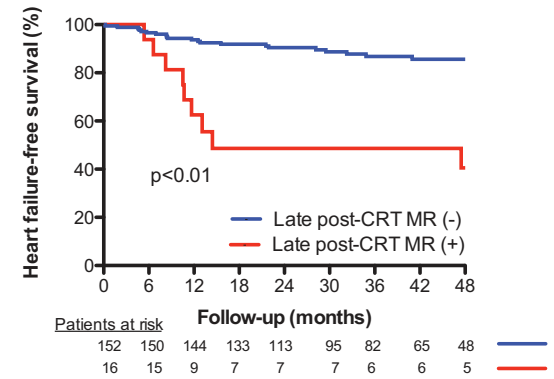
A



B



C



	Baseline			Early post-CRT			Late post-CRT		
	Overall	MR≥moderate	No or mild MR	MR≥moderate	No or mild MR	P-value	MR≥moderate	No or mild MR	P-value
Number of patients	198	45	153	16	182		17	155	
Age (years)	71±11	71±12	71±11	70±14	71±11	0.40	69±11	71±11	0.91
Male gender, n (%)	128 (64)	29(64)	99(65)	10 (63)	118 (65)	0.97	10 (59)	101 (65)	0.85
BMI (kg/m ²)	27±5	27±6	27±5	28±7	27±5	0.81	28±7	27±5	0.72
Diabetes, n (%)	59 (30)	19(42)	40(26)	5 (31)	54 (30)	0.038	5 (29)	46 (30)	1.0
Dyslipidemia, n (%)	75 (38)	15(33)	60(39)	7 (44)	68 (37)	0.46	4 (24)	63 (41)	0.63
Hypertension, n (%)	84 (42)	16(36)	68(44)	4 (25)	80 (44)	0.289	6 (35)	63 (41)	0.14
Coronary Artery Disease, n (%)	71 (36)	14(31)	57(37)	5 (31)	66 (36)	0.45	5 (29)	56 (36)	0.69
Atrial Fibrillation n (%)	14 (7)	38(84)	28(18)	6 (38)	36 (20)	0.065	4 (24)	31 (20)	0.11
NYHA functional class III-IV, n (%)	95 (48)	30(67)	65(42)	13 (81)	82 (45)	0.004	4 (24)	67 (43)	0.005
QRS width (ms)	166±26	160±26	167±27	156±28	167±27	0.13	146±25	168±27	0.11
Left Bundle Branch Block, n (%)	152 (77)	34(76)	118(77)	12 (75)	140 (77)	0.827	13 (76)	119 (77)	0.77
Beta-blockers n (%)	179 (90)	42(93)	137(90)	14 (88)	165 (91)	0.573	16 (94)	140 (90)	0.66
Blockers renin angiotensin system n (%)	175 (88)	40(89)	135(88)	14 (88)	161 (88)	0.90	16 (94)	137 (88)	1.0

Table 1 : Clinical baseline characteristics according to the presence of significant secondary MR (MR≥moderate) at baseline, early and late after CRT.

	Baseline			Early post-CRT			Late post-CRT		
	Overall	MR \geq moderate	No or mild MR	MR \geq moderate	No or mild MR	P-value	MR \geq moderate	No or mild MR	P-value
Number of patients	198	45	153	16	182	17	155		
Left Ventricular Ejection Fraction (%)	26 \pm 5	24 \pm 5	27 \pm 5	26 \pm 8	31 \pm 8	28 \pm 9	41 \pm 11	<0.0001	
Left Ventricular End-Diastolic volume (mL)	245 \pm 70	262 \pm 75	24 \pm 68	265 \pm 75	229 \pm 71	233 \pm 75	187 \pm 67	0.013	
Left Ventricular End-Diastolic diameter (mm)	67 \pm 8	70 \pm 8	65 \pm 8	70 \pm 8	64 \pm 8	67 \pm 10	60 \pm 10	0.001	
Left Ventricular End-Systolic Volume (mL)	182 \pm 58	201 \pm 63	177 \pm 55	196 \pm 60	161 \pm 60	170 \pm 62	116 \pm 61	0.001	
Global Longitudinal Strain (%)	8.0 \pm 2.7	7.4 \pm 2.5	8.1 \pm 2.8	7.8 \pm 3.1	8.0 \pm 2.7	7.2 \pm 3.8	10.3 \pm 4.0	0.003	
Left Atrial Volume (mL)	73 \pm 27	88 \pm 27	69 \pm 26	66 \pm 17	49 \pm 21	57 \pm 16	46 \pm 20	0.012	
Left Atrial Tenting (cm2)	3.16 \pm 0.94	4.10 \pm 0.9	2.9 \pm 0.8	4.34 \pm 1.28	2.68 \pm 0.77	4.18 \pm 1.49	2.64 \pm 0.83	<0.0001	
Mitral ERO (mm2)	0 (0-9)	13 (11-20)	0 (0-3)	14 (12-17)	0 (0-0)	12 (11-21)	0 (0-0)	<0.0001	
sPAP (mmHg)	38 \pm 13	44 \pm 11	36 \pm 13	44 \pm 11	36 \pm 12	49 \pm 13	34 \pm 10	<0.0001	
TAPSE (mm)	20 \pm 5	18 \pm 6	20 \pm 5	17 \pm 5	20 \pm 5	16 \pm 4	20 \pm 5	0.001	
Right Ventricular S wave (cm/s)	9.4 \pm 3.3	8.5 \pm 3.4	9.7 \pm 3.2	8.6 \pm 2.2	10.2 \pm 3.1	8.7 \pm 2.1	10.4 \pm 2.8	0.026	

Table 2 : Echocardiographic characteristics at each stage according to the presence of significant secondary MR (MR \geq moderate) at baseline, early and late after CRT.

	Overall mortality			Cardiovascular mortality			CHF hospitalization					
	Adjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value	Adjusted HR	95% CI	P-value			
Age (years)	1.33	0.69	2.58	0.39	1.99	0.83	4.77	0.12	2.19	0.99	4.83	0.052
Atrial Fibrillation	1.08	1.04	1.12	<0.001	1.12	1.06	1.19	<0.001	1.02	0.99	1.06	0.225
Coronary Artery Disease	1.02	0.50	2.05	0.97	1.51	0.65	3.50	0.34	0.91	0.39	2.17	0.84
NYHA III-IV	1.27	0.71	2.26	0.43	1.31	0.58	2.95	0.52	0.89	0.41	1.92	0.77
Baseline LV end-systolic volume (mL)	1.98	0.99	3.93	0.05	1.56	0.61	3.98	0.36	1.18	0.53	2.59	0.69
Baseline LV ejection fraction (%)	1.01	1.00	1.01	0.009	1.01	1.00	1.02	0.005	1.002	0.99	1.01	0.49
QRS width (ms)	0.99	0.93	1.06	0.92	0.99	0.91	1.08	0.83	0.92	0.85	0.99	0.047
LBBB	0.99	0.98	1.01	0.33	0.98	0.96	0.99	0.015	0.99	0.97	1.00	0.059
	0.99	0.48	2.06	0.99	0.59	0.23	1.54	0.28	0.45	0.19	1.03	0.059
Age (years)	2.48	1.10	5.57	0.028	2.90	1.06	7.92	0.038	5.52	2.27	13.45	<0.001
Atrial Fibrillation	1.08	1.04	1.12	<0.001	1.12	1.06	1.18	<0.001	1.02	0.98	1.06	0.32
Coronary Artery Disease	0.97	0.48	1.96	0.94	1.52	0.65	3.55	0.33	0.81	0.34	1.95	0.64
NYHA III-IV	1.39	0.77	2.51	0.27	1.39	0.61	3.18	0.44	0.94	0.43	2.04	0.88
Baseline LV end-systolic volume (mL)	1.78	0.89	3.54	0.10	1.48	0.58	3.79	0.42	1.03	0.46	2.32	0.95
Baseline LV ejection fraction (%)	1.00	1.00	1.01	0.012	1.01	1.00	1.02	0.005	1.00	0.99	1.01	0.57
QRS width (ms)	1.00	0.94	1.07	0.95	1	0.92	1.09	0.99	0.92	0.84	0.99	0.039
LBBB	0.99	0.98	1.00	0.39	0.98	0.96	0.99	0.03	0.99	0.97	1.00	0.059
	0.96	0.47	1.98	0.91	0.58	0.22	1.54	0.28	0.41	0.18	0.94	0.036
LV reverse remodelling	3.77	1.30	10.92	0.014	5.36	1.11	25.96	0.037	7.33	2.21	24.29	0.001
Age (years)	0.26	0.11	0.62	0.002	0.16	0.04	0.64	0.009	0.23	0.09	0.61	0.003
Atrial Fibrillation	1.10	1.04	1.17	<0.0001	1.16	1.05	1.28	0.003	1.01	0.97	1.06	0.56
Coronary Artery Disease	0.52	0.19	1.48	0.22	0.76	0.21	2.70	0.67	0.43	0.13	1.37	0.15
NYHA III-IV	1.27	0.59	2.75	0.54	1.04	0.30	3.54	0.96	1.05	0.40	2.78	0.92
Baseline LV end-systolic volume (mL)	2.48	0.94	6.56	0.068	1.58	0.43	5.84	0.50	0.87	0.31	2.41	0.79
Baseline LV ejection fraction (%)	1.01	1.00	1.02	0.003	1.01	1.00	1.02	0.009	1.00	0.99	1.01	0.84
QRS width (ms)	1.03	0.94	1.13	0.50	0.99	0.87	1.12	0.83	0.91	0.83	1.01	0.066
LBBB	1.00	0.99	1.02	0.54	0.99	0.97	1.02	0.78	1.00	0.99	1.02	0.60
	0.83	0.33	2.09	0.70	0.31	0.07	1.27	0.10	0.32	0.12	0.87	0.025

Table 3 : Relationship between presence of significant secondary MR (MR \geq moderate) at baseline, early and late after CRT and all-cause mortality, cardiovascular mortality and heart failure (HF) hospitalization during follow up by Cox multivariate analysis.

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Désynchronisation et physiopathologie du remodelage ventriculaire gauche dans l'insuffisance cardiaque

L'objectif de ce travail était de mieux appréhender les mécanismes impliqués dans la réponse à la resynchronisation biventriculaire en insistant sur la caractérisation écho-cardiographique du substrat éligible à un traitement par resynchronisation cardiaque (TRC). Afin de valider dans notre cohorte les critères de réponse au TRC, nous avons évalué l'impact pronostic au long cours de l'amélioration du strain longitudinal du ventricule gauche (VG), de la fraction d'éjection VG et des volumes VG 6 à 9 mois après un TRC. L'amélioration du volume téléstolique du VG (remodelage inverse) semble être le marqueur le plus pertinent du pronostic au long cours après TRC. De plus, l'insuffisance mitrale secondaire significative persistante malgré un TRC semble être un facteur pronostic important indépendant du remodelage VG. Nous avons démontré qu'il existe un certain degré de désynchronisation mécanique (fondé sur la mesure des délais entre paroi) dans les insuffisances cardiaques à fraction d'éjection préservée qui est semblable aux insuffisances cardiaques à fraction d'éjection basse à QRS fins et supérieur aux témoins hypertendus. Cependant, les paramètres de désynchronisation échographiques considérés comme les substrats de la réponse au TRC (fondés sur la contraction type bloc de branche gauche) ne sont que très rarement retrouvés chez ces patients. Ces paramètres sont fréquemment présents dans les insuffisances cardiaques à fraction d'éjection basse avec un QRS large et une indication de TRC. Le strain longitudinal du septum interventriculaire permet de caractériser 3 patterns de contraction septale eux même prédicteurs du remodelage inverse, des hospitalisations pour insuffisance cardiaque, de la mortalité cardiovasculaire et de la mortalité toute cause après un TRC. L'élargissement de la largeur du QRS après un TRC est quant à elle un prédicteur de l'absence de remodelage inverse, et d'un excès de mortalité cardiovasculaire et toute cause après un TRC. L'association d'un pattern de contraction septal peu prédicteur de réponse au TRC et d'un élargissement du QRS après le TRC permet d'identifier des patients avec une probabilité de réponse très faible au TRC.

Mots clés : Thérapie de resynchronisation cardiaque. Asynchronisme cardiaque. Insuffisance cardiaque. Echocardiographie. Electrocardiogramme.

Left ventricle dyssynchrony and remodeling physiopathology in heart failure

The objective of this work was to better understand the mechanisms involved in the response to biventricular resynchronization by focusing on the echocardiographic characterization of the substrate eligible for cardiac resynchronization treatment (CRT). In order to validate the CRT response criteria in our cohort, we evaluated the long-term prognostic impact of improvements in left ventricular (LV) longitudinal strain, LV ejection fraction and LV volumes 6 to 9 months after a CRT. The improvement of the LV endsystolic volume (reverse remodeling) appears to be the most relevant substrate for long-term prognostic after CRT. In addition, significant secondary mitral insufficiency despite a CRT appears to be a significant prognostic factor independent of LV remodeling. We have demonstrated that there is a degree of mechanical dyssynchrony (based on the measurement of delays between walls) in heart failure with a preserved ejection fraction that is similar to heart failure with low ejection fraction and thin QRS and superior to hypertensive controls. However, the ultrasound dyssynchrony parameters considered as the substrates of CRT response (based on left bundle branch block typical contraction) are seldom found in these patients. These parameters are frequently present in heart failure with low ejection fraction with a wide QRS and an indication for CRT. The longitudinal strain of the inter-ventricular septum allows to characterize 3 patterns of septal contraction that are predictors of reverse remodeling, hospitalizations for heart failure, cardiovascular mortality and all-cause mortality after CRT. The widening of the QRS after a CRT is a predictor of the absence of reverse remodeling, an excess of cardiovascular and all-cause mortality after CRT. The association of a septal contraction pattern with a low CRT response and a QRS enlargement after TRC can be used to identify patients with a very low probability of response to CRT.

Key words: Cardiac resynchronization therapy. Cardiac dyssynchrony. Heart failure. Echocardiography. Electrocardiogram.

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