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Dysfonction myocardique du sepsis : de la physiopathologie au traitement

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École doctorale Sciences de la vie et de la santé

THÈSE

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par

Keyvan RAZAZI

**Dysfonction myocardique du sepsis : de la
physiopathologie au traitement**

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RESUME Dysfonction myocardique du sepsis : de la physiopathologie au traitement

Objectifs : Explorer de façon multimodale la physiopathologie et le traitement de la dysfonction myocardique du sepsis (DMS) au cours du choc septique humain.

Méthodes : Nous avons investigué les mécanismes potentiels suivants au cours de la DMS : l'implication de la nécrose ou de l'inflammation myocardique explorées par imagerie par résonance magnétique (IRM) cardiaque ; le rôle des conditions de charge explorées par échocardiographie avancée ; l'implication de l'insuffisance surrénalienne relative ; le rôle des médiateurs du sepsis exploré par approche biologique multi-analytique et le rôle de la senescence. Nous avons aussi mené une enquête auprès des réanimateurs francophones sur la gestion de la DMS. Enfin, nous avons analysé l'efficacité et la tolérance de la dobutamine par échocardiographie avancée dans une étude observationnelle multicentrique.

Résultats : L'enquête auprès des réanimateurs a révélé une définition de la DMS non consensuelle, une utilisation préférentielle de l'échocardiographie comme outil de monitoring du choc septique et de la dobutamine comme inotrope de choix en cas de DMS, mais avec des pratiques hétérogènes sur ses critères d'initiation ou d'arrêt. En imagerie de coupe, l'IRM myocardique de patients avec une DMS n'a montré ni inflammation ni défaut de perfusion. En échocardiographie, nous avons démontré une relation inverse entre les paramètres de postcharge et les indices de contractilité du ventricule gauche. La signature acoustique était un indice précoce de DMS secondaire. En biologie multi-analyte, la classification hiérarchique d'une vingtaine de médiateurs du sepsis a identifié 3 clusters biologiquement cohérents. Le cluster lié à la réponse inflammatoire innée (IL6, TNF- α , IL1- β , sST2...) était associé à la DMS et aux défaillances d'organes alors que celui lié à l'immunité adaptative (IL17, IFN) était associé à la résolution du sepsis et la survie. Nous avons aussi démontré l'association de l'insuffisance surrénale relative avec la DMS, contrairement à la senescence évaluée par la longueur des télomères des leucocytes circulants. Enfin, nous avons démontré dans une étude multicentrique que la dobutamine améliore les paramètres de fonction systolique et diastolique au cours de la DMS, mais est associée à une mauvaise tolérance via l'aggravation de la vasoplégie et de la tachycardie.

Conclusions : Ce travail confirme le rôle des médiateurs circulants dans la genèse de la DMS, souligne l'interaction des conditions de charge dans sa détection, précise le rôle de l'échocardiographie dans sa gestion et caractérise les effets de la dobutamine dans son traitement.

SUMMARY: Myocardial dysfunction in sepsis: from pathophysiology to treatment

Objectives: To explore the pathophysiology and treatment of septic myocardial dysfunction (SMD) during human septic shock.

Methods: We explored the following potential mechanisms during SMD: involvement of myocardial necrosis or inflammation explored by cardiac magnetic resonance imaging (MRI); the role of loading conditions explored by advanced echocardiography; the implication of relative adrenal insufficiency; the role of telomere shortening and that of sepsis mediators explored using a multi-analyte biological approach. We also conducted a survey of French-speaking intensivists on the management of SMD. Finally, we explored the efficacy and safety of dobutamine by advanced echocardiography in a multicenter observational study.

Results: The survey of intensivists revealed a non-consensual definition of SMD, a preferential use of echocardiography as a tool for monitoring septic shock and dobutamine as the inotrope of choice to treat SMD, but with heterogeneous practices in its initiation or termination. Myocardial MRI of patients with SMD showed no inflammation or necrosis. We demonstrated an inverse relationship between afterload parameters and left ventricular contractility indices. The speckle tracking-derived strain was an early indicator of secondary SMD. The hierarchical clustering of 20 sepsis mediators identified three biologically consistent clusters. The cluster linked to the innate inflammatory response (e.g., IL6, TNF- α , IL1- β , sST2) was associated with SMD and organ failure, while that linked to adaptive immunity (IL17, IFN) was associated with sepsis resolution and survival. We also demonstrated the association of relative adrenal insufficiency with SMD. Leucocyte telomere length was not associated with SMD. Finally, we showed in a multicentre study that dobutamine improves parameters of systolic and diastolic function during SMD, but is associated with poor tolerance through worsening vasoplegia and tachycardia.

Conclusions: Our work confirms the role of circulating mediators in the genesis of SMD, underlines the interaction of loading conditions in its detection, specifies the role of echocardiography in its management and characterizes the effects of dobutamine in its treatment.

Mots clés : sepsis ; choc septique ; dysfonction myocardique ; IRM ; échocardiographie ; postcharge ; biomarqueurs ; cytokines ; insuffisance surrénale relative ; senescence ; dobutamine.

Keywords : sepsis ; septic shock ; myocardial dysfunction ; MRI ; echocardiography ; afterload ; biomarkers ; cytokines ; relative adrenal insufficiency ; senescence ; dobutamine.

Laboratoire dans lequel la thèse a été réalisée :

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ABBREVIATIONS

- ADN : acide désoxyribonucléique
- ATP : adénosine-triphosphate
- CIVD : coagulation intravasculaire disséminée
- DMS : dysfonction myocardique du sepsis
- ETO : échocardiographie transoesophagienne
- ETT : échocardiographie transthoracique
- FEVG fraction d'éjection du ventricule gauche
- iNOS : NO synthase inductible
- IRM : imagerie par résonance magnétique
- IRS : insuffisance surrénale relative
- NO : monoxyde d'azote
- PAF : Platelet Activating Factor
- PCR : Polymerase Chain Reaction ou réaction de polymérisation en chaîne
- ROS : reactive oxygene species
- VD : ventricule droit
- VES : volume d'éjection systolique
- VG : ventricule gauche
- VTD : volume télédiastolique
- 2D : 2 dimensions
- 3D : 3 dimensions

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ETAT DES CONNAISSANCES

Le sepsis est une réponse inflammatoire systémique secondaire à une agression infectieuse de l'hôte conduisant à des défaillances d'organes. Il s'agit d'un problème majeur de santé publique. Environ 225 patients développent un sepsis pour 100 000 habitants en France, avec une mortalité de 34% et un coût moyen par cas de 16 000 euros (Dupuis et al. 2020). Le choc septique, la forme la plus grave de sepsis, se définit comme la nécessité de perfusion de catécholamines, et concerne 10% des patients de réanimation, avec une incidence en constante augmentation, et une mortalité de l'ordre de 40% (J.-L. Vincent et al. 2019). Le choc septique peut être classé parmi les états de choc de type distributif. La physiopathologie du choc septique, qui résulte de l'invasion de l'organisme par des agents infectieux (bactéries à Gram négatif et à Gram positif, champignons, virus), est complexe (Angus et van der Poll 2013). De nombreux systèmes cellulaires (macrophages, leucocytes, plaquettes, cellules endothéliales, etc.) et humoraux (complément, coagulation, protéases) sont activés. L'activation cellulaire par les produits bactériens, en particulier l'endotoxine, entraîne la libération de cytokines pro-inflammatoires (par exemple le $TNF\alpha$ et l' $IL-1\beta$). Ces cytokines entraînent la libération de nombreux autres médiateurs : NO (monoxyde d'azote), molécules d'adhésion, médiateurs lipidiques (PAF), autres cytokines pro-inflammatoires (IL-6, IL-8, interférons) et anti-inflammatoires (récepteurs solubles au TNF, IL-4, IL-10, etc.).

L'activation cellulaire et la libération des médiateurs pro-inflammatoires sont responsables d'altérations cellulaires et microcirculatoires qui vont s'étendre au système vasculaire et entraîner : i) une augmentation de la perméabilité capillaire ; ii) une défaillance cardio-circulatoire, qui associe une hypovolémie absolue (secondaire à hyperperméabilité capillaire, une augmentation des pertes insensibles, et à un troisième secteur) et une hypovolémie relative par vasodilatation périphérique. L'élément prédominant reste cependant la vasoplégie artérielle et veineuse, qui conditionnera le traitement symptomatique initial (remplissage vasculaire et

drogues vasoconstrictives, notamment la noradrénaline) ; iii) une modification de la régulation de la perfusion de chaque organe à l'origine d'une distribution inadaptée des débits sanguins régionaux, entraînant une diminution de la perfusion tissulaire, une altération de la microcirculation et l'apparition des dysfonctions d'organes ; iv) une activation de la coagulation, conduisant à une coagulation intravasculaire disséminée (CIVD). Cette CIVD est fréquente (environ 30 % des cas), d'intensité variable, corrélée à la survenue d'un syndrome de défaillance multiviscérale et à la mortalité (J. A. Russell, Rush, et Boyd 2018). On note en outre une atteinte myocardique précoce conduisant à une altération de la fonction systolique et diastolique ventriculaire qui est réversible avec la guérison du sepsis.

Définition et rôle pronostique de la dysfonction myocardique du sepsis (DMS).

Il n'y a pas de consensus sur la définition de la DMS. Ce terme rend compte d'une atteinte protéiforme. Le sepsis peut être responsable d'une atteinte systolique avec diminution de la fraction d'éjection du ventricule gauche (VG), d'une dysfonction diastolique du VG et/ou une atteinte du ventricule droit. Cette dysfonction myocardique est aigüe et complètement réversible en quelques jours. Elle a tout d'abord été décrite par Parker et al. en 1984 chez 20 patients par une technique de radiocinéma (M. M. Parker et al. 1984). La dysfonction contractile observée était alors associée à une dilatation du VG permettant selon les auteurs de maintenir un débit cardiaque « adéquat ». La technique utilisée est probablement responsable d'une surestimation des volumes du VG. Les études échocardiographiques ont aussi retrouvé une dilatation du VG, mais plutôt modérée, de l'ordre de 20 % (Etchecopar-Chevreuril et al. 2008).

L'échocardiographie est probablement le meilleur examen au lit du patient afin d'évaluer la fonction cardiaque. Elle permet d'évaluer facilement le cœur du patient septique, notamment les volumes des cavités, la fonction systolique, diastolique du VG, la fonction ventriculaire droite et la précharge (Vieillard-Baron et al. 2006). L'incidence de la dysfonction systolique du

VG lors du sepsis varie beaucoup dans les différentes études (Vieillard-Baron 2011). Le sepsis diminuant les résistances vasculaires systémiques, la postcharge du VG est typiquement effondrée. Ainsi, la même valeur de fraction d'éjection du VG (FEVG) peut correspondre à différents niveaux d'atteinte de la contractilité intrinsèque du VG (Robotham et al. 1991). Par exemple, si la postcharge du VG est très basse, une FEVG estimée normale à 60% pourrait tout de même correspondre à une altération significative de la contractilité intrinsèque. En effet, le volume téléstolique est lié de façon linéaire à la pression téléstolique. Pour un état contractile donné, et une précharge donnée, le volume d'éjection systolique et la fraction d'éjection seront d'autant plus réduits que la pression téléstolique est grande. En d'autres termes, c'est le niveau de la pression téléstolique qui détermine en principe le volume d'éjection systolique pour un état contractile et un volume initial donnés. Ainsi, plus les échocardiographies sont répétées et notamment après restauration de la postcharge, plus la dysfonction systolique pourrait être démasquée. Ce fait pourrait au moins en partie expliquer la variation de prévalence de la DMS de 18 % à 60% dans la littérature (Vieillard-Baron 2011). De plus, les définitions de la DMS sont différentes dans les études (FEVG <50% ou <45% etc..) (Beesley et al. 2018). Il est probable que la contractilité intrinsèque du VG soit en fait constamment altérée et que la dysfonction systolique ne soit visible qu'après restauration de la postcharge du VG.

La dysfonction systolique myocardique n'est pas constamment associée à une augmentation de la mortalité lors du choc septique (Sevilla Berrios et al. 2014). En revanche, la dysfonction diastolique semble plus constamment associée dans les méta-analyses à une augmentation de la mortalité (Filippo Sanfilippo et al. 2015). On peut cependant remarquer que la définition de la dysfonction diastolique n'est actuellement pas consensuelle (Nagueh et al. 2009; Ponikowski et al. 2016).

Les mécanismes suspectés de la DMS

La physiopathologie de la DMS n'est pas élucidée. De nombreux mécanismes ont été supposés, qui impliquent de très nombreuses voies métaboliques.

Homéostasie calcique et couplage excitation-contraction

Le calcium intracytoplasmique conditionne la contractilité myocardique. Les mouvements calciques sont régulés par les canaux calcium de type L pour la contraction et par la pompe calcique ATP dépendante sarcoplasmique, l'échangeur Na-Ca²⁺ pour la relaxation. Toutes ces voies peuvent être altérées lors du sepsis via différents mécanismes (Flynn, Chokkalingam Mani, et Mather 2010).

Bêta-récepteurs

La stimulation β adrénergique augmente la contractilité cardiaque en augmentant le calcium intracellulaire via une protéine G (Gs) par un mécanisme médié par l'AMPC qui au final permettra la phosphorylation et donc l'activation des canaux calciques de type L. La stimulation β favorise également la relaxation des myocytes via la phosphorylation de phospholamban améliorant l'activité de la pompe calcique ATP dépendante sarcoplasmique et donc la fonction diastolique. Dans les modèles animaux endotoxiniques ou de choc septique (Kadoi et al. 1996), le nombre de β récepteurs est diminué. Ainsi, la stimulation des récepteurs β par la dobutamine entraîne une réponse diminuée en terme d'AMPC et de transduction du signal (Silverman et al. 1993) chez les patients en choc septique par rapport aux patients en sepsis sans choc. Ces mécanismes expliquent l'absence ou la diminution de l'effet de la dobutamine dans une grande proportion de cas (Jones et Romano 1990; Cariou et al. 2008).

Dysfonction mitochondriale

Les mitochondries sont nécessaires à l'homéostasie du calcium intracellulaire et la production d'ATP. Les études animales et autopsiques humaines retrouvent une modification de la structure des mitochondries lors du sepsis. Cette dysfonction mitochondriale est aggravée par l'altération du métabolisme du NO, les cytokines, et les radicaux libres de l'oxygène, mais est

par contre atténuée par les « Heat Shock Proteins » (HSP 72 et Grp 75 notamment) (H.-W. Chen et al. 2003; Stuart, Cyr, et Neupert 1994; Mizzen, Kabling, et Welch 1991; Flynn, Chokkalingam Mani, et Mather 2010). Une théorie, démontrée dans un modèle murin (Levy et al. 2005), suggère que la DMS représente un état d'adaptation pour réduire la consommation d'énergie afin de s'accommoder au faible niveau de production d'ATP des mitochondries dysfonctionnelles (Singer 2014), semblable au phénomène d'hibernation lors de l'ischémie myocardique (Camici, Prasad, et Rimoldi 2008).

Le monoxyde d'azote (NO)

Le NO est fabriqué par les cellules endothéliales à partir de la L arginine grâce à la NO synthase. Plusieurs formes de NO synthase existent, dont une forme inductible (type2) qui produit des quantités importantes de NO au cours du sepsis. Plusieurs mécanismes ont été suggérés pour expliquer l'effet délétère du NO produit par la NO synthase inductible : une diminution de l'effet des récepteurs beta adrénergiques, une réduction du flux intrasarcoplasmique de calcium par diminution directe de l'action des canaux calciques responsables de la contractilité myocardique et/ou par réduction de la sensibilité des myofilaments au calcium par phosphorylation de la troponine, et une augmentation de la perméabilité mitochondriale liée aux agents oxydants associés au NO (Xu et al. 2012; Zanotti-Cavazzoni et Hollenberg 2009).

La voie du complément

La réponse humorale activée après un sepsis entraîne une cascade de production de protéines du complément. C5 peut être clivé en C5b qui détruit la paroi bactérienne et C5a, un agent puissamment pro inflammatoire avec une action dépressive myocardique via la production de cytokines mais également de façon indépendante (Hoesel, Niederbichler, et Ward 2007). Le récepteur de C5, le C5aR a une expression constitutive sur les cardiomyocytes pouvant entraîner une dépression myocardique précoce. Le sepsis augmentant la production de C5a et C5aR peut par ailleurs expliquer une dysfonction myocardique différée (Niederbichler et al. 2006).

Damage-associated molecular patterns (DAMPs): histones et high-mobility group box 1 (HMGB1)

Les histones extracellulaires et HMGB1 fonctionnent comme des « damage-associated molecular patterns » (DAMPs) endogènes. Les histones extracellulaires réduisent le potentiel de membrane des mitochondries et les niveaux d'ATP, entraînant des dommages cellulaires. De plus, les histones perturbent l'homéostasie du calcium. Les concentrations d'histones circulantes sont étroitement corrélées aux concentrations de troponine T des patients en choc septique.

Molécules d'adhésion cellulaire ICAM et VCAM

Intercellular adhesion molecule 1 (ICAM-1) et vascular cell adhesion molecule 1 (VCAM-1) régulent l'infiltration tissulaire des neutrophiles. Dans un modèle de cœur isolé de souris, la baisse de 40% de pression générée par le VG après l'injection de lipopolysaccharide (LPS) était inhibée par l'ajout d'anticorps bloquant ICAM ou VCAM, mais pas par la déplétion en neutrophiles (Raeburn et al. 2002). Les auteurs suggèrent un mécanisme altérant le flux de calcium intracellulaire ou une production de radicaux libre d'oxygène.

Facteur(s) dépresseur(s) myocardique(s)

Il existe un lien entre le degré de dysfonction des cardiomyocytes de rat (sur la vitesse de raccourcissement et leur longueurs) apparu après application du sérum de patient en choc septique et la gravité des patients chez qui le sérum a été prélevé (Parrillo et al. 1985). Cet effet n'est pas retrouvé avec le sérum des patients après guérison du sepsis ni avec d'autres patients de réanimation sans sepsis. D'autres études ont montré par la suite l'effet de différentes cytokines, notamment TNF- α et Il 1 β (Stein et al. 1996), Il 6 (Pathan et al. 2004). De nombreuses études animales et in vitro ont montré l'effet dépresseur myocardique de ces cytokines. Cependant, ces dernières ont un effet complexe que l'on peut séparer en deux stades. Un effet immédiat de courte durée qui peut être soit dépresseur soit stimulateur myocardique ne nécessitant pas d'expression génique, et un effet retardé et durable en quelques heures ou

jours, constamment dépresseur myocardique et nécessitant un second médiateur. Les voies de la réponse précoce sont celles du sphingolipide, de la NO synthase constitutive, de l'acide arachidonique, et des altérations du calcium intracellulaire. La réponse différée est secondaire à la production de NO par la NO synthase inductible (iNOS), de radicaux libres de l'oxygène et à une altération du signal des récepteurs β adrénergiques. L'effet retardé est responsable d'une diminution de la contraction du VG et d'une altération de la relaxation VG. On peut noter que l'utilisation des immunothérapies anticancéreuses utilisant le TNF- α ou l'IL-2 est limitée par un effet dose dépendant cardiovasculaire et inotrope négatif. Un essai thérapeutique utilisant un anticorps monoclonal anti TNF- α chez 10 patients en choc septique réfractaire (J. L. Vincent et al. 1992) a montré une augmentation certes transitoire mais significative de la fréquence cardiaque et du travail d'éjection du VG. Au total, l'existence d'un facteur dépresseur myocardique circulant au cours du sepsis semble hautement probable. Toutefois, l'identification du ou des médiateurs du sepsis principalement impliqués dans la DMS reste discutée tout comme reste aussi incertain le fait qu'il s'agisse d'un médiateur unique ou d'un ensemble de médiateurs dont l'action serait synergique.

Insuffisance surrénalienne relative

Les corticoïdes sont les principaux médiateurs de la réponse au stress. Dans un contexte d'agression de l'organisme, on observe une stimulation de la production de CRH (corticotropin releasing hormone) et d'ACTH (Adrénocorticotrophique-Hormone), ainsi qu'une diminution des protéines de liaisons au cortisol et du rétrocontrôle négatif induites par les cytokines pro-inflammatoires provoquant une augmentation du taux de cortisol libre actif (Beishuizen, Thijs, et Vermes 2001; Hamrahian, Oseni, et Arafah 2004; Lamberts, Bruining, et de Jong 1997; Schein et al. 1990). Ces modifications ont pour objectif de maintenir l'homéostasie de l'organisme, avec une augmentation des récepteurs adrénergiques au niveau cardiaque, une augmentation de la sensibilité aux catécholamines au niveau vasculaire (Saito et al. 1995;

Silverman et al. 1993) et une redistribution du glucose vers les cellules insulino-dépendantes. Cependant, la réponse de l'axe corticotrope à une importante réaction inflammatoire prolongée peut être imparfaite. De plus, une résistance aux glucocorticoïdes peut apparaître, élément qui est de mauvais pronostic (Annane et Bellissant 2000). L'insuffisance surrénale relative (ISR) est définie comme un défaut relatif de production de glucocorticoïdes sans anomalie organique sur l'axe hypothalamo-hypophyso-surrénalien. L'ISR est caractérisée par un niveau de cortisol absolu normal ou élevé mais insuffisant pour contrôler la réponse inflammatoire liée à l'agression, donc avec une réponse inadaptée à un état de stress. Les dernières recommandations internationales (SCCM et ESICM) (Djillali Annane, Pastores, Rochweg, et al. 2017) proposent d'identifier l'ISR par le test au Synacthène forte dose (250 µg). L'ISR constitue le rationnel physiopathologique initial à l'utilisation de la corticothérapie substitutive au cours du choc septique (Djillali Annane, Pastores, Arlt, et al. 2017). Elle a été surtout décrite au cours du choc septique, mais existe aussi dans d'autres pathologies du patient grave de réanimation, comme le choc cardiogénique (Ducrocq et al. 2018; Bagate et al. 2017). Du point de vue hémodynamique, l'ISR est associée à une vasoplégie excessive et une résistance à l'effet des vasopresseurs (D. Annane et al. 1998a). Toutefois, l'axe surrénalien est aussi impliqué dans la dysfonction myocardique, suggérant l'étude de son implication éventuelle dans la DMS.

Senescence cellulaire

La senescence traduit l'arrêt du cycle cellulaire. Les télomères sont des séquences ADN répétitives TTAGGG associées à des protéines situées à la fin des chromosomes. Ils stabilisent les extrémités des chromosomes, ce qui permet l'intégrité et la stabilité du génome. La longueur des télomères est considérée comme un marqueur du vieillissement car elle diminue avec l'âge, la division cellulaire et l'exposition à différents stress oxydatifs. Lorsque les télomères sont raccourcis au-delà d'un seuil, il peut se produire un dommage de l'ADN entraînant la senescence ou la mort cellulaire via l'apoptose (Blackburn 2000). La longueur des télomères

peut être mesurée dans les leucocytes sanguins périphériques. Différentes méthodes ont été décrites : Southern blot, hybridation par fluorescence in situ « flowFISH » , ou une PCR quantitative (Savage 2018; Savale et al. 2009; Cawthon 2002). Au cours de cette dernière méthode, la plus utilisée, l'ADN est tout d'abord isolé puis une qPCR quantifie la séquence des télomères en normalisant sur la quantité d'un gène ne possédant qu'une seule copie. Ce rapport (T/S ratio) permet de comparer la longueur des télomères. Le raccourcissement des télomères est associé à plusieurs pathologies chroniques (démence, fibrose pulmonaire, bronchopneumopathie obstructive) (Savage 2018; Savale et al. 2009) notamment cardiovasculaires (artériosclérose, cardiopathie ischémique, hypertension artérielle) (Fyhrquist, Saijonmaa, et Strandberg 2013). L'association entre le raccourcissement des télomères et la DMS semble donc intéressante à étudier.

Circulation coronaire et dommage myocardique

En dépit de l'augmentation habituelle des biomarqueurs cardiaques au cours du sepsis, les études autopsiques (Takasu et al. 2013; Schmittinger et al. 2013) retrouvent très peu d'apoptose des cardiomyocytes (<0.2%). Cunnion et al ont retrouvé le même débit coronaire chez 7 patients septiques avec une DMS en comparaison avec des patients sans DMS (Cunnion et al. 1986). Dhainault et al. ont montré une normalité du débit, de l'extraction myocardique en oxygène et du lactate intrac coronaire (Dhainault et al. 1987). Toutefois, il semble nécessaire d'explorer la microcirculation coronaire chez les patients septiques avec DMS pour complètement infirmer cette hypothèse.

Méthodes d'évaluation de la fonction myocardique

Echocardiographie

L'évaluation de la FEVG par échographie bi-dimensionnelle (2D) est un examen de routine au lit du patient en réanimation, depuis que celle-ci a supplanté le cathétérisme artériel pulmonaire dans l'évaluation hémodynamique du patient en pratique clinique quotidienne (Cecconi et al. 2014). Cependant, cette évaluation de la FEVG en 2D est limitée par le fait qu'elle est

dépendante des conditions de charge (précharge et postcharge) (Robotham et al. 1991), dont les variations sont importantes en réanimation, et par le fait que les modèles géométriques utilisés (modèle des cylindres dans la technique de Simpson) sont mis en défaut en cas de déformation ventriculaire importante. Une nouvelle technique échographique, pourrait permettre de mieux évaluer la contractilité myocardique par un outil moins dépendant des conditions de charge, la signature acoustique « (speckle tracking »).

Speckle tracking en échocardiographie

La signature acoustique repose sur l'identification des réverbérations des ultrasons au niveau du myocarde en échographie bidimensionnelle, qui sont différentes d'un point à l'autre de l'image, et forment une sorte d'empreinte pour chaque segment étudié. Ces réverbérations sont identifiées cadre par cadre et permettent de suivre les mouvements dans le plan radial, longitudinal et circonférentiel, en une seule acquisition. Ces empreintes de *speckle* sont reconnues par un logiciel utilisant un algorithme mathématique permettant de calculer les valeurs de déplacement, vitesse, déformation (« strain »), vitesse de déformation (« strain rate ») d'un segment myocardique donné. Cette technique est possible en échographie trans-oesophagienne (ETO) et en échographie trans-thoracique (ETT), et ne dépend pas de l'angle d'alignement. La déformation représente le changement de longueur du myocarde en réponse à une force appliquée et est exprimé sans unité, en pourcentage de changement. Cette technique a été validée par rapport aux méthodes de référence de mesure de la déformation myocardique que sont l'IRM tagguée et la sonomicrométrie (Amundsen et al. 2006; Cho et al. 2006; Helle-Valle et al. 2005). Elle permet de mesurer une fonction systolique globale par le biais de la mesure d'une déformation longitudinale globale en coupe 4 cavités, et de la mesure d'un taux de déformation (Mondillo et al. 2011). L'autre intérêt réside dans le fait que, de par la détection automatisée des contours de l'endocarde, cette méthode est objective et n'est pas dépendante de l'expérience de l'opérateur et très reproductible (S. Cheng et al. 2013; Costa et al. 2014). La

signature acoustique semble donc intéressante pour explorer de façon plus objective et plus sensible la DMS au lit du malade.

L'IRM cardiaque

L'IRM cardiaque est la méthode de référence pour la mesure des volumes et de la fonction ventriculaire. Elle est de plus capable de caractériser les lésions telles que l'inflammation myocardique à l'aide de séquences spécifiques, avec ou sans recours à l'injection de produit de contraste (Monney et al. 2012). Le rehaussement tardif après injection de gadolinium (RT) est un procédé sensible pour la détection et pour la caractérisation de l'étendue de la nécrose ou fibrose myocardique post-infarctus (Kim et al. 2000; Mahrholdt et al. 2002). Le produit de contraste se distribue exclusivement dans l'espace extracellulaire. Sa vitesse d'élimination est rapide dans du myocarde normal et ralentie dans les zones de fibrose ou de nécrose intramyocardique. Ainsi, l'hyperintensité du signal sur les images tardives (rehaussement tardif par le produit de contraste) permet de détecter les zones de nécrose ou de cicatrice myocardique. La différence fondamentale entre les lésions d'infarctus et de myocardite réside dans leur distribution en rehaussement tardif. L'infarctus myocardique est caractérisé par un rehaussement tardif sous-endocardique (Hunold et al. 2005) respectant les territoires vasculaires tandis que la myocardite se caractérise par un rehaussement tardif sous-épicardique ou médio-mural patchy touchant fréquemment la paroi latérale et basale (Ferreira et al. 2018). Les séquences en pondération T1 et T2 permettent la détection de l'œdème tissulaire (Abdel-Aty et al. 2005; Ferreira et al. 2018). Une augmentation globale immédiate de l'intensité du signal myocardique après gadolinium traduisant la présence d'une réaction inflammatoire qui est associée à une hyperhémie myocardique (Friedrich et al. 1998). L'IRM semble donc intéressante pour évaluer la présence éventuelle d'inflammation ou de nécrose au cours de la DMS.

Traitement de la DMS

Une antibiothérapie initiale précoce et adaptée associée au contrôle de la source de l'infection reste la pierre angulaire du traitement du sepsis. Les recommandations pour la prise en charge hémodynamique du choc septique suggèrent le recours à un remplissage vasculaire important à la phase précoce, ainsi que l'utilisation en première intention de noradrénaline comme vasopresseur, avec rajout éventuel de dobutamine en cas de dysfonction cardiaque associée à des signes d'hypoperfusion persistant malgré le remplissage vasculaire (R. P. Dellinger et al. 2013; Evans et al. 2021). Plusieurs travaux suggèrent qu'une amélioration de l'hémodynamique sous dobutamine est associée à un meilleur pronostic (Rhodes et al. 1999; Vallet et al. 1993; Anand Kumar et al. 2008). Toutefois, la réponse à la dobutamine (en terme de débit cardiaque ou de perfusion tissulaire) est hétérogène au cours du choc septique (Enrico et al. 2012; De Backer et al. 2006; Hernandez et al. 2013a) et l'amélioration de la perfusion tissulaire est mal corrélée à celle du débit cardiaque (Jellema et al. 2006a; Hernandez et al. 2013a; De Backer et al. 2006). En augmentant la fréquence cardiaque, la dobutamine peut théoriquement altérer la diastole et/ou augmenter la demande métabolique du myocarde. De plus, la dobutamine peut abaisser les résistances vasculaires systémiques et aggraver la vasoplégie (Jellema et al. 2006a). L'analyse de la réponse hémodynamique à la dobutamine au cours du choc septique nécessite donc d'évaluer non seulement la variation du volume d'éjection systolique et du débit cardiaque, mais aussi l'évolution de la fonction systolique, diastolique, ainsi que des conditions de charge, notamment la postcharge.

Questions non résolues

En dépit de'une littérature importante sur le sujet, de nombreux aspects de la physiopathologie et du traitement de la DMS restent non résolus.

- La définition de la DMS souffre d'une variabilité liée à deux limites : l'une relative aux outils de mesure de la fonction cardiaque considérés, et l'autre à la potentielle

interaction des conditions de charge, notamment la postcharge. Ce dernier point pourrait expliquer la relation complexe de la dysfonction systolique avec la mortalité. Ces limites rendent nécessaire une exploration avancée de la DMS à l'aide des outils échocardiographiques avancés, avec évaluation concomitante des conditions de charge.

- Le facteur circulant précisément responsable de la DMS reste discuté à ce jour. Sur ce point, une analyse simultanée des principaux médiateurs du sepsis mérite d'être conduite, afin d'explorer un éventuel effet synergique. Dans ce même cadre, le rôle de l'insuffisance surrénale relative (largement impliquée dans la physiopathologie des états septiques) et celui de la senescence (dont l'interaction avec le syndrome inflammatoire est majeure) devraient être explorés. Enfin, l'existence d'une inflammation et/ou nécrose myocardique lors de la DMS du choc septique humain reste à explorer.
- Le rôle des inotropes au cours du choc septique reste controversé, avec des pratiques possiblement hétérogènes. Il semble indispensable de préciser l'efficacité et la tolérance de l'inotrope de référence (la dobutamine) dans le contexte de la DMS.

Toutes ces questions non résolues font l'objet des travaux de cette thèse.

PRINCIPAUX OBJECTIFS DE LA THESE

L'objectif de ce travail de thèse était d'étudier la physiopathologie et le traitement de la DMS au cours du choc septique humain. Pour ce faire, nous avons réalisé les études suivantes :

1/ Caractérisation des mécanismes de la DMS :

- Recherche de nécrose ou d'inflammation par IRM cardiaque ;
- Rôle des conditions de charge sur la DMS et intérêt du speckle tracking
- Rôle des médiateurs du sepsis au cours de la DMS ;
- Relation entre l'ISR et la DMS ;
- Rôle de la senescence cellulaire dans la DMS

2/ Enquête auprès des réanimateurs francophones sur la gestion de la DMS

3/ Evaluation de la dobutamine pour le traitement de la DMS

RESULTATS ET DISCUSSION DES ETUDES

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Article 1 :

IRM myocardique chez 2 patients présentant une DMS

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Myocardial viability in human septic heart

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The mechanisms of myocardial depression during sepsis are not fully understood. Two patients with severe sepsis exhibited acute heart failure with decreased left ventricle ejection fraction (LVEF $\leq 40\%$) on transesophageal echocardiography and increased troponin levels (seven and ten times the normal range). Cardiac magnetic resonance imaging (MRI) showed wall motion abnormalities with decreased contractility (LVEF of 24 and 40 %, respectively), normal or moderately increased size (left ventricle end diastolic volume, LVEDV of 58 and 88 mL/m², respectively), a homogenous myocardial enhancement, and a normal viability of all myocardial segments with no evidence of myocarditis [Fig. 1/Video 1 in ESM (first patient) and Video 2 in ESM (second patient)]. Under treatment, hemodynamic failure resolved within a

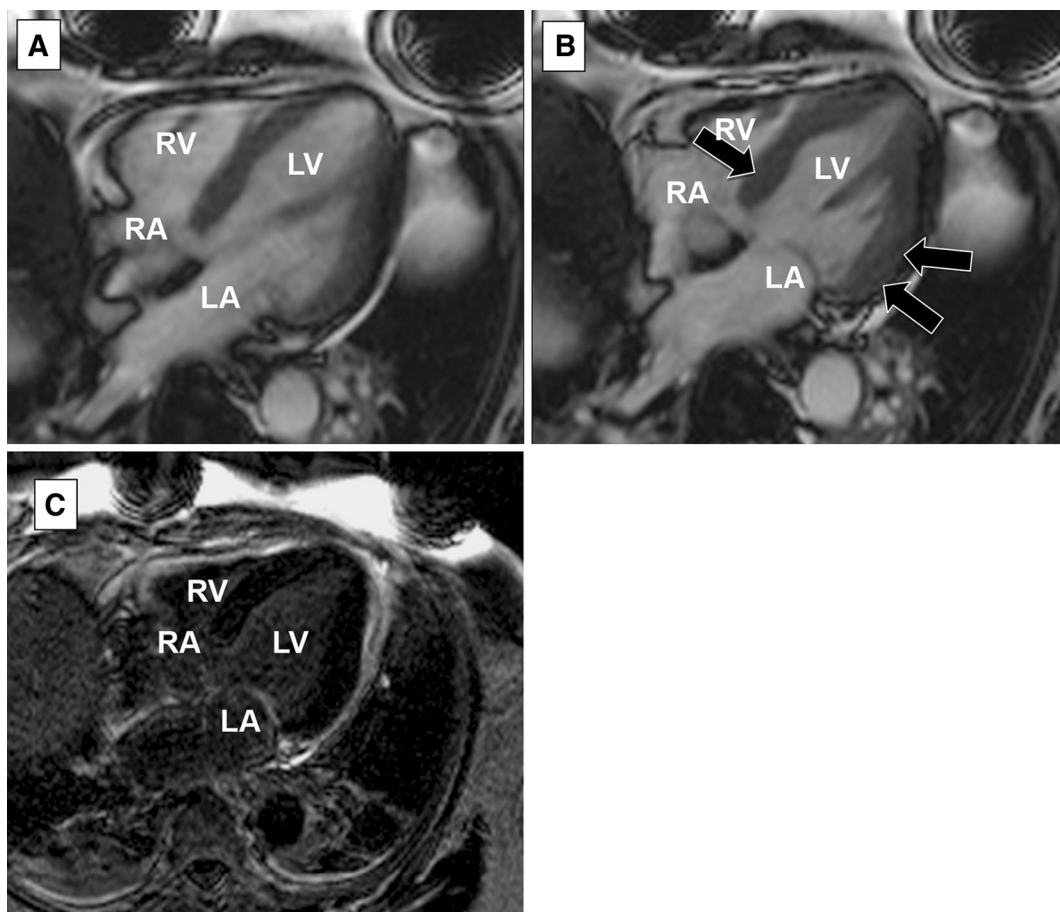


Fig. 1 Four-chamber plane diastolic (a) and systolic (b) cine cardiac magnetic resonance images revealing global left ventricular dysfunction with lateral wall and basal septum hypokinesia (*black arrows*). Four-chamber plane late gadolinium enhanced image acquired 10 min after gadolinium injection revealed a lack of myocardium enhancement of the left ventricular wall that appeared

as a black structure (c). This absence of myocardial enhancement reflects the presence of viable myocardium. Non-viable myocardium would have enhanced vividly after contrast administration because of accumulation of gadolinium within damaged myocardial tissue. *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle

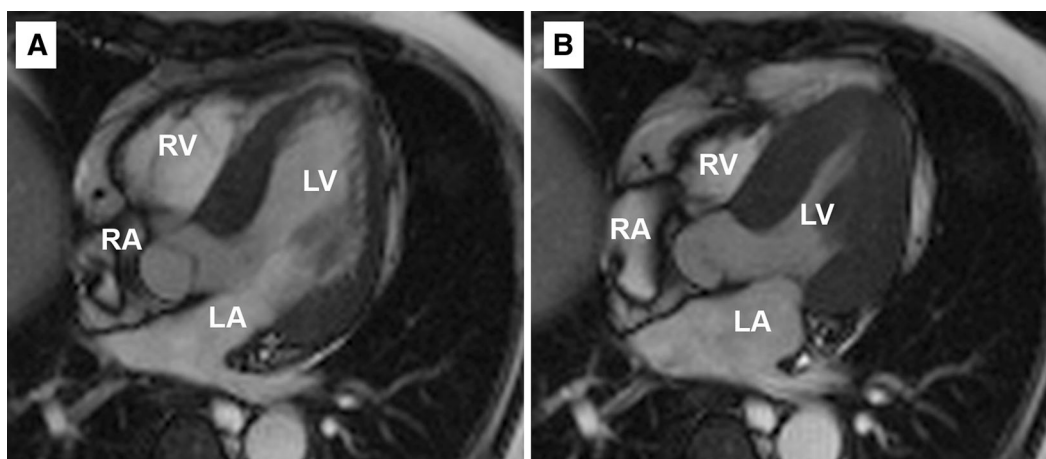


Fig. 2 Diastolic (a) and systolic (b) cine cardiac magnetic resonance images acquired in the four-chamber plane 1 month after hospital discharge revealing normalization of left ventricular function. *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle

few days in both patients and myocardial dysfunction and dilatation had completely reversed on a control transthoracic echocardiography. Control cardiac MRI performed 6 weeks after the first imaging in the first patient showed a complete recovery of cardiac contractility (LVEF of 57 %) with normal size (LVEDV of 44 mL/m²). Myocardial perfusion and viability were also normal, with no

evidence of scar or inflammation (Fig. 2/Video 3 in ESM). These results are in line with the hypothesis of myocardial stunning or catecholamine stress as the main cause of septic heart dysfunction.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Nous avons montré dans ce travail que la DMS n'est pas une myocardite septique comme elle est parfois nommée par les réanimateurs et qu'il n'y a pas de zone de nécrose myocardique comme dans l'infarctus du myocarde. Un autre cas clinique avait retrouvé les mêmes constatations sur la nécrose myocardique mais avait par contre retrouvé un aspect de rehaussement sous épicaudique antéro et inféro latéral associé à un réhaussement médio-mural septo-basal (De Lazzari et al. 2017). Ces données nécessitent donc d'être confirmées à plus large échelle. Mais la difficulté de transporter des patients instables sur le plan hémodynamique pour un tel examen reste un obstacle important.

Article 2 :

Dysfonction systolique ventriculaire gauche au cours du choc septique : rôle des conditions de charge

ORIGINAL



Left ventricular systolic dysfunction during septic shock: the role of loading conditions

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Abstract

Purpose: The clinical significance of septic myocardial dysfunction is controversial, a fact that may be explained by the influence of loading conditions. Many indices may be useful to characterize cardiac function during septic shock, but their feasibility and physiological coherence in the clinical setting are unknown.

Methods: Hemodynamic and echocardiographic data with tissue Doppler and speckle tracking were prospectively recorded on the first 3 days of human septic shock. Hypokinesia, normokinesia, and hyperkinesia were defined as a left ventricular ejection fraction (LVEF) of <45, 45–60, and >60%, respectively. Twelve hemodynamic indices exploring contractility and loading conditions were assessed and analyzed.

Results: Two hundred and ninety-seven echocardiographies were performed in 132 patients. During the first 24 h (H_{1-24}), 48 (36.4%) patients were hyperkinetic, 55 (41.7%) were normokinetic, and 29 (22.0%) patients were hypokinetic. Thirteen patients had a secondary hypokinesia absent at H_{1-24} but present at H_{25-48} or H_{49-72} , for an overall incidence of 42 (31.8%) during the first 3 days. Despite a limited feasibility (<50%), global LV longitudinal peak systolic strain was impaired in a majority (>70%) of the patients assessed, including all those with depressed LVEF, and declined early in patients whose LVEF secondarily deteriorated. Most contractility indices were inversely correlated with afterload indices. Hyperkinetic patients exhibited the worst reduction in afterload indices. Hospital mortality was significantly higher in patients with LV hyperkinesia than in their counterparts: 30 (62.5%) vs. 35 (41.7%), $p = 0.02$.

Conclusions: Speckle tracking-derived strain was reduced in the majority of patients with septic shock, revealing covert septic myocardial dysfunction, but had poor feasibility. We found an inverse correlation between most of the contractility and afterload indices. Precise evaluation of afterload is crucial for adequate interpretation of LV systolic function in this setting.

Keywords: Sepsis, Cardiac dysfunction, Afterload

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Take-home message Our study supports the hypothesis of a widespread alteration of LV contractility during human septic shock and suggests that knowledge of afterload, a major prognostic factor, is crucial for adequate interpretation of LV systolic function in this setting.

Introduction

Septic myocardial dysfunction (SMD) was described during septic shock by Parker et al. in 1984 [1], but its prevalence, clinical significance, and prognosis are still being debated [2]. The prevalence of left ventricle (LV) systolic dysfunction varies widely (18–65%) during human septic shock, depending on studies [2]. This variability may be explained by timing of evaluation, the accuracy of the routine indices used to assess LV systolic function, and

most importantly their dependency on loading conditions [3]. Some authors have hypothesized that in the more severe patients, vasoplegia and reduced afterload may favor preserved or high LV ejection fraction (LVEF) [4], whereas the preservation or restoration of afterload could unmask poor intrinsic LV contractility [2]. However, a comprehensive demonstration of these assumptions in the clinical setting is lacking.

In recent years, new echocardiographic tools have been developed to assess LV function, such as speckle tracking, which evaluates LV deformation over time. Because this technique is angle-independent and less pressure-dependent and more sensitive than LVEF [5, 6], it might allow a more in-depth analysis of the prevalence of LV systolic dysfunction during septic shock and its early detection. Other parameters that can help to evaluate cardiac contractility include tissue Doppler imaging, LV end-systolic maximal elastance, and ventricular–arterial coupling. However, the feasibility, clinical significance, and physiological coherence of these different indices have not been assessed during human septic shock.

The aims of the present study were twofold: (i) to assess the feasibility and physiological coherence of the various indices of cardiac function proposed to assess hemodynamic during septic shock; (ii) to test the role of loading conditions on evaluation of cardiac contractility in septic shock.

Patients and methods

Patients

Patients who met septic shock criteria (as defined according to the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) Consensus Conference [7]) were prospectively included at the medical ICU of Henri Mondor University Hospital (Creteil, France) between November 2010 and March 2013. Patients were included at the onset of septic shock, as defined by start of vasopressor infusion. Non-inclusion criteria were chronic heart failure, defined as a baseline (before ICU admission) LVEF below 45% or a severe valve heart disease. The study was approved by the institutional ethics committee of the French Intensive Care Society as a component of standard care and patient consent was waived. Written and oral information about the study was given to the families. Patient severity was evaluated by the McCabe and Jackson score for underlying diseases, the SAPS II score for acute illness at ICU admission, and the SOFA score for organ dysfunction during septic shock. Norepinephrine was the first-choice vasopressor therapy (used to target a mean arterial pressure of 65 mmHg or more); dobutamine was added in the presence of decreased LVEF (<45%) with ongoing signs of

hypoperfusion despite adequate mean arterial pressure (epinephrine could be considered if the latter condition was not met). Follow-up for the study was until hospital discharge.

Echocardiography

To evaluate cardiac function, we performed transthoracic (TTE) or multiplane transesophageal echocardiographies (TEE, when TTE did not allow accurate measurements because of poor acoustic windows) each day during the first 72 h of septic shock (or until vasopressor weaning or death, if they occurred before the 72nd hour). These echocardiographies were performed by trained operators (competence in advanced critical care echocardiography) using an iE33 system (Philips Ultrasound, Bothell, WA, USA) with a standard procedure, to assess LV and right ventricle (RV) size, filling, function, and output, as detailed in the Electronic Supplementary Material (ESM). All measures performed during each examination were averaged over a minimum of three cardiac cycles (five to ten in case of non-sinus rhythm). Because calendar day 1 only represented a few hours in some cases, we separated echocardiographic data based on time elapsed since inclusion, dividing them into three periods: from the first to the 24th hour (H_{1-24}), from the 25th to the 48th hour (H_{25-48}), and from the 49th to the 72nd hour (H_{49-72}). On each of these assessments, LVEF was defined as depressed (<45% or when an inotrope infusion was needed to achieve a value $\geq 45\%$), normal (between 45 and 60%), or increased (>60%) [8]. Hypokinesia was defined as the occurrence of depressed LVEF at H_{1-24} (primary hypokinesia) or after (secondary hypokinesia); the remaining patients were classified as hyperkinetic (LVEF was never depressed and increased at least once) or normokinetic (LVEF was never depressed and never increased).

Speckle tracking imaging

Apical long-axis (four- and two-chamber) clips obtained with a frame rate ≥ 50 Hz underwent off-line speckle tracking analyses using the semi-automated Philips' Qlab 8.1 CMQ package (Philips Ultrasound, Bothell, WA, USA) by two trained operators (see ESM). In the Lagrangian strain calculation of strain = displacement/relaxed length, displacement was measured as a weighted average of the myocardial deformation across the myocardium with the weighting greatest at the endocardium. The relaxed length was measured at the endocardial boundary. The cutoff used to assess depressed contractility by speckle tracking was an absolute value of global LV longitudinal peak systolic strain below 16.5% [9].

Assessment of contractility and loading conditions

Preload was assessed using estimates of LV filling pressures (E/A and E/e' ratios from pulsed-wave Doppler early (E) and late (A) and tissue Doppler early (e') diastolic wave velocity at the lateral mitral valve annulus) and respiratory variations of vena cava (as surrogates of fluid responsiveness). Afterload was assessed using diastolic arterial pressure (invasive measurement), systemic vascular resistance, end-systolic arterial elastance, and LV end-systolic wall stress (see ESM). LV systolic function was assessed using indices obtained by two-dimensional echocardiography (LVEF), tissue Doppler imaging (tissue Doppler peak systolic wave at the lateral mitral valve annulus) [10], speckle tracking imaging (global longitudinal peak systolic strain and strain rate of the LV), LV end-systolic maximal elastance, and ventricular–arterial coupling, which is the ratio of LV end-systolic maximal elastance and end-systolic arterial elastance (see ESM for formulas).

Statistical analysis

The data were analyzed using the IBM SPSS Statistics for Windows (Version 24.0, IBM Corp Armonk, NY, USA) and R 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous data were expressed as medians [25–75th centiles] unless otherwise specified, and were compared using the Kruskal–Wallis test followed by pairwise Mann–Whitney test with Benjamini–Hochberg correction to control the false discovery rate at the 0.05 level. Categorical variables, expressed as percentages, were evaluated using the Chi-square test or Fisher exact test. The two aims of our study were achieved as follows. First, we tested the feasibility of various indices of cardiac function, and assessed their physiological coherence using hierarchical clustering; this method builds homogeneous clusters based on dissimilarities or distances between cases and proceeds iteratively to join the most similar cases (see ESM). Because longitudinal strain has been suggested as a particularly sensitive method to assess contractility, we tested its usefulness to predict secondary hypokinesia. Second, we assessed the role of loading conditions on cardiac contractility by using bivariate correlations that were further summarized in a correlation matrix (corrplot package within the R environment). Correlations were tested using the Spearman method with Benjamini–Hochberg correction to control the false discovery rate at the 0.05 level. Two-tailed p values less than 0.05 were considered significant.

Results

Patient characteristics and feasibility of echocardiographic parameters

The study flow chart is provided in Fig. S1. The study comprises 132 patients (89 men and 43 women), with

a median age of 63.8 [50.6–74.7] years, including 106 (80%) under mechanical ventilation. All patients required a vasopressor infusion to maintain blood pressure and 92 (70%) had an arterial lactate concentration above 2 mmol L⁻¹ [11]; 56 (42%) patients died in ICU. A total of 279 echocardiographies (132 at H_{1–24}, 74 at H_{25–48}, and 73 at H_{49–72}) were performed in these patients during the first 3 days of septic shock. The feasibility of echocardiographic parameters varied widely (Fig. 1). Global LV longitudinal strain rate had the worst feasibility (42%).

LV kinetics

At H_{1–24}, 29 (22.0%) patients were hypokinetic (LVEF < 45%), 55 (41.7%) were normokinetic (LVEF between 45 and 60%), and 48 (36.4%) were hyperkinetic (LVEF > 60%). Overall, during the first 3 days of septic shock, LV hypokinesia was diagnosed in a total of 42 (31.8%) patients [including 29 (22.0%) with primary hypokinesia (present at H_{1–24}) and 13 (9.8%) with secondary hypokinesia (absent at H_{1–24} but present at H_{25–48} or H_{49–72})] (Fig. 2). All patients' clinical characteristics and comorbidities were similar between groups at initial assessment (H_{1–24}), except for a higher prevalence of cirrhosis in patients with primary hyperkinesia as compared to their counterparts (Table 1). As expected, patients with primary hypokinesia had reduced LV contractility indices and received more inotropes (Table 1). Global LV longitudinal peak systolic strain was impaired in a majority of the patients that could be assessed for this parameter: at H_{1–24}, 57/78 (73.1%) and 63/78 (80.3%) patients had an absolute value below 16.5 and 18.5%, respectively, including all those with an LVEF < 45%. As expected, LVEF and absolute values of global LV longitudinal peak systolic strain were lower at H_{1–24} in patients with primary hypokinesia as compared to their counterparts; in addition, the latter parameter was already lower at H_{1–24} in patients with normal LVEF but who exhibited a secondary hypokinesia (Fig. 3).

Role of loading conditions

LV end-diastolic volumes and preload indices were similar between LV kinetics groups at H_{1–24}; in contrast, patients with primary hyperkinesia exhibited the most severe reduction in afterload indices (Table 1). An unsupervised computer-generated hierarchical clustering of echocardiographic parameters at H_{1–24} identified three coherent clusters involving the following physiological pathways: contractility, afterload, and preload (Fig. 4a). In the correlation matrix (Fig. 4b), most contractility indices were not associated with preload indices, but were inversely correlated with afterload indices. The correlations of LVEF with LV longitudinal peak systolic strain and LV end-systolic

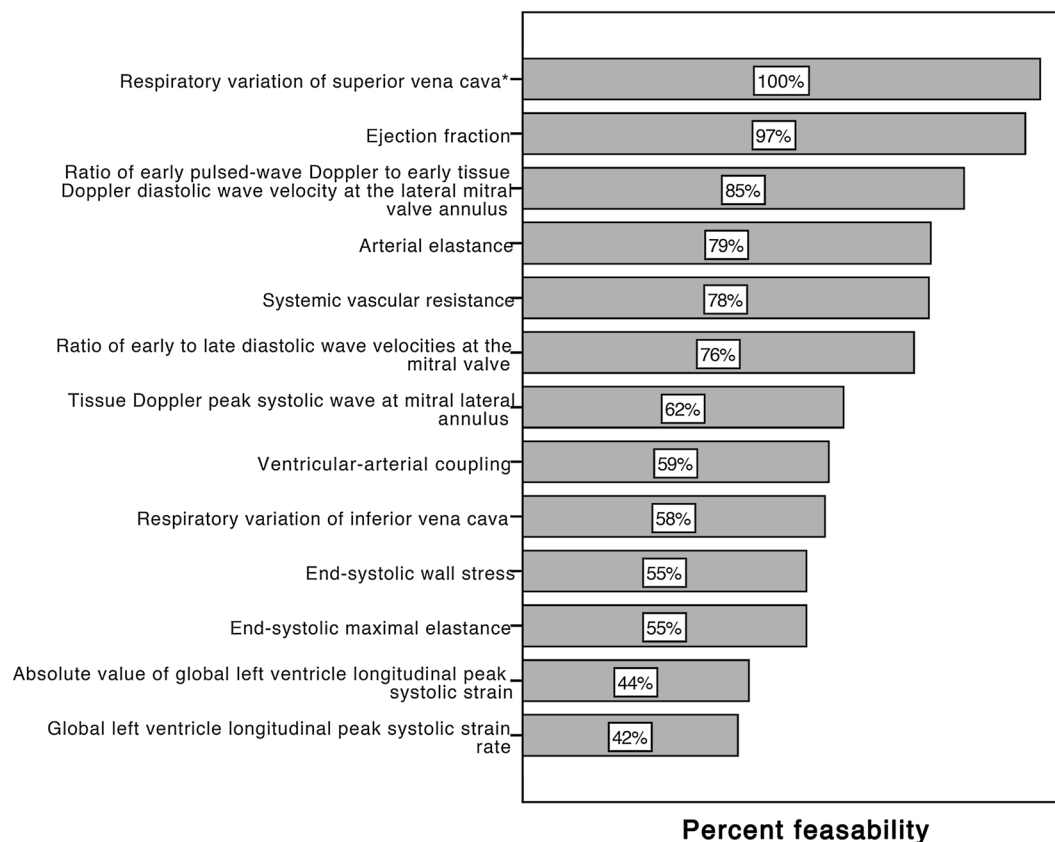


Fig. 1 Feasibility of echocardiographic parameters assessed during a total of 279 echocardiographies during the first three 3 days of septic shock. *Superior vena cava feasibility was computed considering the 76 transesophageal echocardiographies

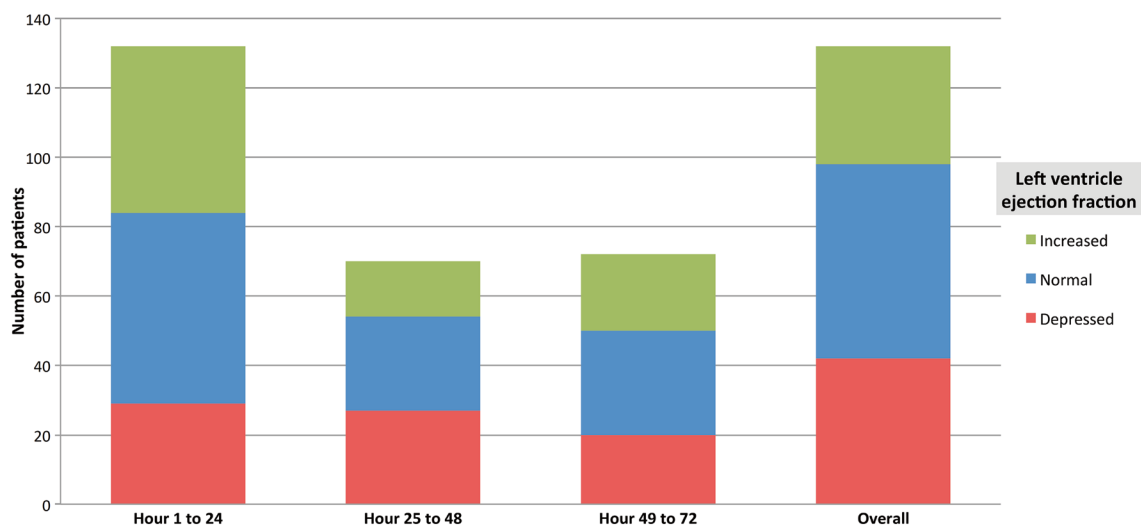


Fig. 2 Left ventricle ejection fraction (LVEF) during the first 3 days of septic shock. Y-axis represents the number of patients

wall stress at H_{1-24} are shown in Fig. 5a and b as an illustration. In-ICU and in-hospital mortality were significantly higher in patients with LV hyperkinesia

as compared to their counterparts: 26 (54.2%) vs. 30 (35.7%), $p = 0.04$ and 30 (62.5%) vs. 35 (41.7%), $p = 0.02$, respectively.

Table 1 Clinical and echocardiographic characteristics of patients according to left ventricular ejection fraction during the first 24 h of septic shock

	N	LVEF			p value
		Hyperkinesia (n = 48/132)	Normokinesia (n = 55/132)	Hypokinesia (n = 29/132)	
Clinical characteristics and comorbidities					
Age, years	132	63 [50–75]	65 [54–75]	64 [50–71]	0.99
Male gender, n (%)	132	35 (73%)	31 (56%)	23 (79%)	0.06
McCabe and Jackson class	132				0.14
0		17 (35%)	28 (51%)	17 (59%)	
1		20 (42%)	22 (40%)	8 (27%)	
2		11 (23%)	5 (9%)	4 (14%)	
SAPS II at ICU admission	131	52 [44–66]	58 [36–71]	54 [44–75]	0.61
Chronic renal replacement therapy, n (%)	132	2 (4%)	1 (2%)	1 (3%)	0.77
Chronic respiratory failure, n (%)	132	2 (4%)	0 (0%)	0 (0%)	0.13
Cancer or hematological malignancy, n (%)	132	7 (15%)	10 (18%)	5 (17%)	0.88
Cirrhosis, n (%)	132	12 (25%)	5 (9%)	2 (7%)	0.04
Organ failures and hemodynamics during the first 24 h of septic shock					
SOFA score	131	12 [8–15]	10 [8–13]	13 [10–15]	0.04
Norepinephrine treatment, n (%)	132	48 (100%)	55 (100%)	24 (83%)	0.003
Maximal daily dose of norepinephrine ($\mu\text{g kg}^{-1} \text{min}^{-1}$)	132	0.7 [0.4–1.4]	0.8 [0.4–1.3]	0.8 [0.5–1.8]	0.69
Epinephrine treatment, n (%)	132	0 (0%)	0 (0%)	6 (21%)	<0.001
Dobutamine treatment, n (%)	132	0 (0%)	4 (7%)	10 (35%)	<0.001
Mean daily cumulative fluid balance (L/day)	126	2.1 [0.8–3.8]	2.1 [1.5–3.8]	2.4 [0.8–4.3]	0.85
Mean arterial blood pressure (mmHg)	119	72 [66–79]	74 [69–85]	77 [70–83]	0.29
Diastolic arterial pressure (mmHg)	119	52 [47–60]	57 [50–64]	63 [50–68]	0.053
Heart rate (bpm)	122	99 [84–120]	105 [89–119]	107 [91–121]	0.58
Arterial blood lactates (mmol/L)	131	2.6 [1.2–5.9]	2.5 [1.6–3.7]	4.1 [2.5–5.6]	0.07
Echocardiography-derived indices during the first 24 h of septic shock					
Preload					
Respiratory variation of inferior vena cava (%)	83	15 [0–60]	11 [0–50]	6 [5–11]	0.41
Respiratory variation of superior vena cava (%)	53	8 [5–18]	12 [4–21]	6 [2–8]	0.35
E/A ratio at mitral valve	107	0.9 [0.8–1.2]	0.9 [0.7–1.2]	0.8 [0.7–1.1]	0.24
E/e' ratio at lateral mitral annulus	115	7 [6–9]	8 [6–9]	6 [6–7]	0.24
LV end-diastolic volume (mL)	47	73 [47–83]	59 [54–82]	81 [57–111]	0.28
LV end-systolic volume (mL)	47	24 [15–30]	27 [20–43]	48 [37–79] ^{a,b}	0.001
Contractility					
Global LV longitudinal peak systolic strain (%)	67	−18 [−20 to −14]	−14 [−17 to −11]	−9 [−13 to −8] ^{a,b}	<0.001
Global LV longitudinal peak systolic strain rate (s^{-1})	64	1.4 [1.1–1.5]	1.1 [0.9–1.6]	0.7 [0.5–1.3] ^{a,b}	0.006
Tissue Doppler peak systolic wave at mitral lateral annulus (cm s^{-1})	86	11 [9–15]	10 [8–13]	7 [6–12]	0.04
Ventricular–arterial coupling	89	3.1 [2.3–4.3]	1.5 [1.2–2.0] ^a	1.1 [0.6–1.4] ^{a,b}	<0.001
LV end-systolic maximal elastance (mmHg mL^{-1})	86	5.6 [4.0–6.8]	3.6 [2.8–4.7] ^a	2.7 [1.6–3.2] ^{a,b}	<0.001
Afterload					

Table 1 continued

	N	LVEF			p value
		Hyperkinesia (n = 48/132)	Normokinesia (n = 55/132)	Hypokinesia (n = 29/132)	
End-systolic arterial elastance (mmHg mL ⁻¹)	114	1.9 [1.5–2.3]	1.9 [1.7–2.6]	2.5 [2.2–2.8] ^{a,b}	<0.001
Systemic vascular resistance (mmHg L ⁻¹ min)	114	1.0 [0.7–1.2]	1.1 [0.9–1.4]	1.2 [1.0–1.9] ^a	0.009
LV end-systolic wall stress (mmHg L)	86	2.7 [1.5–3.4]	3.6 [2.3–5.0] ^a	5.4 [4.3–8.9] ^{a,b}	<0.001
RV function					
RV dilatation, n/N (%)	98	23/37 (62%)	20/40 (50%)	12/21 (57%)	0.56
Cor pulmonale, n/N (%)	108	3/39 (8%)	5/46 (11%)	2/23 (9%)	0.88
Global function					
Stroke volume assessed via LV outflow tract (mL)	122	62 [55–80]	54 [43–67] ^a	45 [38–53] ^{a,b}	<0.001
Stroke index (mL m ⁻²)	122	35 [27–45]	31 [24–35] ^a	24 [20–31] ^{a,b}	0.004
Cardiac index (mL min ⁻¹ m ⁻²)	97	3.5 [2.5–4.4]	3.1 [2.4–3.8]	2.2 [1.6–3.2] ^{a,b}	0.006

SAPS simplified acute physiologic score, ICU intensive care unit, SOFA sequential organ failure assessment, LV left ventricle, RV right ventricle

^a $p < 0.05$ (corrected Mann–Whitney test after Kruskal–Wallis test) as compared to hyperkinesia

^b $p < 0.05$ (corrected Mann–Whitney test after Kruskal–Wallis test) as compared to normokinesia

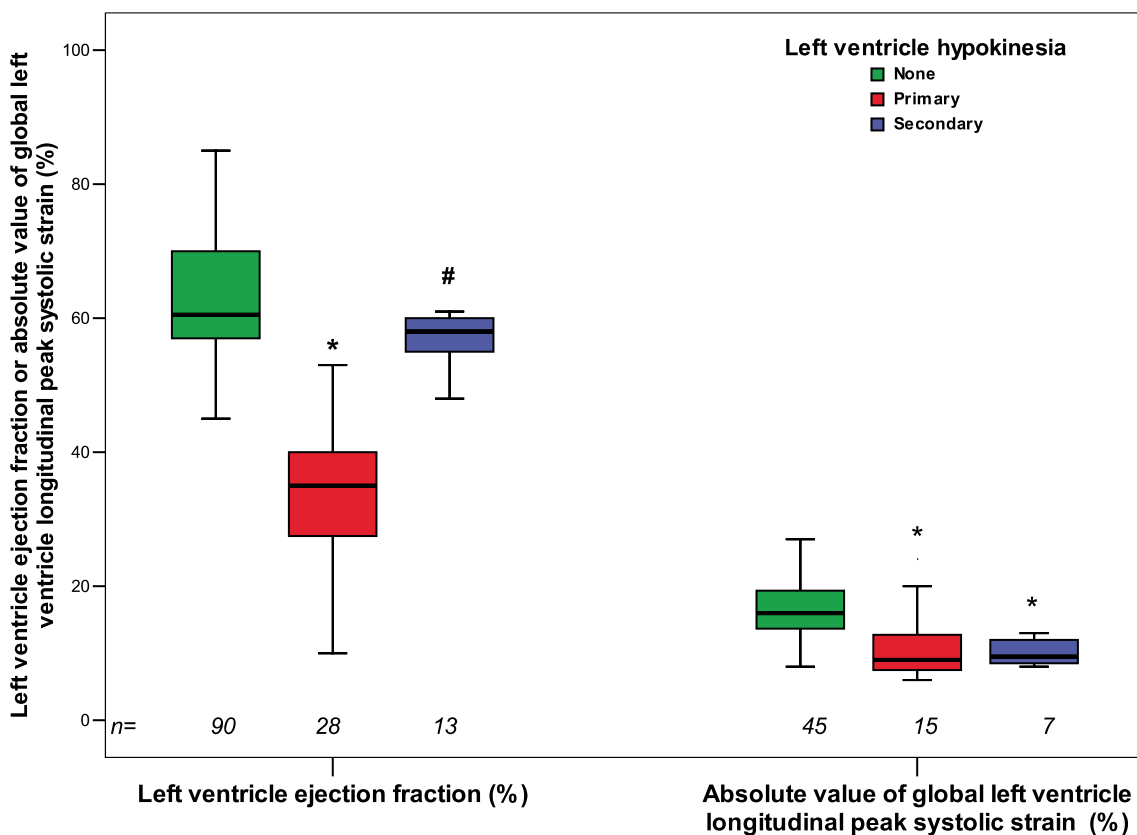
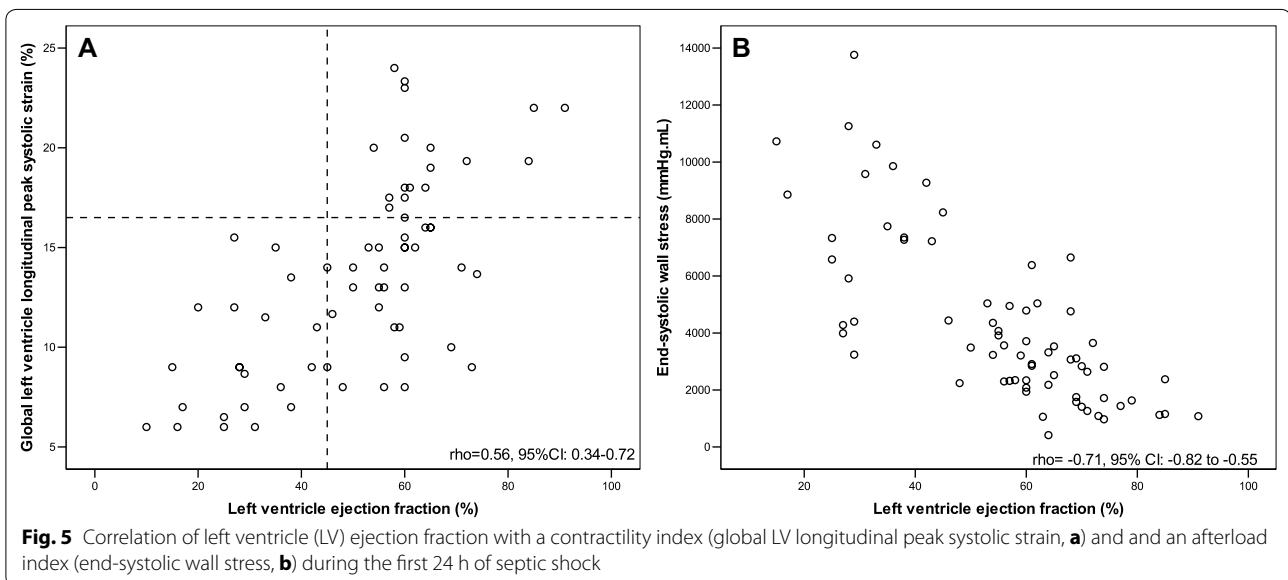
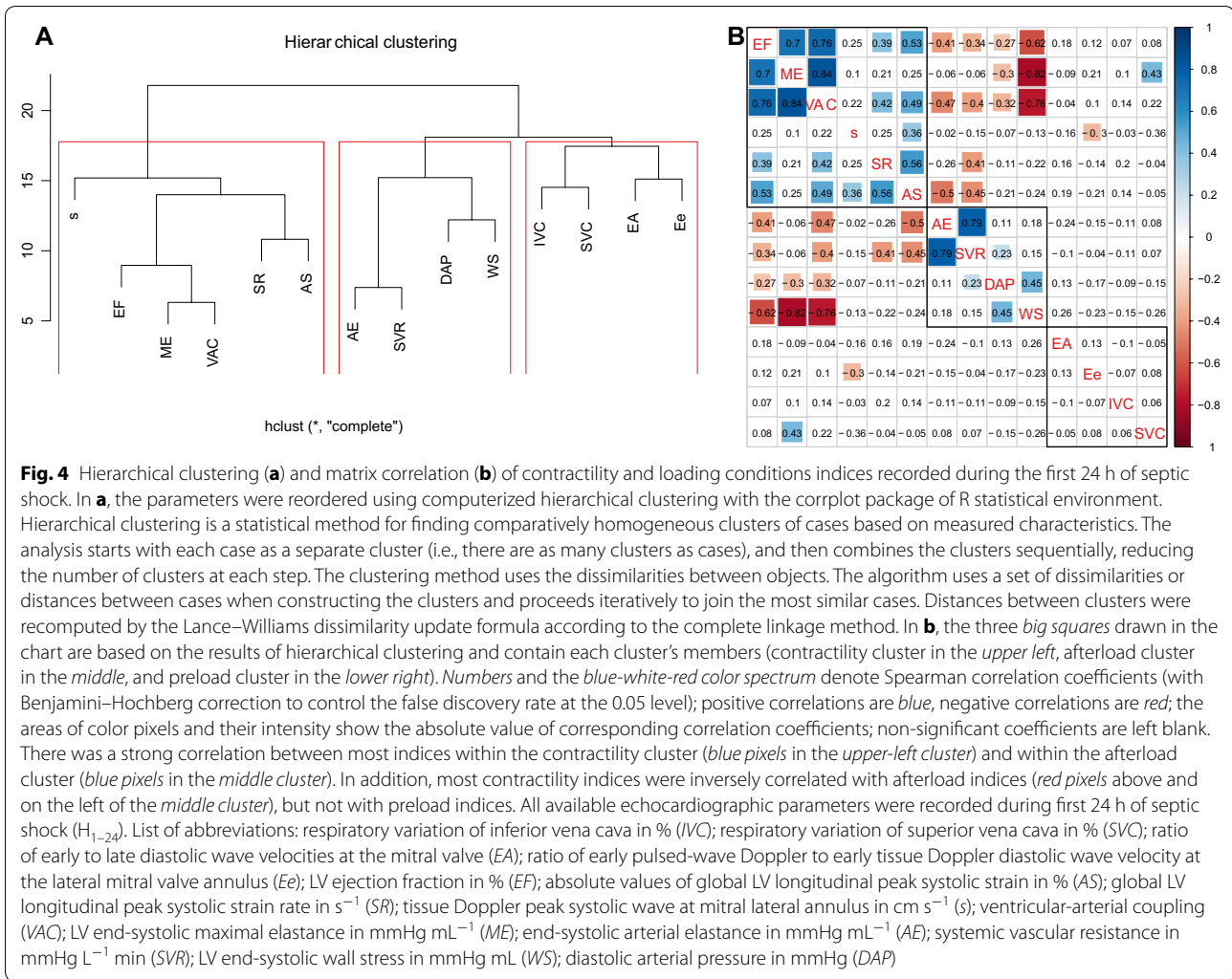


Fig. 3 Left ventricle ejection fraction (EF) and absolute values of global left ventricle longitudinal peak systolic strain (AS) during the first 24 h of septic shock (H_{1-24}), according to the occurrence and timing of hypokinesia: no hypokinesia (green boxes), primary hypokinesia (present at H_{1-24} , red boxes), or secondary hypokinesia (absent at H_{1-24} but present at H_{25-48} or H_{49-72} , blue boxes). The box-and-whisker plots represent median (thick horizontal bar), 25th and 75th percentiles (bottom/top of the boxes), 5th and 95th percentiles (thin horizontal bars). * $p < 0.05$ (corrected Mann–Whitney test after Kruskal–Wallis test) as compared to no hypokinesia; # $p < 0.05$ (corrected Mann–Whitney test after Kruskal–Wallis test) as compared to primary hypokinesia



Discussion

We herein report a reduction of LV contractility in one-third (as assessed by LVEF) and more than two-thirds (as assessed by speckle tracking-derived LV longitudinal peak systolic strain) of patients during septic shock. The latter index was reduced early in patients whose LVEF secondarily deteriorated. There was an inverse correlation between contractility and afterload indices, with hyperkinetic patients exhibiting the most severe reduction in afterload indices.

Prevalence of hypokinesia and feasibility of echocardiographic indices

The 32% prevalence of hypokinesia evaluated by LVEF in our study is consistent with previous large-size studies [12, 13]. This prevalence varied widely in smaller cohorts and these discrepancies could be explained in part by differences in selection criteria (e.g., septic shock vs. severe sepsis), times of assessment and/or thresholds used to define reduced LVEF (e.g., 45 vs. 50%) [14–16]. When assessed by speckle tracking, the prevalence of SMD in our patients was much higher (>70%) and all patients with reduced LVEF had impaired LV longitudinal peak systolic strain. In addition, LV longitudinal peak systolic strain at H_{1-24} was lower in patients with secondary hypokinesia as compared to those with preserved LVEF on successive examinations. These findings suggest that speckle tracking may prove useful in predicting secondary overt SMD and may help reveal mild SMD not apparent with conventional echocardiography [6, 17]. Our data also corroborate animal studies suggesting an almost ubiquitous depression of intrinsic LV contractility during sepsis when assessed using speckle tracking or the gold standard technique of pressure–volume loops, which is independent from loading conditions [18, 19]. Unfortunately, this technique is not routinely applicable at the bedside. We found the feasibility of echocardiographic indices to be highly variable in our study. Although strain measurement is angle-independent, less subjective than other measurements (computer-generated), and very sensitive to detect altered contractility, its feasibility during septic shock (less than 50% in our study) seems limited by the need for high frame rate and adequate image quality [20].

Role of loading conditions

Variability in LVEF (and the resulting prevalence of human SMD) may mainly reflect the influence of loading conditions. LVEF and other systolic indices reflect the coupling between LV contractility and LV afterload [21], the latter being particularly reduced during septic shock. In other words, normal LVEF may be observed when afterload is severely impaired, despite seriously decreased

intrinsic LV contractility; conversely, arterial tone preservation or restoration may unmask depressed LVEF [4]. Afterload was scrutinized using various parameters in our study, all of which were significantly reduced in the group of patients with hyperkinesia as compared with other patients. Among contractility parameters, only tissue Doppler peak systolic wave at the lateral mitral valve annulus did not significantly correlate with afterload. These findings are in accordance with previous studies suggesting its relative independence from loading conditions [10].

A recent study [22] documented that dynamic LV intraventricular obstruction triggered by hypovolemia in hyperdynamic patients at the early stage of septic shock (within the first 6 h following admission to the ICU) was associated with a worse prognosis. We did not specifically explore LV intraventricular obstruction in our study, but the absence of significant correlation between contractility parameters and preload indices is consistent with substantial fluid resuscitation at the time of our echocardiographic examinations. We found comparable diastolic LV volumes in patients with hypokinesia as compared to others, in keeping with previous studies suggesting the lack of preload adaptation during septic shock [23]. On the contrary, systolic LV volumes were significantly reduced in hyperkinetic patients, suggesting that hyperkinesia was due to a reduction in afterload (with increased stroke volume) rather than to hypovolemia. Cor pulmonale may theoretically alter LV filling and promote LV hyperkinesia [2]; although RV dilatation was common in this series of patients with septic shock, cor pulmonale, which is usually associated with severe ARDS [24], was rare (<10%) and evenly distributed in groups with hyperkinesia, normokinesia, and hypokinesia.

Outcome of SMD

In our study, the reduction of LV contractility was not associated with increased mortality, regardless of the parameter used. On the contrary, there was an association between hyperkinesia, reduced afterload, and increased mortality. These results are in accordance with previous reports suggesting reduced survival in septic and non-septic patients with increased contractility indices using conventional [23, 25] or tissue Doppler echocardiography [26]. Whether vasoplegia drives the excess mortality in septic hyperkinetic patients is a question warranting future research. The role of baseline cardiovascular alterations in cirrhotic patients with septic shock should also be scrutinized.

Implications, strengths and limitations

The strengths of our study include its prospective design and size, the severity of the patients selected, the

comprehensive evaluation of myocardial contractility and loading conditions with control for false discovery rate, and the use of tissue Doppler and strain imaging. Our study has the following implications in the clinical and research settings: (i) systolic strain is a sensitive tool to depict covert SMD; (ii) knowledge of afterload is crucial to adequately interpret LV systolic function during human septic shock; and (iii) LV hypokinesia is not associated with excess mortality during septic shock. This point has significant clinical implications, as the use of inotropes during septic shock is generally driven by the assessment of systolic function in general, and of LVEF in particular. As pointed out in a recent review on the topic [3], most of the recent clinical literature has focused on cardiac performance to characterize septic cardiomyopathy, without considering the impact of systemic arterial circulation and heart–vessel interaction, so that readers may underestimate the crucial role of the latter. Very few clinical studies, of limited power (<30 patients), have attempted to investigate this interaction [4, 27], doing so by exploring a single parameter of LV afterload and using conventional echocardiographic indices. Our study is the first to comprehensively assess this interaction, using multiple parameters including new echocardiographic tools such as speckle tracking, in a large population of severe patients with septic shock.

Our study also has limitations. First, the design was monocentric and the number of patients with evolution over time was too low to scrutinize this point. Second, the study was not fully blinded and results of conventional echocardiographic measurements influenced patient treatment. Patients with decreased LVEF received more inotropes, a strategy which might have altered their hemodynamics and outcome. Dobutamine was shown to improve macrocirculation [28] and microcirculation [29] during septic shock, and future trials are needed to assess whether it alters the outcome of septic shock patients with LV hypokinesia at echocardiography. Third, we did not perform a reproducibility study, did not assess all potentially interesting parameters (e.g., mitral annular plane systolic excursion), and the inconsistent feasibility of the assessed parameters generated missing data.

Conclusion

LV longitudinal strain was more than twice as often depressed than LVEF during septic shock, revealing covert SMD; early strain reduction was found in patients with secondary hypokinesia, but this technique had poor feasibility. LV hypokinesia did not alter the prognosis of septic shock, given the common use of inotropes in this subgroup. Contractility indices were inversely correlated

with afterload, with the exception of tissue Doppler peak systolic wave at the lateral mitral valve annulus. Our data suggest a widespread reduction of LV contractility during human septic shock and highlight the fact that precise evaluation of afterload is crucial to adequately interpret LV systolic function in this setting.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-017-4698-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

None.

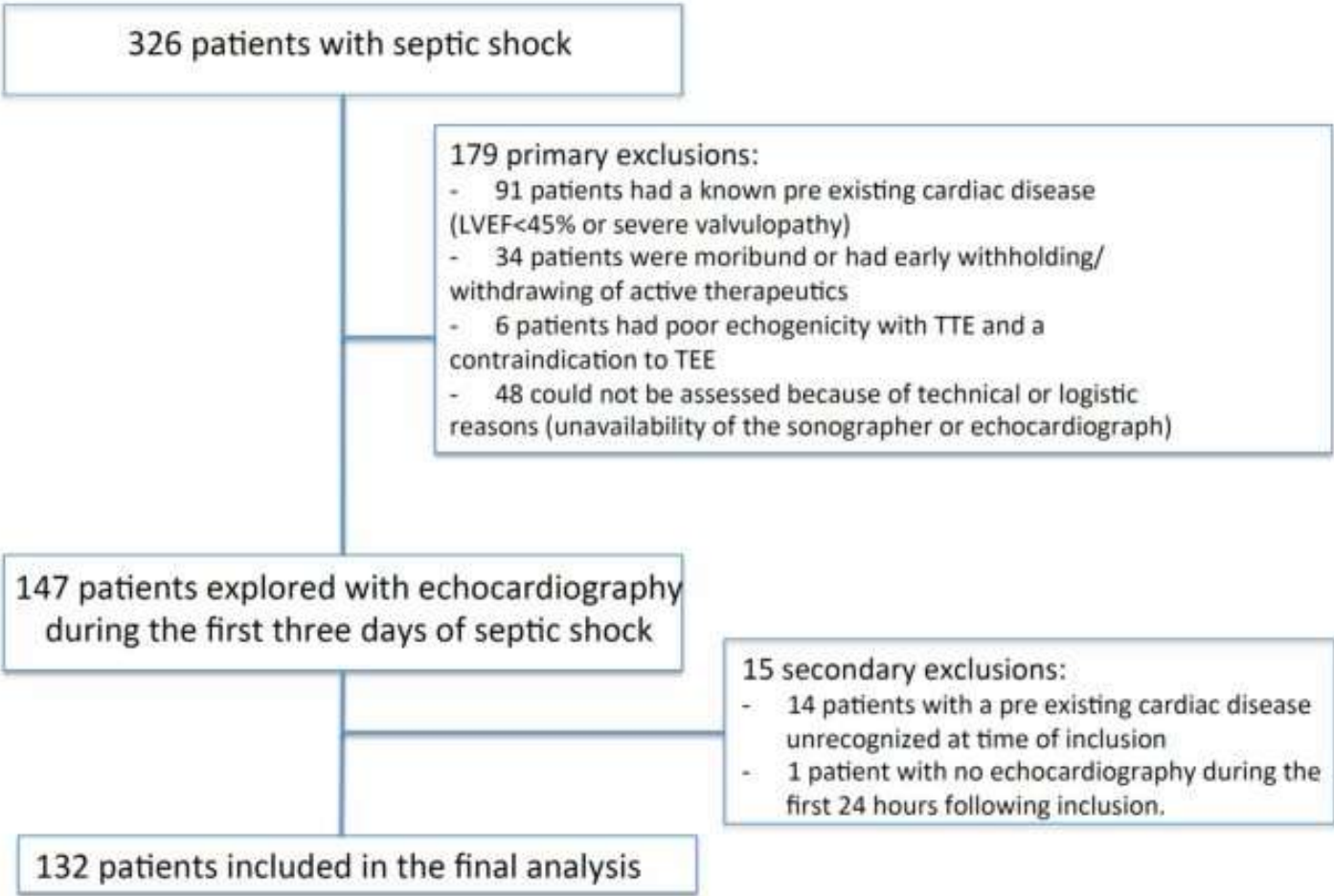
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Electronic supplement

PATIENTS AND METHODS

Echocardiography

To evaluate cardiac function, we used repeated transthoracic (TTE) or multiplane transesophageal echocardiographies (TEE, when TTE didn't allow accurate measurements because of poor acoustic windows) during the first three days of septic shock. These echocardiographies were performed by trained operators (competence in advanced critical care echocardiography) [1] using an iE33 system (Philips Ultrasound, Bothell, WA) with a standard procedure [2]. Briefly, the following echocardiographic views were examined: four-chamber and two-chamber long-axis views to assess left ventricle (LV) ejection fraction (computed from LV volumes using the bi-plane Simpson method [3] when image quality was good, or visually estimated when poor image quality did not allow sufficient identification of the endocardium) [4], tissue Doppler peak systolic wave at the lateral mitral valve annulus [5], right ventricle size (a dilated RV was defined by an end-diastolic RV/LV area ratio >0.6) [6], long-axis M-mode view of the superior (TEE) or inferior (TTE) vena cava to assess their respiratory variability [7] (with the following formulas: (maximal diameter on inspiration - minimal diameter on expiration) / minimal diameter for IVC [8]; (maximal diameter on expiration - minimal diameter on inspiration) / maximal diameter for SVC [9]), LV filling pressures [using pulsed-wave Doppler early (E) and late (A) diastolic wave velocities at the mitral valve, and tissue Doppler early (e') diastolic wave velocity at the lateral mitral valve annulus] [10]. Pulsed-wave Doppler flows were obtained at the aortic valve to assess aortic velocity-time integral for cardiac output computation. Echocardiographic images were digitally stored, and a computer-assisted evaluation was performed off-line by two trained operators (FB, AS). Echocardiographies were performed on the first, second and third day

after onset of septic shock. All measures were averaged over a minimum of three cardiac cycles (five to ten in case of non-sinus rhythm).

Speckle tracking imaging

Apical long-axis (four- and two-chamber) clips obtained with a frame rate ≥ 50 Hz underwent off-line speckle tracking analyses using the semi-automated Philips' Qlab 8.1 CMQ package (Philips Ultrasound, Bothell, WA) by two trained operators (FB, AS). The average of three consecutive heart cycles was used to calculate global longitudinal peak systolic strain and strain-rate of the LV.

Assessment of contractility and loading conditions

Preload was assessed using estimates of LV filling pressures (E/A and E/e' ratios) [10] and respiratory variations of vena cava (as surrogates of fluid responsiveness) [7]. Afterload was assessed using the following indices: i) diastolic arterial pressure (which is often used as a surrogate of LV afterload in clinical practice) [11]; ii) systemic vascular resistance (the most commonly used measure of vascular tone) [12] = $\frac{80 * \text{mean arterial pressure (mm Hg)}}{\text{cardiac output (L.min}^{-1}\text{)}}$;

iii) end-systolic arterial elastance (to reflect the pulsatile component of peripheral load) [13-15] = $\frac{\text{systolic arterial pressure (mm Hg)}}{\text{stroke volume (mL)}}$;

iv) LV end-systolic wall stress (to reflect the combined effects of peripheral loading conditions and factors internal to the heart according to Laplace's principle) [12] = $\text{systolic arterial pressure (mm Hg)} * \text{LV end - systolic volume (mL)}$.

LV systolic function was assessed using indices obtained by two-dimensional echocardiography (LVEF), tissue Doppler imaging (tissue Doppler peak systolic wave at the lateral mitral valve annulus), speckle tracking imaging (global longitudinal peak systolic

strain and strain-rate of the LV), and two additional indices to reflect net cardiovascular performance and heart-arterial interaction, respectively, as:

i) LV end-systolic maximal elastance = $\frac{\text{systemic arterial pressure (mm Hg)}}{\text{LV end-systolic volume (mL)}}$ [16, 17], and ii)

ventricular-arterial coupling, which is the ratio of LV end-systolic maximal elastance and end-systolic arterial elastance, namely = $\frac{\text{stroke volume (mL)}}{\text{LV end-systolic volume (mL)}}$ [13]. LV end-systolic volume

was obtained from the Simpson method [3] and stroke volume was derived from left ventricle outflow track diameter and aortic velocity-time integral.

Statistical Analysis

Number of patients:

We could not anticipate expected values of afterload indices, but hypothesized that at least 125 patients with septic shock would be required to achieve a minimal number of 25 individuals in each of the three subgroups of contractility (hyperkinesia, normokinesia and hypokinesia) considering a frequency of 20% in the smallest category [18].

Hierarchical clustering of contractility and loading conditions indices:

Contractility and loading conditions indices recorded during the first 24 hours of septic shock. The parameters were the following: respiratory variation of inferior vena cava in % (IVC); respiratory variation of superior vena cava in % (SVC); ratio of early to late diastolic wave velocities at the mitral valve (EA); ratio of early pulsed-wave Doppler to early tissue Doppler diastolic wave velocity at the lateral mitral valve annulus (Ee); LV ejection fraction in % (EF); absolute values of global LV longitudinal peak systolic strain in % (AS); global LV longitudinal peak systolic strain rate in s⁻¹ (SR); tissue Doppler peak systolic wave at mitral lateral annulus in cm.s⁻¹ (s); ventricular-arterial coupling (VAC); LV end-systolic maximal

elastance in mmHg.mL^{-1} (ME); end-systolic arterial elastance in mmHg.mL^{-1} (AE); systemic vascular resistance in $\text{mmHg.L}^{-1}.\text{min}$ (SVR); LV end-systolic wall stress in mmHg.mL (WS); diastolic arterial pressure in mmHg (DAP).

The parameters were reordered using computerized hierarchical clustering with the `hclust` and `corrplot` packages of R statistical environment. Hierarchical clustering is a statistical method for finding comparatively homogeneous clusters of cases based on measured characteristics. The analysis starts with each case as a separate cluster (i.e. there are as many clusters as cases), and then combines the clusters sequentially, reducing the number of clusters at each step. The clustering method uses the dissimilarities between objects. The algorithm uses a set of dissimilarities or distances between cases when constructing the clusters and proceeds iteratively to join the most similar cases. Distances between clusters were recomputed by the Lance-Williams dissimilarity update formula according to the complete linkage method. In general, there are many choices of cluster analysis methodology. The `hclust` function in R uses the complete linkage method for hierarchical clustering by default. This particular clustering method defines the cluster distance between two clusters to be the maximum distance between their individual components. At every stage of the clustering process, the two nearest clusters are merged into a new cluster. The process is repeated until the whole data set is agglomerated into one single cluster. Complete linkage has a tendency to produce compact bunches. We chose this method to minimize the spread within each cluster [19].

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Nous avons montré dans ce travail que les paramètres de contractilité du VG sont inversement corrélés aux paramètres de postcharge du VG. Ceci peut expliquer en partie la dysfonction myocardique secondaire visible uniquement après restauration partielle de la postcharge du VG. L'influence des conditions de charge sur la fraction d'éjection est connue depuis longtemps mais l'approche en cluster hiérarchique a permis une appréciation globale de l'interaction des différents paramètres échocardiographiques. Le mauvais pronostic associé à l'hyperkinésie du VG et donc à la postcharge basse avait déjà été retrouvé dans des précédentes études (Vieillard Baron et al. 2001). Dans notre travail, l'onde systolique s' à l'anneau mitral latéral n'était pas corrélée aux conditions de charge. Ce résultat était concordant avec une précédente étude où le paramètre qui variait le moins lors de la modification des conditions de charge sous ECMO était déjà l'onde systolique s' à l'anneau latéral (Aissaoui et al. 2012). Cependant, d'autres études ont montré une augmentation de cette onde s' après diminution de la postcharge, par exemple après traitement chirurgical de sténose aortique (Nieh et al. 2015).

Notre travail suggère aussi l'intérêt de la déformation acoustique pour la détection précoce et plus exhaustive de la DMS. La faisabilité dans notre étude de cette technique était faible mais elle était faite en post traitement à l'époque. La possibilité de le faire maintenant au lit du patient permet d'améliorer cette faisabilité à plus de 90% (Bagate et al. 2021). D'autres études ont permis de confirmer que la signature acoustique permet de détecter précocement la DMS (Ng et al. 2016; Dalla et al. 2015). Une méta-analyse incluant huit études de patients en choc septique (F. Sanfilippo et al. 2018) suivie d'autres études de patients en choc septique (Hai et al. 2020) ou en sepsis (Innocenti et al. 2021) ont montré qu'un strain VG altéré était associé à un mauvais pronostic.

Article 3 :


Analyse par technique multiplex des médiateurs du sepsis lors du choc septique de l'adulte : une étude préliminaire sur la dépression myocardique et les dysfonctions d'organe.

RESEARCH

Open Access



A multiplex analysis of sepsis mediators during human septic shock: a preliminary study on myocardial depression and organ failures

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Abstract

Background: The mechanisms of organ failure during sepsis are not fully understood. The hypothesis of circulating factors has been suggested to explain septic myocardial dysfunction. We explored the biological coherence of a large panel of sepsis mediators and their clinical relevance in septic myocardial dysfunction and organ failures during human septic shock.

Methods: Plasma concentrations of 24 mediators were assessed on the first day of septic shock using a multi-analyte cytokine kit. Septic myocardial dysfunction and organ failures were assessed using left ventricle ejection fraction (LVEF) and the Sequential Organ Failure Assessment score, respectively.

Results: Seventy-four patients with septic shock (and without immunosuppression or chronic heart failure) were prospectively included. Twenty-four patients (32%) had septic myocardial dysfunction (as defined by LVEF < 45%) and 30 (41%) died in ICU. Hierarchical clustering identified three main clusters of sepsis mediators, which were clinically meaningful. One cluster involved inflammatory cytokines of innate immunity, most of which were associated with septic myocardial dysfunction, organ failures and death; inflammatory cytokines associated with septic myocardial dysfunction had an additive effect. Another cluster involving adaptive immunity and repair (with IL-17/IFN pathway and VEGF) correlated tightly with a surrogate of early sepsis resolution (lactate clearance) and ICU survival.

Conclusions: In this preliminary study, we identified a cluster of cytokines involved in innate inflammatory response associated with septic myocardial dysfunction and organ failures, whereas the IL-17/IFN pathway was associated with a faster sepsis resolution and a better survival.

Keywords: Septic shock, Myocardial depression, Biomarkers, Mortality

Introduction

Sepsis is a complication caused by the body's overwhelming and life-threatening response to infection. This dysregulated host response to infection is mediated by several endogenous factors (involving inflammatory response and non-immunologic pathways) and may lead to tissue damage, organ failure and death. During

sepsis, systemic activation of the innate immune system by microbes, microbial components and products of damaged tissue results in a severe and persistent inflammatory response characterized by an excessive release of inflammatory cytokines, known as the "cytokine storm."

Circulatory failure is one of the hallmark alterations in sepsis and involves a variable combination of hypovolemia, vasoplegia and myocardial dysfunction [1]. Septic myocardial dysfunction was first described by Parker et al. [2]. Its mechanisms are not fully understood. Parrillo et al. [3] showed that sera obtained from patients with septic shock depressed rat myocardial cell contractility

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in vitro, and proposed the concept of a circulating myocardial depressant factor. Subsequent in vitro and experimental studies have proposed several cytokines as myocardial depressant factor candidates, including tumor necrosis factor alpha (TNF- α), interleukin-1 beta (IL-1 β) and interleukin-6 (IL-6) [4–8]. These studies are limited by the variability of models and species used. Reports examining the association of circulating cytokine concentrations with septic myocardial dysfunction in the clinical setting are scarce [9]. The involvement of a large number of known [6–8] and emerging [e.g., soluble suppression of tumorigenicity-2 (sST2)] [10, 11] candidate sepsis mediators derived from experimental studies should be tested in human septic shock.

Besides septic myocardial dysfunction, the inflammatory response may be implicated in the pathophysiology of other organ failures and repair during septic shock, as well as in bacterial clearance. Sepsis mediators show a high degree of interaction. Their biological coherence (i.e., the consistency of different mediators involved in the same biological pathway), potential synergy and clinical significance have not been comprehensively assessed during human septic shock.

The aims of the present study were twofold: (1) first, to assess the biological coherence of a large panel of endogenous factors proposed to evaluate host response and damage during human septic shock and (2) second, to explore the role of these mediators over septic myocardial dysfunction, organ failures and outcome.

Methods

Patients

Patients who met septic shock criteria (as defined according to the ACCP/SCCM Consensus Conference [12]) were prospectively included at the medical ICU of Henri Mondor University Hospital (Creteil, France). Non-inclusion criteria were chronic heart failure [defined as a baseline left ventricle ejection fraction (LVEF) below 45%], severe valvulopathy or immunodepression (including human immunodeficiency virus infection, hematology malignancy, solid organ or bone marrow transplant, immunosuppressive therapy or chemotherapy). This study was approved by our institutional review board (CPP Ile de France IX), as a component of standard care, and informed consent was waived. Written and oral information about the study was given to the patients or families. Patient's severity was evaluated by the McCabe and Jackson score for underlying diseases [13], the SAPS II score for acute illness at ICU admission [14] and the SOFA score for organ dysfunction at septic shock onset [15]. Norepinephrine was the first-choice vasopressor therapy (used to target a mean arterial pressure of 65 mmHg or more); dobutamine was added in the

presence of decreased LVEF (<45%) with ongoing signs of hypoperfusion despite adequate mean arterial pressure; epinephrine could be considered if the latter condition was not met. Surrogate of sepsis resolution was assessed with lactate clearance, calculated as the relative difference between lactate at septic shock onset and after 24 h of resuscitation [16]. Follow-up for the study was until hospital discharge.

Echocardiography

To evaluate cardiac function, we repeated transthoracic or multi-plane transesophageal echocardiographies (when transthoracic route did not allow for accurate measurements because of poor acoustic windows) on the first and second days of septic shock. These echocardiographies were performed by trained operators (competence in advanced critical care echocardiography) using an iE33 system (Philips Ultrasound, Bothell, WA) with a standard procedure [17]. The four-chamber and two-chamber long-axis views were used to assess LVEF (computed from LV volumes using the biplane Simpson method when image quality was good or visually estimated when poor image quality did not allow sufficient identification of the endocardium). All measures were averaged over a minimum of three cardiac cycles (five to ten in case of non-sinus rhythm). On each assessment, LVEF was defined as depressed (<45% or when an inotrope infusion was needed to achieve a value \geq 45%) or preserved (\geq 45% with no inotrope infusion). Septic myocardial dysfunction was defined as the occurrence of a depressed LVEF on day 1 or on day 2.

Sample preparation and cytokine measurement

On the first day of septic shock, we assessed plasma concentration of 24 putative sepsis mediators including inflammatory markers (IL-1 α , IL-1 β , IL1-RA, IL-6, IL-10, IL-12, IL-15, IL-17, IL-33, IFN- γ , TNF- α , CD40L, HSP70, sFAS, sFAS ligand, sST2, granzyme, TRAIL, PAI1 and VEGF), chemokines (IL-8, MCP1) and adhesion molecules (sVCAM, sICAM). All these mediators involved in inflammation, coagulation, endothelial activation, cell death and tissue repair were simultaneously measured by a single operator (MS) blinded to the clinical data. sST2 was measured with human magnetic Luminex screening assay (R&D, Bio-Techne, Lille, France), and the remaining sepsis mediators were measured with a multi-analyte Milliplex human cytokine kit (Millipore Corporation, Billerica, MA, USA). Sepsis mediators were analyzed using fluorescence intensities rather than concentrations, since conversion to concentration resulted in a loss of power [18].

Statistical analysis

The data were analyzed using the IBM SPSS Statistics for Windows (version 19.0, IBM Corp Armonk, NY) and R 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous data were expressed as medians [25th–75th centiles] unless otherwise specified and were compared using the non-parametric Kruskal–Wallis test followed by pairwise Mann–Whitney test. Correlations were tested using the nonparametric Spearman’s method. Categorical variables, expressed as percentages, were evaluated using the Chi-square test or Fisher’s exact test. The two aims of our study were achieved as follows. First, we tested the biological coherence of various sepsis mediators using hierarchical clustering; this method builds homogeneous clusters based on dissimilarities or distances between cases and proceeds iteratively to join the most similar cases. Second, we assessed the role of sepsis mediators on cardiac contractility, organ dysfunction and outcome by using bivariate correlations that were further summarized using focused principal component analysis (FPCA, “psy” package within the R environment) [19]. FPCA is a graphical representation similar to principal component analysis, but adapted to data with dependent/independent variables. We also explored potential interactions among sepsis mediators involved in septic myocardial dysfunction by assessing synergy factors as proposed by Cortina-Borja et al. [20]. Synergy factor is an easy-to-use and clear-to-interpret statistic to measure both the size and significance of binary interactions in complex diseases with all types of susceptibility factors, both risk and protective [21]. Synergy factor is calculated as the ratio of the observed odds ratio for both factors combined to the predicted odds ratio assuming independent effects of each factor. If synergy factor >1 (<1) with statistical significance, then there is a positive (negative) interaction between two risk factors. To calculate synergy factors, we partitioned the population for each tested mediator into two sets with higher versus lower concentrations based on the median value of fluorescence intensities [20]. All multiple comparisons (correlations and synergy factors) were corrected with Benjamini–Hochberg method to control the false discovery rate at the 0.05 level [22]. Significant univariate risk factors were used to adjust the association of sepsis mediators with ICU mortality using backward stepwise logistic regression analysis; to simplify their interpretation, sepsis mediator results were given for 1 standard deviation of the log-transformed fluorescence intensity of the cohort for this analysis [23]. Two-tailed p values <0.05 were considered significant.

Results

Patient characteristics

Among 326 patients screened for septic shock during the study period, 252 were excluded because of one of the following reasons: chronic heart failure ($n=105$), immunosuppression ($n=59$), moribund state ($n=34$), poor transthoracic echogenicity with contraindication to transesophageal route ($n=6$), or sonographer or echocardiograph unavailability ($n=48$). Thus, the present study comprises 74 patients (47 men and 27 women). The main source of infection was pulmonary (49%).

Biological coherence of sepsis mediators

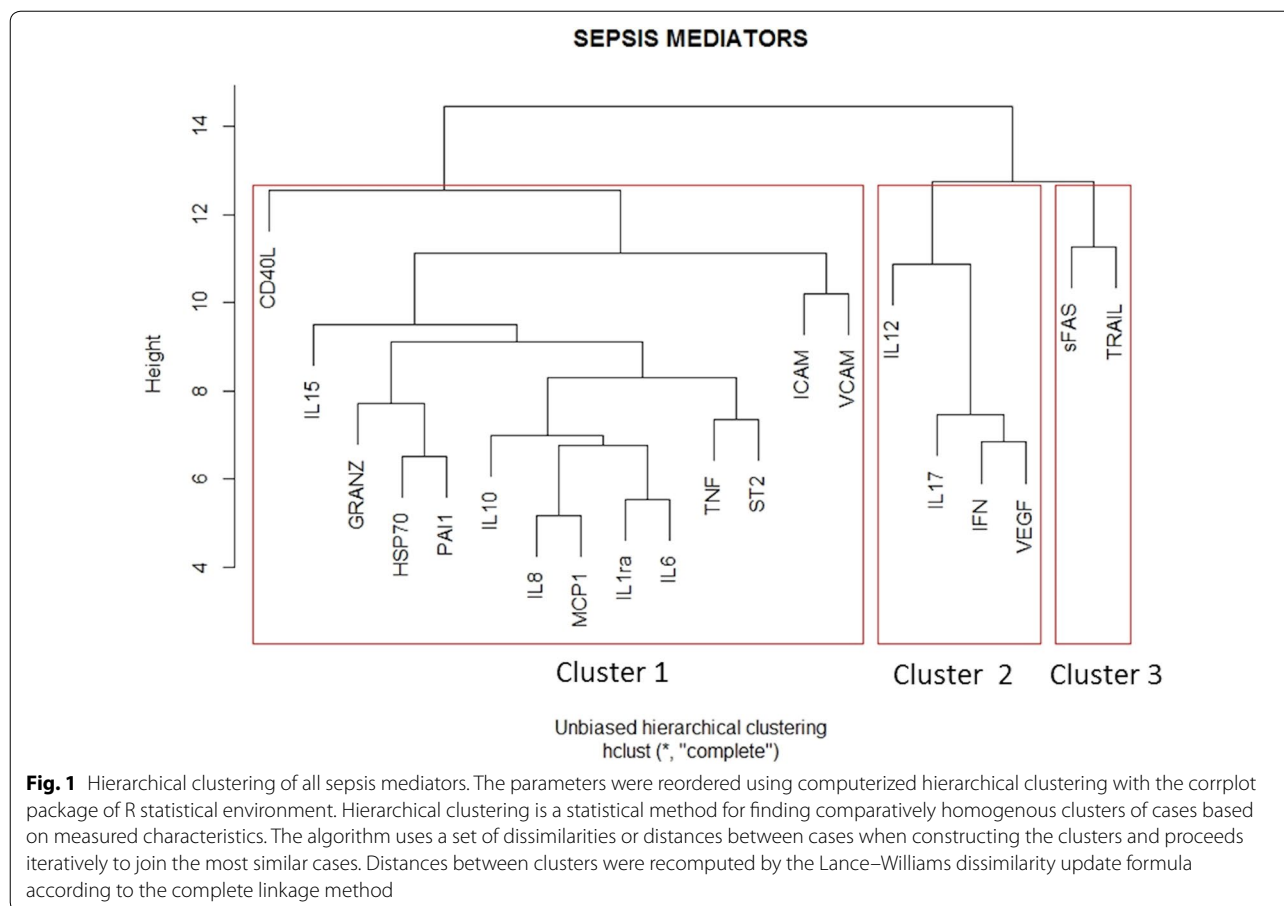
IL-1 α , IL-1 β , IL-33 and sFAS ligand were excluded from analyses due to unreliable concentration ranges. An unsupervised computer-generated hierarchical clustering of the remaining 20 sepsis mediators was performed without consideration of clinical data. This analysis identified three main clusters suggesting coherent biological pathways (Fig. 1): The first cluster (CD40L, IL-8, MCP1, IL1-RA, IL-6, IL-15, TNF- α , IL-10, ICAM, sST2, VCAM, granzyme, HSP70 and PAI1) mainly involved innate immunity; the second cluster (IL-12, IL-17, IFN, VEGF) mainly involved adaptive immunity and repair; and the third cluster (sFAS, TRAIL) was related to cell death.

Septic myocardial dysfunction

A total of 112 echocardiographies were performed during the first 2 days of septic shock in the 74 patients. LVEF was assessed using the Simpson method for 78 echocardiographies (70%) and visually estimated for the remainders. Septic myocardial dysfunction was diagnosed in a total of 24 patients (32%). Clinical characteristics and comorbidities were similar between patients with or without hypokinesia except for a higher SAPS II score at ICU admission in the former group; this group also exhibited more organ failures than the latter, but with similar mortality (see Additional file 1: Tables S1 and S2).

Association of sepsis mediators with septic myocardial dysfunction

All inflammatory markers significantly associated with septic myocardial dysfunction (CD40L, IL-8, MCP1, IL1-RA, IL-6, IL-15, TNF- α , sST2, granzyme and HSP70) belonged to the first cluster (Fig. 2a, b). The prevalence of septic myocardial dysfunction increased linearly with the number of augmented sepsis mediators (above the median value of fluorescence intensity), suggesting an additive effect on the risk of myocardial



dysfunction (Fig. 3). The number of augmented sepsis mediators (above the median value of fluorescence intensity) from the first cluster remained associated with septic myocardial depression even after adjusting on patient's severity (using SAPS II score at ICU admission): adjusted odds ratio of 1.25, 95% CI 1.08–1.45, $p = 0.004$. Ninety-one pairs of mediators of the first cluster were assessed for synergy factor analysis: Almost all of them (89 pairs, 98%) showed no significant interaction, also suggesting an additive effect (see Additional file 1: Table S3).

Association of sepsis mediators with organ failures and outcome

Many mediators from the first cluster were associated with patient's severity (as assessed by SAPS II score), organ failures (as assessed by SOFA score) and death (Fig. 4a, b). On the contrary, most mediators from the second cluster (IL-17, IFN- γ and VEGF) were associated with a surrogate of early sepsis resolution (lactate clearance at 24 h) and ICU survival (Fig. 4a, b). The association of IL-17 (chosen as a surrogate of the second cluster) with ICU survival persisted (adjusted odds ratio of 0.33,

95% CI 0.17–0.66, $p < 0.001$) after adjustment on patient's severity (using SAPS II score at ICU admission), organ failures (using SOFA score at septic shock onset) and IL-15 concentration (chosen as a surrogate of the first cluster to reflect innate immunity) (see Additional file 1: Table S4).

Discussion

Unlike most studies reported in the literature, we have comprehensively explored plasma mediators in human septic shock with a multiplex assay and specific statistical tools. We identified three clusters suggestive of meaningful biological pathways. One cluster with innate inflammatory cytokines was associated with myocardial and other organ dysfunction, whereas another cluster involving the adaptive immunity was associated with surrogates of early sepsis resolution and in ICU survival.

Myocardial depressant factor

The first cluster included innate inflammatory cytokines such as IL-6, IL1-RA, TNF- α , MCP1, IL-8 and sST2. The majority of these cytokines have been previously individually associated either with septic

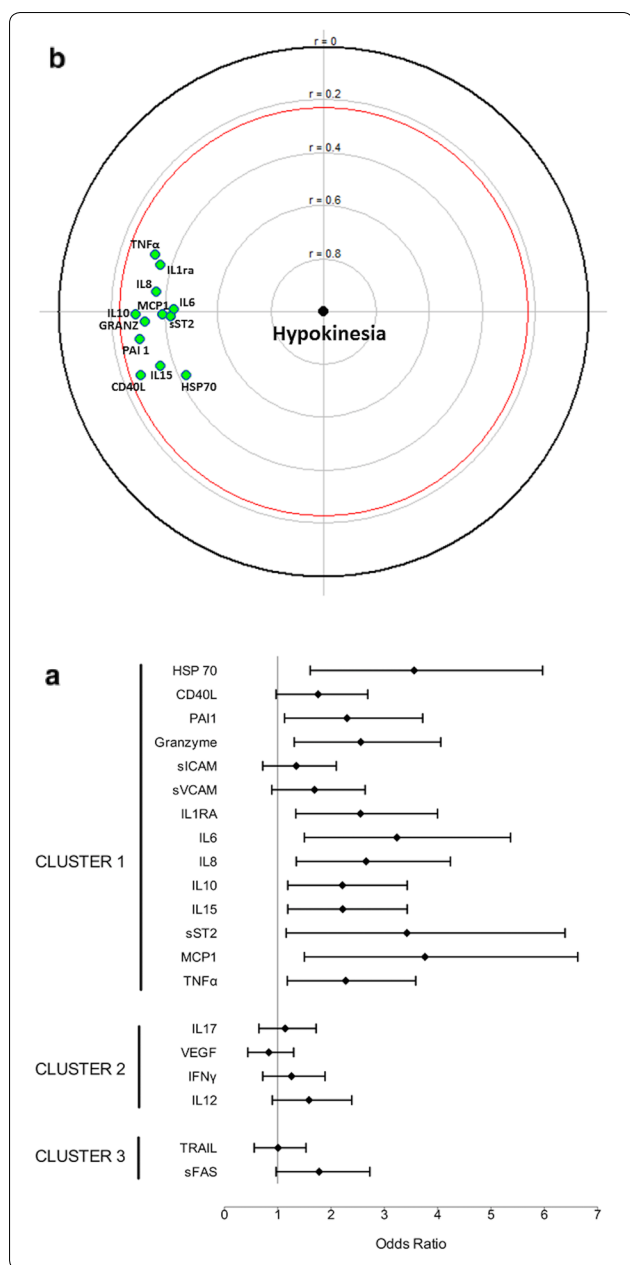


Fig. 2 Forest plot for odds ratios (**a**) and focused principal component analysis (FPCA, **b**) for the association between sepsis mediators and septic myocardial dysfunction. FPCA is a simple graphical display of correlation structures focusing on a particular dependent variable. The display reflects primarily the correlations between the dependent variable and all other variables (covariates) and secondarily the correlations among the covariates. The dependent variable (septic myocardial dysfunction, SMD) is at the center of the diagram, and the distance of this point to a covariate faithfully represents their pairwise Spearman correlation coefficient (using ranked values of continuous variables). Green covariates are positively correlated with the dependent variable. For parsimony, only covariates significantly correlated with the dependent variable (with a p value < 0.05 and inside the red circle) are displayed. The diagram also shows relationships between covariates as follows: Correlated covariates are close (for positive correlations, allowing identification of clusters) or diametrically opposite vis-à-vis the origin (for negative correlations), whereas independent covariates make a right angle with the origin. See text for sepsis mediators' abbreviations

myocardial dysfunction or with mortality during septic shock. Parrillo et al. [3] were the first in 1985 to suggest the presence of circulating myocardial depressant substance(s) in the sera of septic shock patients. Indeed, sera obtained in the acute phase of septic shock patients with septic myocardial dysfunction decreased in vitro myocardial cell shortening. Moreover, sera from the same patients before shock or after recovery and sera from patients with other cardiac disease or from critically ill non-septic patients induced no significant changes. Kumar showed that TNF- α and IL-1 β induced cardiac myocyte depression in vitro [7].

Immunoabsorption of both TNF- α and IL-1 β abrogated in vitro myocardial depressant activity of sera from humans with septic shock. Trials conducted in the 1990s with a monoclonal TNF- α antibody during septic shock revealed a transient improvement in cardiovascular parameters [24], but failed to alter the mortality rate of patients [25]. Using gene microarray analysis, Pathan et al. [26] suggested that IL-6 was a mediator of myocardial depression in children with meningococcal septic shock. Other candidates for myocardial depressant factor have also been recently suggested. Our study is the first to show a correlation between septic myocardial dysfunction and sST2 (an interleukin-1 receptor family member which is markedly induced by mechanical strain in cardiac myocytes) [27]. Most mediators of the first cluster had an additive effect on septic myocardial dysfunction. Our study suggests that a cluster of mediators involved in innate immunity rather than an individual factor might influence the onset of septic myocardial dysfunction. At the cellular level, this dysfunction may be mediated through the alteration of other downstream cellular mediators (e.g., sphingomyelinase, nitric oxide or phospholipase A2-dependent signaling).

Our results contradict some previous reports. Bouhemad et al. found no correlation between three cytokines (TNF- α , IL-8 and IL-10) and myocardial systolic dysfunction [28]. Landesberg et al. also failed to show a significant correlation between inflammatory cytokines (IL-1 β , IL-6, IL-8, IL-10, IL-18, TNF- α and MCP1) and systolic dysfunction [9]. The above-mentioned studies included a limited number of patients with systolic myocardial dysfunction (11 and 13 patients, respectively). In addition, plasma cytokines were collected within 2 days after the diagnosis of sepsis. This delay may have underestimated

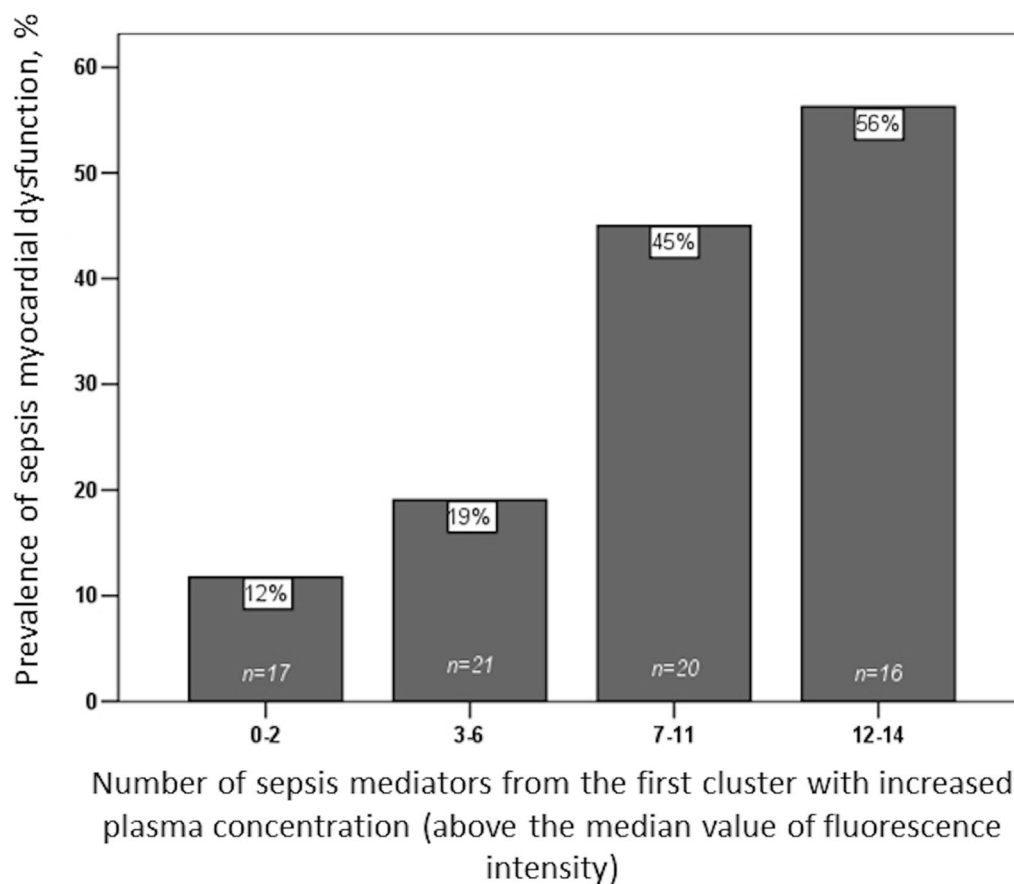


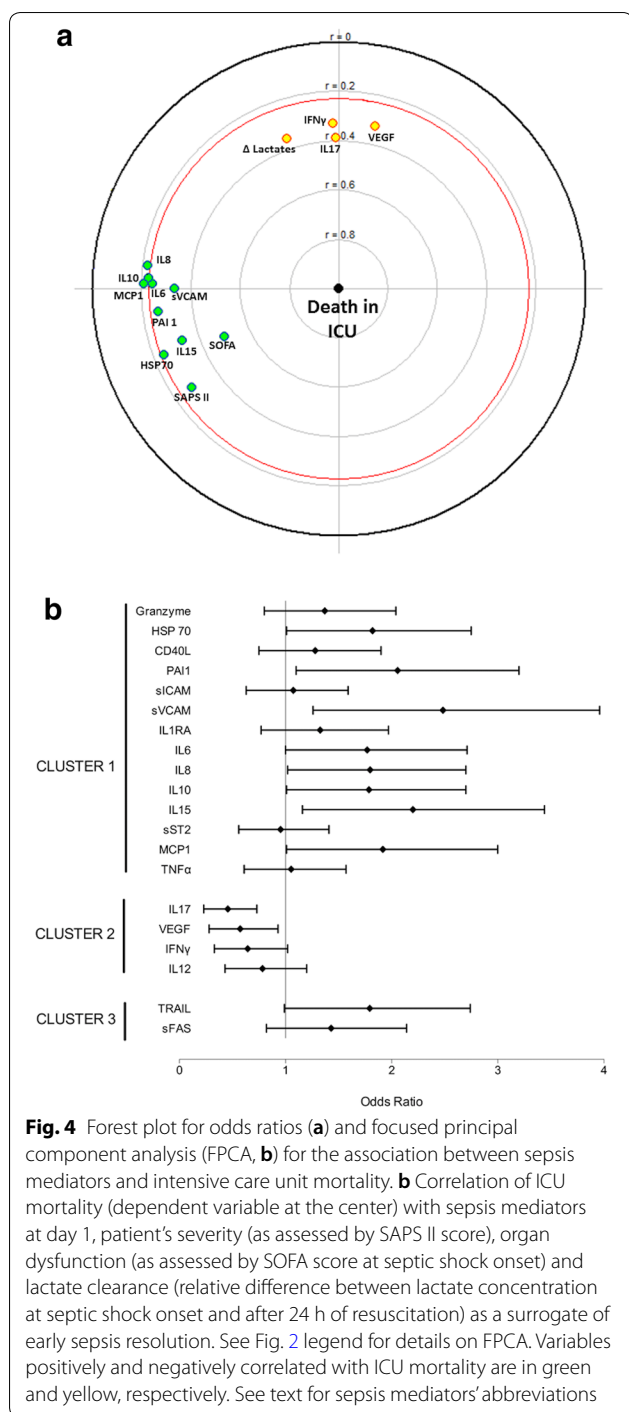
Fig. 3 Prevalence of septic myocardial dysfunction according to the number of increased sepsis mediators (above the median value) from the first cluster

the initial peak concentrations [29]. Cardiomyocyte injury or death, maybe theoretically induced by toxins, complements or DAMP during septic shock. However, factors involved in apoptosis (sFAS, TRAIL) and belonging to cluster 3 were not associated with septic myocardial dysfunction in our study. These results are in line with autopsy studies, which did not show evidence of irreversible acute injury or cell death in deceased patients with septic myocardial dysfunction [30].

Organ failures and outcome

Our finding that cytokines from the first cluster were associated with morbidity and mortality is in accordance with previously published studies [9, 31–34]. Interestingly, the second cluster involving IL-17/IFN pathway and VEGF correlated tightly with a surrogate of early sepsis resolution (lactate clearance) and was significantly associated with ICU survival. CD4⁺ T helper (Th) cells play a central role in the adaptive immune response by stimulating B cells and cytotoxic T cells and by releasing different types of cytokines in tissues to mediate protection against a wide

range of pathogenic microorganisms. IFN- γ -producing Th1 cells have typically been associated with immune response to viruses and intracellular bacteria, and IL-17-producing Th17 play a role in immunity against fungi and extracellular bacteria. Impaired Th17 responses diminish bacterial clearance and increase epithelial vulnerability [35]. Our results are in line with previous data, suggesting that Th17 differentiation impacts mortality during severe sepsis [36]. Increased levels of IL-17 and IFN may reflect an effective inflammatory response to infection with enhanced bacterial clearance [37, 38]. Moreover, IL-17 can upregulate VEGF [39] to restore mucosal endothelial/epithelial function and stimulate healing [40]. Our study suggests that it is rather the initial balance between mediators of “innate immunity” (the first cluster) and those of “adaptive immunity and repair” (the second cluster) than a two-stage process that determines organ failure and outcome during septic shock. Early cytokine profiling may be a molecular tool helpful to identify different patient populations and a useful instrument for future clinical trials targeting the immune system in patients with septic shock.



Strengths and limitations

The strengths of our study include its prospective design, the severity of the patients selected, the multiplex assay of sepsis mediators and the comprehensive analysis with control for false discovery rate. Limitations of our study include its monocentric design, the relatively small number of patients and the lack of a validation cohort. Our

findings need an independent validation in a similarly well-phenotyped cohort. Although patients with known chronic heart failure were excluded from the study, we could not completely exclude occult chronic heart failure in some cases. Among the 24 patients with septic myocardial dysfunction in our study, 19 had a preserved LVEF on a baseline echocardiography performed before ICU admission or a follow-up echocardiography performed 1 week after septic shock. Only five patients had no baseline echocardiography and no follow-up echocardiography (because they died within the first 2 day of septic shock); all these five patients had an elevated troponin concentration, suggesting sepsis myocardial depression was likely [41] and occult chronic heart failure was unlikely. Despite these limitations, our study shows that measuring some sepsis mediators may be helpful to depict robust patient profiles.

Conclusion

In this preliminary study, a comprehensive analysis of sepsis mediators revealed meaningful biological pathways during human septic shock. One cluster involved in innate immunity was associated with septic myocardial dysfunction and organ failures. In contrast, another cluster involving IL-17/IFN pathway and VEGF correlated with early sepsis resolution and was associated with ICU survival. Our findings may enrich the design of future clinical trials targeting the cardiovascular and immune systems in patients with septic shock.

Additional file

Additional file 1. Table S1. Characteristics of patients with septic shock according to septic myocardial dysfunction (n=74). **Table S2.** Characteristics of patients with septic shock according to outcome (n=74). **Table S3.** Matrix of synergy factors exploring interactions between sepsis mediators of the first cluster as susceptibility factors of septic myocardial dysfunction. **Table S4.** Multivariable analysis of factors associated with death in intensive care unit during septic shock by logistic regression.

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None.

Authors’ contributions

Dr. Razazi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Razazi and Dr. Mekontso Dessap contributed to initial study design, analysis, interpretation of data, drafting of the submitted article, critical revisions for intellectual content and providing final approval of the version to be published. Dr. De Prost, Dr. Carreaux, Dr. Boissier, Mathieu Surenaud, Dr. Bedet, Dr. Seemann, Dr. Brun-Buisson and Dr. Hue contributed to study design and analysis, interpretation of data, drafting of the submitted article, critical revisions for intellectual content and providing final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available as consent for publication of raw data was not obtained from study participants, but are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by an institutional review board (CPP Ile de France IX), as a component of standard care, and informed consent was waived. Written and oral information about the study was given to the patients or families.

Consent for publication

Not applicable.

Competing interests

All authors report no conflict of interest relevant to this study.

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Table S1. Characteristics of patients with septic shock according to septic myocardial dysfunction (n=74).

	No hypokinesia (n=50)	Hypokinesia (n=24)	P value
Clinical characteristics and comorbidities			
Age (years)	65 [48-78]	68 [57-80]	0.33
Male gender, n (%)	30 (60%)	17 (71%)	0.37
Chronic Obstructive Pulmonary Disease	2 (%)	0	>0.99
Chronic kidney disease requiring long-term dialysis	2 (4%)	1 (4%)	>0.99
Liver cirrhosis	1 (2%)	0	>0.99
Mc Cabe and Jackson class			0.45
0	33 (66%)	19 (79%)	
1	16 (32%)	5 (21%)	
2	1 (2%)	0 (0%)	
SAPS II at ICU admission	49 [35-63]	58 [48-86]	0.02
Source of infection — no. (%)			0.23
Lung	28 (56%)	8 (33%)	
Abdomen	7 (14%)	6 (25%)	
Urinary tract	10 (20%)	5 (21%)	
Others	5 (10%)	5 (21%)	
Bacteraemia	25 (50%)	14 (58%)	0.50
Gram negative bacilli	32 (64%)	12 (50%)	0.25
Surgery	14 (29%)	7 (29%)	>0.99
Appropriateness of empirical antimicrobial therapy	46 (92%)	23 (96%)	>0.99
Organ failures#			
Sequential Organ Failure Assessment score	10 [8-12]	12 [9-15]	0.04
Arterial lactates (mmol/L)	2.3 [1.2-4.1]	3.4 [2.4-6.5]	0.03
PaO ₂ /FiO ₂ ratio (mmHg)	191 [104-256]	148 [99-295]	0.66
Serum creatinine (mmol/L)	142 [75-234]	246 [141-314]	0.01
Dose of norepinephrine (µg/kg/min)	0.65 [0.30-1.28]	1.12 [0.29-2.02]	0.35
Outcome			
Dobutamine during ICU	0	13 (54%)	
Epinephrine during ICU	0	5 (21%)	
Mechanical ventilation	43 (86%)	21 (88%)	>0.99
Moderate-to-severe ARDS	21 (42%)	9 (38%)	0.80
Dialysis for acute renal failure	10 (20%)	7 (29%)	0.38
LOS in ICU, all patients (days)	11 [5-28]	6 [2-12]	0.04
LOS in ICU, survivors only (days)	13 [6-24]	10 [6-24]	0.82
Death in ICU	21 (42%)	9 (38%)	0.71
Death in hospital	22 (44%)	9 (38%)	0.60

Abbreviations: SAPS= Simplified Acute Physiology Score, ARDS= Acute Respiratory Distress Syndrome; ICU= Intensive Care Unit, LOS= length of stay, #available data were averaged over the first 48 hours of septic shock.

Table S2. Characteristics of patients with septic shock according to outcome (n=74).

	ICU survival (n=44)	ICU death (n=30)	P value
Clinical characteristics and comorbidities			
Age (years)	64 [51-76]	69 [52-79]	0.25
Male gender, n (%)	27 (61%)	20 (67%)	0.81
Chronic Obstructive Pulmonary Disease	1 (2%)	1 (3%)	>0.99
Chronic kidney disease requiring long-term dialysis	2 (5%)	1 (3%)	>0.99
Mc Cabe and Jackson class			0.33
0	13 (75%)	19 (63%)	
1	11 (25%)	10 (33%)	
2	0	1 (3%)	
SAPS II at ICU admission	50 [36-61]	62 [47-87]	0.02
Community acquired infection	27 (61%)	15 (50%)	0.61
Health care associated infection	5 (11%)	5 (17%)	
Nosocomial infection	12 (27%)	10 (33%)	
Source of infection — no. (%)			0.037
Lung	17 (39%)	19 (63%)	
Others	27 (61%)	11 (37%)	
Bacteraemia	26 (59%)	13 (43%)	0.18
Gram negative bacilli	26 (59%)	18 (60%)	>0.99
Surgery	16 (37%)	5 (17%)	0.06
Appropriateness of empirical antimicrobial therapy	41 (93%)	28 (93%)	>0.99
Organ failure at day-1			
Maximal dose of norepinephrine at day1 ($\mu\text{g.kg}^{-1}.\text{min}^{-1}$)	0.67 [0.27-1.22]	0.83 [0.45-2.6]	0.14
SOFA score at day-1	9 [8-11]	13 [11-15]	<0.001
Mechanical ventilation at day-1	35 (80%)	26 (87%)	0.43
Moderate-to-severe ARDS at day-1	14 (32%)	14 (47%)	0.20
Arterial lactate at day-1 (mmol/L)	2.6 [1.5-3.9]	3.2 [1.3-7.1]	0.30

Data are median [1st quartile-3rd quartile] or number (percentage); Abbreviations: SAPS= Simplified Acute Physiology Score; ARDS= Acute Respiratory Distress Syndrome; ICU= intensive care unit, SOFA= Sequential Organ Failure Assessment;

Table S3. Matrix of synergy factors exploring interactions between sepsis mediators of the first cluster as susceptibility factors of septic myocardial dysfunction.

Synergy factors	HSP70	sICAM	sVCAM	IL1RA	IL6	IL8	IL10	IL15	sST2	MCPI	TNF α	PAI1	sCD40L
Granzyme	0.40	1.33	0.26	2.03	11.2	3.33	8.8	96.0*	1.6	11.9	0.31	2.0	9.5
HSP70		4.6	1.3	0.03	0.20	0.23	0.85	2.2	0.4	0.56	0.46	0.16	0.73
sICAM			2.7	0.29	0.98	0.54	0.76	3.3	0.68	0.72	1.4	1.3	0.30
sVCAM				0.13	0.14	0.23	0.34	1.2	0.05	0.37	0.27	0.27	2.6
IL1RA					0.97	0.44	1.6	2.03	1.16	2.7	0.35	0.51	0.62
IL6						0.69	-	3.6	0.83	7.2	0.37	3.6	0.19
IL8							1.7	12.9	-	-	0.34	0.22	1.01
IL10								18.4	0.89	5.97	0.42	8.81	4.85
IL15									7.71	49.5*	2.95	9.37	2.51
sST2										4.46	0.31	0.99	0.82
MCPI											0.78	1.35	3.47
TNF α												0.20	1.77
PAI1													2.51
sCD40L													

*p<0.05 after Benjamini-Hochberg correction

Table S4. Multivariable analysis of factors associated with death in intensive care unit during septic shock by logistic regression.

Predictor	Odds Ratio (95% Confidence Interval), p value	
	Univariate	Adjusted (multivariable)
SAPS II score at admission (per point)	1.04 (1.02-1.05), p<0.001	NS
SOFA score on the first day of septic shock (per point)	1.3 (1.16-1.44), p<0.001	1.7 (1.3 - 2.2), p<0.001
IL17 (per SD of the log transformed fluorescence intensity)	0.41 (0.23-0.73),p=0.003	0.33 (0.17 – 0.66), p=0.001
IL15 (per SD of the log transformed fluorescence intensity)	2.0 (1.2-3.4), p=0.012	NS

The variables included in the analysis were: SAPS II at admission, SOFA score on the first day of septic shock, IL17 and IL15;

Abbreviations: NS: not significant; SOFA= Sequential Organ Failure Assessment; SAPS= simplified acute physiology score, SD=standard deviation.

Nous avons montré dans cette étude que la DMS était associée à un ensemble de cytokines impliquées dans l'immunité innée. De précédentes études avaient déjà montré l'association de certaines cytokines avec la dysfonction myocardique (A. Kumar et al. 1996; Pathan et al. 2004; Fisher et al. 1996; J. L. Vincent et al. 1992). D'autres cytokines comme le sST2, membre de la famille des récepteurs de l'IL1, n'avaient jamais été étudiées dans cette pathologie. De plus, nous avons montré un effet additif de ces cytokines.

D'autres études n'avaient par contre pas retrouvé d'association entre les cytokines et la dysfonction myocardique (Bouhemad et al. 2008; Landesberg et al. 2015), avec cependant des effectifs des patients faibles et des prélèvements parfois plus tardifs par rapport au début du choc septique, ainsi que des dosages de cytokines bas suggérant un dosage après le pic de concentration de cytokines (Antonucci, Taccone, et Scolletta 2015).

Article 4 :

Association entre l'insuffisance surrénale relative et la cardiomyopathie septique : une étude préliminaire.

LETTER



Association between relative adrenal insufficiency and septic cardiomyopathy: a preliminary report

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Dear Editor,

Relative adrenal insufficiency (RAI) is a controversial entity, which is characterized by an insufficient response to an adrenal stimulation in the absence of organic abnormality on the hypothalamic–pituitary–adrenal axis. RAI has been mostly studied during septic shock (SS), where it seems associated with a worse prognosis [1]. Similar results were recently reported during cardiogenic shock [2]. Hemodynamic alterations during SS include vasoplegia in most patients and myocardial dysfunction in some of them [3]. RAI has been associated with altered peripheral vasopressor response during SS [4]. It may also be involved in cardiac dysfunction in settings other than sepsis [5]. To date, the adrenal profile in septic cardiomyopathy (SCM) has not been investigated.

Patients who met SS criteria (ACCP/SCCM Consensus Conference) and had an adrenal stimulation test during the first day of SS were prospectively included at the medical ICU of Henri Mondor University Hospital (Creteil, France). Non-inclusion criteria were chronic heart failure and prior corticosteroid therapy. The study was approved by the institutional ethics committee of the French Intensive Care Society as a component of standard care and patient consent was waived. SCM was defined as the appearance at echocardiography of hypokinesia (left ventricle ejection fraction <45% or when inotrope infusion was needed to achieve a value \geq 45%) during the first day after SS onset. Patients were not volume responsive and

major valvular abnormalities and coronary artery disease were excluded by echocardiography. Adrenal stimulation test (250 μ g of tetracosactrin) was performed before administering any low-dose steroid therapy for SS. Maximal cortisol response (Δ_{\max}) was defined as the difference between maximal post-stimulation concentration (T_{\max}) and baseline total cortisol (T_0). RAI was defined as $T_0 < 10$ μ g/dL or $\Delta_{\max} < 9$ μ g/dL, as recommended.

Table 1 shows the characteristics of the 52 patients included in this study (over 132 eligible patients) according to occurrence of SCM. RAI occurred in 33 patients (63%) and was significantly more frequent in patients with SCM as compared to their counterparts: 14 (88%) vs. 19 (53%), $p = 0.03$. This association persisted by logistic regression after adjustment based on SAPS II score: OR = 5.53, 95% CI 1.19–40.28, $p = 0.03$.

We herein demonstrate a higher prevalence of RAI in patients with SCM as compared to their counterparts. This result was not necessarily expected because RAI has been previously linked to vasoplegia with impaired responsiveness to vasopressor therapy [4], and a recent study found an inverse correlation between most of the contractility and afterload indices during SS [3]. Our results may suggest an involvement of RAI in cardiac dysfunction during SS. The major reported hemodynamic effect of low-dose steroid therapy is the increase in arterial pressure related to restored systemic vascular resistances, but higher doses of steroid have been shown to improve cardiac index by regulation of myocardial beta-adrenergic receptors, which are impaired during SS.

Study limitations include its monocentric and exploratory nature with a limited sample size, the potential interaction of etomidate use, the variability of plasma cortisol, inadequacies between total and free cortisol,

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Table 1 Clinical and biological characteristics of patients according to septic cardiomyopathy

Variables	Total (n = 52)	Septic cardiomyopathy		p value
		Yes (n = 16)	No (n = 36)	
Age (years)	61.1 (±16.0)	66.8 (±10.2)	58.6 (±17.6)	0.04
Immunosuppression	17 (32.7%)	5 (31.3%)	12 (33.3%)	0.88
SAPS II score	58.0 (±20.7)	70.4 (±20.2)	52.4 (±18.7)	<0.01
SOFA score at day 1	11.3 (±3.7)	13.0 (±3.6)	10.5 (±3.5)	0.03
Type of infection				0.52
Community-acquired	30 (57.7%)	9 (56.3%)	21 (58.3%)	
Healthcare-associated	6 (11.5%)	3 (18.8%)	3 (8.3%)	
Nosocomial	16 (30.8%)	4 (25%)	12 (33.3%)	
Hemodynamic profile				
LVEF (%)	54 (41–60)	38 (29–45)	58 (53–65)	<0.01
Cardiac index (L/min/m ²)	3.0 (±1.1)	2.3 (±0.9)	3.3 (±1.0)	<0.01
Etomidate use	43 (82.7%)	15 (93.8%)	28 (77.8%)	0.24
Arterial blood gases at admission				
pH	7.29 (7.19–7.37)	7.24 (7.09–7.41)	7.31 (7.22–7.37)	0.16
PaCO ₂ (mmHg)	37 (30–47)	35 (29–47)	38 (30–47)	0.55
PaO ₂ /FIO ₂ ratio (mmHg)	199 (125–325)	198 (117–343)	203 (140–319)	0.98
Lactatemia (mmol/L)	2.6 (1.4–4.0)	2.6 (1.4–4.0)	2.6 (1.4–4.0)	0.95
Corticotropin test				
T ₀ (µg/dL)	30.2 (20.5–53.2)	37.9 (21.7–65.7)	28.3 (20.5–51.3)	0.18
Δ _{max} (µg/dL)	7.7 (2.6–20.4)	6.1 (0.5–8.2)	8.9 (4.1–26.8)	0.05
RAI	33 (63.5%)	14 (87.5%)	19 (52.8%)	0.03
Other biologic data at day 1				
Creatinine (µg/L)	160 (76–301)	269 (158–338)	116 (74–222)	0.02
Protidemia (g/L)	55.5 (±10.7)	53.3 (±8.6)	56.4 (±11.5)	0.36
Albuminemia (g/L)	22.9 (±5.8)	20.1 (±4.4)	24.2 (±6.1)	0.10
Treatments				
Low-dose steroids during septic shock*	43 (82.7%)	16 (100%)	27 (75%)	0.06
Dobutamine infusion	9 (17.3%)	9 (56.3%)	0 (0%)	<0.01
Norepinephrine dose (mg/h)	3.3 (1.5–6)	3.8 (1.3–7.5)	3.1 (1.5–5.8)	0.79
Duration of vasopressor therapy (days)	4 (3–6)	4 (2–6)	4 (3–7)	0.75
Complications and outcomes				
Tracheal intubation	46 (88.5%)	16 (100%)	30 (83.3%)	0.16
Acute respiratory distress syndrome	23 (44.3%)	6 (37.5%)	17 (47.2%)	0.51
Ventilation duration (days)	10 (5–14)	10 (6–12)	8 (4–15)	0.67
Renal replacement therapy	16 (30.8%)	6 (37.5%)	10 (27.8%)	0.48
ICU length of stay (days)	11 (6–18)	13 (3–27)	11 (6–17)	0.75
Hospital length of stay (days)	24 (9–38)	26 (3–37)	23 (10–38)	0.72
ICU mortality	19 (36.5%)	8 (50%)	11 (30.6%)	0.18
Hospital mortality	22 (42.3%)	8 (44.4%)	14 (38.9%)	0.45

Values are expressed as mean (±standard deviation) or median (1st–3rd quartile) as appropriate

SAPS II Simplified Acute Physiology Score II, SOFA Sequential Organ Failure Assessment, LVEF left ventricular ejection fraction, ICU intensive care unit, T₀ baseline plasma cortisol (before short corticotropin test), Δ_{max} maximal cortisol response (see text for definition), RAI relative adrenal insufficiency (see text for definition)

* Low dose steroids were administered after the short corticotropin stimulation test on the basis of the severity of the patient's condition and the decision of the intensivist in charge. Cortisol: 1 µg/dL = 27.6 nmol/L

and the contentious nature of the adrenal stimulation test. In order to better investigate RAI and SCM, further studies of larger size (with appropriate adjustment

based on potential confounders) are needed to confirm these results and assess the effect of low-dose steroids on SCM.

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Compliance with ethical standards**Conflicts of interest**

The authors report no conflicts of interest.

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Nous avons montré dans cette étude une association entre l'insuffisance surrénale relative et la dysfonction myocardique systolique au cours du choc septique. Il y a bien évidemment beaucoup de facteurs confondants qui ont pu interagir ; les niveaux de cortisol pouvant notamment être corrélés aux niveaux d'IL6 (den Brinker et al. 2005). Ainsi, une relation de causalité ne peut être établie. Cependant, au cours de l'insuffisance surrénale aiguë (maladie d'Addisson), une dysfonction myocardique peut apparaître (Bouachour et al. 1994). De plus, les doses substitutives de corticoïdes données au cours du choc septique ont un effet cardiovasculaire et immunomodulateur sur la concentration de cytokines. Ainsi, on pourrait supposer que les doses substitutives de corticoïdes aient un effet sur la dysfonction myocardique du sepsis. Une évaluation cardiaque de cette substitution à l'aide des nouveaux outils échocardiographiques semblent intéressante.

Article 5 :

Raccourcissement des télomères au cours du choc septique: influence des médiateurs du sepsis, rôle sur les dysfonctions d'organes et sur la DMS.

RESEARCH LETTER

Open Access



Telomere shortening during human septic shock: influence of sepsis mediators, role in organ failures, and septic myocardial dysfunction

Keyvan Razazi^{1,2*} , Elisabeth Marcos⁴, Sophie Hüe⁵, Laurent Boyer^{3,4}, Serge Adnot^{3,4} and Armand Mekontso Dessap^{1,2,4}

Leucocyte telomere length (LTL) is widely considered a marker of cellular ageing. Telomere attrition has been involved in cardiovascular disorders as a result of inflammatory stress [1], but has been scarcely evaluated in acute settings. Septic shock is associated with an overwhelming inflammatory reaction that may be involved in the genesis of organ failure, including septic myocardial dysfunction [2]. The present study aimed to assess whether septic shock is associated with telomere attrition and evaluate the role of sepsis mediators and the impact on organ failures. Fifty-five patients free of chronic heart failure who met septic shock criteria (as defined according to the ACCP/SCCM Consensus Conference) were prospectively included at the medical intensive care unit of Henri-Mondor University Hospital (Créteil, France).

LTL was measured by QuantStudio™ 6 Flex Real-Time quantitative PCR System (Applied Biosystems, Foster, CA); see Table 1 legend. LTL was assessed in septic shock patients (in 55 and 24 patients on day-1 and day-2, respectively) and in 55 healthy controls matched to septic shock patients for age (± 3 years) and gender.

Septic myocardial dysfunction (SMD) was defined as a depressed left ventricle ejection fraction ($<45\%$ or when an inotrope infusion was needed to achieve a

value $\geq 45\%$) on echocardiography performed on day-1 or day-2 of septic shock [2].

We assessed plasma concentration of 24 putative sepsis mediators on day-1, including inflammatory markers (IL-1 α , IL-1 β , IL1-RA, IL-6, IL-10, IL-12, IL-15, IL-17, IL-33, IFN- γ , TNF- α , CD40L, HSP70, sFAS, sFAS ligand, sST2, granzyme, TRAIL, PAI1, and VEGF), chemokines (IL-8, MCP1), and adhesion molecules (sVCAM, sICAM). sST2 and the remaining sepsis mediators were measured with human magnetic Luminex screening assay (R&D, Bio-Techne, Lille, France), and a multi-analyte Milliplex human cytokine kit (Millipore Corporation, Billerica, MA, USA), respectively, and were analyzed using fluorescence intensities [2].

Organ failures and patient severity were assessed using the Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II (SAPS II) score, respectively. Spearman bivariate correlations were used to build a focused principal component analysis (FPCA; “psy” package in R), using LTL as the dependent variable and allowing a simple graphical display of correlation structures.

LTL was similar between controls and septic shock patients (Fig. 1a). We observed a correlation between LTL and age in the control group as expected (Spearman’s $\rho = -0.29$, $p = 0.04$) but not in the septic shock group ($\rho = -0.03$, $p = 0.82$). Table 1 shows the clinical characteristics of septic shock patients according to LTL (below or above median value) on day-1; all

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Table 1 Characteristics of patients with septic shock according to leucocyte telomere length at day 1 (n = 55)

	Lower LTL (n = 27)	Higher LTL (n = 28)	P value
<i>Clinical characteristics and comorbidities</i>			
Age (years)	64 [53–74]	64 [49–72]	0.60
Male gender, n (%)	20 (74%)	12 (43%)	0.02
Chronic obstructive pulmonary disease	0 (0%)	1 (4%)	> 0.99
Chronic kidney disease requiring long-term dialysis	2 (7%)	2 (7%)	0.97
Liver cirrhosis	4 (15%)	3 (11%)	> 0.99
Mc Cabe and Jackson class			0.49
0	11 (39%)	12 (43%)	
1	10 (37%)	13 (46%)	
2	6 (21%)	3 (11%)	
SAPS II at ICU admission	50 [41–79]	59 [39–79]	0.83
Community acquired infection	13 (48%)	16 (57%)	0.50
Lung source of infection	14 (52%)	13 (46%)	0.69
Bacteraemia	11 (41%)	13 (46%)	0.67
Surgery	6 (27%)	4 (16%)	0.48
<i>Organ failures</i>			
Sequential organ failure assessment score	10 [8–13]	11 [8–13]	0.83
Arterial lactates (mmol/L)	2.9 [1.5–5.5]	2.9 [1.4–4.9]	0.87
PaO ₂ /FIO ₂ ratio (mmHg)	164 [115–350]	188 [109–260]	0.79
Serum creatinine (mmol/L)	201 [84–338]	164 [84–264]	0.35
Septic myocardial dysfunction	10 (37%)	9 (32%)	0.70
<i>Outcome</i>			
Mechanical ventilation	25 (93%)	24 (86%)	0.67
Dialysis for acute renal failure	6 (22%)	4 (14%)	0.50
ARDS	18 (67%)	13 (46%)	0.18
ICU acquired infection	12 (43%)	9 (32%)	0.41
Death in ICU	15 (55%)	13 (46%)	0.49
Death in hospital	15 (55%)	16 (46%)	> 0.99

The telomere repeat copy number to single-gene copy number (T/S) ratio was determined using the comparative Ct method ($T/S = 2^{-\Delta\Delta C_t}$) with 36B4 gene for normalization (acidic ribosomal phosphoprotein PO, a single-copy gene). Data are number (percentage) or median [first quartile-third quartile]

LTL leucocyte telomere length, SAPS simplified acute physiology score, PaO₂ partial pressure of oxygen in arterial blood, FIO₂ fraction of inspired oxygen, ARDS acute respiratory distress syndrome, ICU intensive care unit

variables were similar between groups, except for more female gender in patients with higher LTL. There was no statistically significant correlation between LTL on the one hand and SMD (Fig. 1b), SOFA score, SAPS II score, or sepsis mediators (except for sST2, sFASL and granzyme) on the other hand (Fig. 1c). LTL was similar in septic shock survivors and nonsurvivors at day-1, but decreased between day-1 and day-2 in survivors (Fig. 1d).

LTL during septic shock may be determined by factors other than the inflammatory mediators we herein assessed; a prominent role for oxidative stress needs to

be assessed in future studies. The association of LTL with FasL is in accordance with a previous study showing a decreased production of FasL after TCR/CD3 signaling of senescent T cells [3]. Senescence was also associated with reduced expression of the effector molecules granzyme and perforin [4]. The decrease in LTL in septic shock survivors may be explained by a relative hyperfunction of leucocyte against infection in this subgroup [5]. We did not find a correlation between LTL and organ failures, as previously reported by Liu et al. [6].

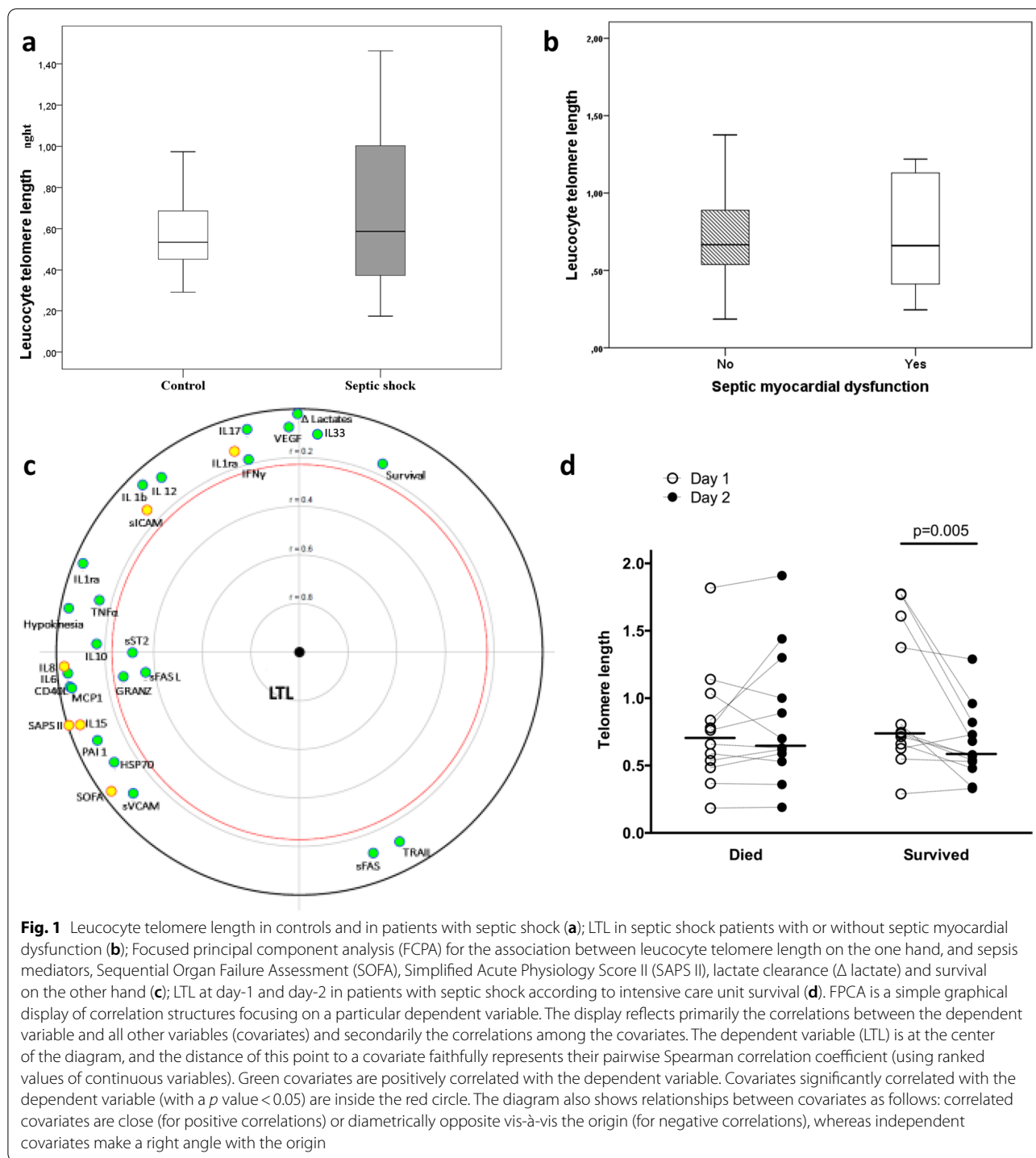


Fig. 1 Leucocyte telomere length in controls and in patients with septic shock (a); LTL in septic shock patients with or without septic myocardial dysfunction (b); Focused principal component analysis (FCPA) for the association between leucocyte telomere length on the one hand, and sepsis mediators, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score II (SAPS II), lactate clearance (Δ lactate) and survival on the other hand (c); LTL at day-1 and day-2 in patients with septic shock according to intensive care unit survival (d). FPCA is a simple graphical display of correlation structures focusing on a particular dependent variable. The display reflects primarily the correlations between the dependent variable and all other variables (covariates) and secondarily the correlations among the covariates. The dependent variable (LTL) is at the center of the diagram, and the distance of this point to a covariate faithfully represents their pairwise Spearman correlation coefficient (using ranked values of continuous variables). Green covariates are positively correlated with the dependent variable. Covariates significantly correlated with the dependent variable (with a p value < 0.05) are inside the red circle. The diagram also shows relationships between covariates as follows: correlated covariates are close (for positive correlations) or diametrically opposite vis-à-vis the origin (for negative correlations), whereas independent covariates make a right angle with the origin

Authors' contributions

KR, EM, and AMD contributed to the study design, analysis and interpretation of data. KR and AMD drafted the initial manuscript and approved the article final version. KR, EM, SH, LB, SA, and AMD contributed to the interpretation of data, critical revision of intellectual content and approval of the submitted version of the article. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets supporting the conclusions are included within the article.

Declarations

Ethics approval and consent to participate

The study was approved by institutional review board (CPP Ile de France IX).

Consent for publication

Not applicable.

Competing interests

All authors report no conflict of interest relevant to this study.

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Nous n'avons pas trouvé dans cette étude d'association entre le raccourcissement des télomères et la DMS. Le raccourcissement des télomères est associé à un pronostic péjoratif et à la gravité du SDRA dans une large cohorte de patients septiques (Liu et al. 2020). Nous avons analysé le raccourcissement des leucocytes circulants et donc nous ne pouvons exclure un effet au niveau tissulaire au sein des cardiomyocytes.

Article 6

Gestion de la DMS en réanimation : une enquête auprès des réanimateurs



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Management of septic myocardial dysfunction in intensive care unit: A survey of French speaking intensivists[☆]



Septic myocardial dysfunction (SMD²) is a well-known feature of human septic shock [1], but international guidelines failed to establish clear definitions and treatment modalities of this entity [2]. We sought to assess opinions and practices in the hemodynamic management of septic shock with a focus on SMD. An online survey electronically sent to French speaking intensivists comprised 30 questions covering the characteristic of respondents and their opinion on the monitoring of septic shock and management of SMD. We also assessed opinions on heart rate control during septic shock, because the latter may interfere with the clinical features and management of SMD.

Two hundred and fifty-nine intensivists from university (42%), public (49%) or private (9%) hospitals replied to the survey, including anaesthesiologists (46%), pulmonologists (10%) and cardiologists (8%) (eTable 1). Fifty percent of respondents had at least 12 years of experience working in intensive care unit. A large majority of physicians (66%) chose echocardiography as their preferred tool to monitor hemodynamics during septic shock, whereas one-fourth used transpulmonary thermodilution and only two intensivists declared using central venous pressure. The younger intensivists (<12 years of experience) practiced echocardiography more frequently (73%), as compared to their counterparts (59%) (Fig. 1). Echocardiography was mainly performed within 24 h after the onset of septic shock. Definition of SMD was not consensual among intensivists: 45% defined it as a decrease in left ventricle ejection fraction (LVEF) whereas the remainder considered a decrease in cardiac output, with (31%) or without (24%) an elevation of left ventricular end diastolic pressure (eTable 2). Left ventricular systolic dysfunction appeared the most important feature of SMD for 91% of respondents, with only 5% and 3% considering left ventricular diastolic dysfunction or right ventricular dysfunction, respectively. A large majority of intensivists (85%) believed that SMD was associated with an increase in mortality. Noradrenalin was the first-choice vasopressor for 95% of physicians. An inotropic agent, mostly dobutamine, was introduced in the presence of SMD, mainly in case of increasing doses of vasopressors (52%) or if there were signs of persistent hypoperfusion (27%), and rarely systematically (13%). Efficacy of inotropic therapy was assessed via improvement in signs of hypoperfusion (e.g., skin mottling, elevated lactate or oliguria) for one half of respondents, whereas the remainder physicians used changes in hemodynamic parameters like the cardiac output (36%), LVEF (13%), or arterial pressure (1%). The

maximal dose of dobutamine and the maximal heart rate allowed with dobutamine infusion were not consensual among respondents. However, an excessive tachycardia during dobutamine infusion was considered to justify its discontinuation for 29% of physicians. The occurrence of sinus tachycardia in septic patients (with or without inotropic therapy) justified a control of heart rate for 41% of respondents. Heart rate control was achieved predominantly with the administration of fluid challenges (60%), while only one-fourth of respondents used a specific drug agent, with amiodarone (52%), beta-blocker (42%), and ivabradine (17%) being the most reported.

We herein report significant heterogeneities regarding the definition and management of SMD. Left ventricular systolic dysfunction during septic shock was firstly described in the 80s, but definition and prognosis of SMD still appear ambiguous. A meta-analysis of 7 studies found that newly-diagnosed left ventricular systolic dysfunction (defined as low LVEF) during sepsis was not associated with increased mortality, although the heterogeneity and the power of these studies limited their interpretation [3]. The role of loading conditions (especially afterload) is of paramount importance when assessing LVEF in septic shock patients [4]. Recent studies suggest an association of diastolic dysfunction with increased mortality during septic shock [5,6], but the definition of diastolic dysfunction is not straightforward [7,8].

Heart rate is one of the major determinants of diastolic function and tachycardia was reported as an independent risk factor for mortality during sepsis [9]. Beta-blockade-driven heart rate control may improve outcomes during septic shock [10]. The preferential use of fluid boluses and amiodarone to achieve heart rate control in our survey may highlight reluctance to use an agent with negative inotropic effects in case of decreased LVEF. Further studies using the bradycardic agent ivabradine (a selective inhibitor of *I_f* channels in the sino-atrial node, devoid of negative effects on cardiac function and blood pressure) should be conducted to test the effect of pure heart rate control in this setting.

Echocardiography now appears as the preferred tool to monitor septic patients, particularly among young intensivists. Echocardiography is less invasive than other techniques but its daily-use at patient bedside requires specific training [11]. The marginal use of central venous pressure during septic shock in our survey is in accordance with recent studies challenging its usefulness for the assessment of fluid responsiveness during septic shock [12].

To conclude, this survey highlights heterogeneity of the knowledge and the management of septic myocardial dysfunction. Further research is needed to allow intensivists to standardize the diagnosis and the treatment of both systolic and diastolic dysfunction in the setting of septic shock.

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² LVEF: left ventricle ejection fraction; SMD: septic myocardial dysfunction.

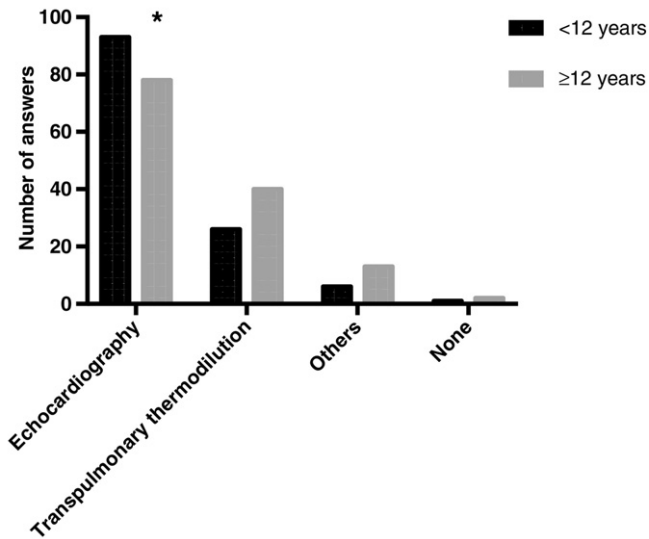


Fig. 1. Preferred tool of 259 intensivists used to monitor hemodynamics during septic shock, according to the number of years of experience working in ICU. *p-Value < 0.05 (Pearson's chi-squared test).

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jcrrc.2017.07.023>.

Conflicts of interest

None.

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eTable 1. Characteristics of respondents

Characteristics of respondents	
<i>Number of intensivists</i>	259 (100)
<i>Type of institution, n (%)</i>	
University Hospital	108 (42)
Public Hospital	123 (47)
Private Hospital	23 (9)
Other institution	5 (2)
<i>Type of ICU, n (%)</i>	
Mixed	184 (71)
Medical	31 (12)
Surgical	44 (17)
<i>Number of beds in ICU</i>	15 (12-20)
<i>Number of admission / year</i>	
<500	65 (25)
500 – 1000	126 (49)
>1000	68 (26)
<i>Medical status</i>	
Hospital practitioner	203 (78)
University professor	30 (12)
Assistant	14 (5)
Assistant professor	8 (3)
Resident	4 (2)
<i>Specialty</i>	
Anaesthesia	119 (46)
Pneumology	27 (10)
Cardiology	20 (8)
Internal medicine	19 (7)
Emergency	17 (7)
Paediatrics	17 (7)
Nephrology	10 (4)
Other	30 (12)
<i>Years of experience</i>	12 (6-20)

Definition of abbreviations: ICU=Intensive care unit. Data are expressed as n (%) or median (1st quartile-3rd quartile).

eTable 2. Monitoring and management of myocardial dysfunction during septic shock

	All intensivists (n=259)	Years of experience		p*
		< 12 (n=132)	≥ 12 (n=127)	
<i>Preferred tool to monitor hemodynamics during septic shock</i>				
Echocardiography	171 (66)	93 (73)	78 (59)	0.016
Transpulmonary thermodilution	66 (25)	26 (20)	40 (30)	0.07
Arterial pulse pressure waveform analysis	7 (3)	4 (3)	3 (2)	0.718
Pulmonary thermodilution	7 (3)	1 (1)	6 (4)	0.120
Oesophageal Doppler	2 (1)	1 (1)	1 (1)	>0.99
Microcirculation	1 (0)	0 (0)	1 (1)	0.490
Central venous pressure	2 (1)	0 (0)	2 (1)	0.498
None	3 (1)	1 (1)	2 (1)	>0.99
<i>Time of echocardiography</i>				
Within 24 hours	243 (94)	120 (94)	123 (93)	0.662
Between day 1 and day 3	223 (86)	111 (92)	112 (91)	0.682
Between day 4 and day 7	20 (8)	9 (7)	11 (9)	0.682
	0 (0)	0 (0)	0 (0)	-
<i>Definition of septic myocardial dysfunction</i>				
Decrease in LVEF	115 (45)	61 (48)	54 (41)	0.249
Decrease in CO with elevation of LVEDP	81 (31)	39 (31)	42 (32)	0.847
Decrease in CO without elevation of LVEDP	63 (24)	27 (21)	36 (27)	0.260
<i>Most important feature of septic myocardial dysfunction</i>				
Left ventricular systolic dysfunction	235 (91)	115 (91)	120 (91)	0.921
Left ventricular diastolic dysfunction	12 (5)	6 (5)	6 (4)	0.945
Right ventricular dysfunction	8 (3)	3 (2)	5 (4)	0.723
None	4 (1)	3 (2)	1 (1)	0.363
<i>Prognosis of septic myocardial dysfunction</i>				
Increased mortality	220 (85)	107 (84)	113 (86)	0.761
Decreased mortality	12 (5)	8 (6)	4 (3)	0.211
None	27 (10)	12 (9)	15 (11)	0.614
<i>First-choice of vasopressors</i>				
Noradrenaline	245 (95)	120 (94)	125 (95)	0.941
Dobutamine	9 (4)	5 (4)	4 (3)	0.745
Dopamine	4 (1)	1 (1)	3 (2)	0.622
Adrenaline	1 (0)	1 (1)	0 (0)	0.490
<i>Inotropic therapy in the presence of septic myocardial dysfunction</i>				
Systematically	35 (13)	20 (16)	15 (11)	0.302
Persistent hypoperfusion [#]	69 (27)	61 (58)	75 (66)	0.241
Increasing dose of vasopressor	136 (52)	38 (36)	21 (27)	0.152
<i>Inotropic agent used</i>				
Dobutamine	228 (88)	110 (87)	118 (89)	0.491
Adrenalin only	11 (4)	7 (6)	4 (3)	0.322
Adrenalin with noradrenalin	11 (4)	5 (4)	6 (5)	0.808
Noradrenalin only	8 (3)	5 (4)	3 (2)	0.439
Levosimendan	1 (0)	0 (0)	1 (1)	>0.99
<i>Monitoring of inotropic therapy effectiveness</i>				
Tissue hypoperfusion [#]	128 (49)	65 (51)	63 (48)	0.578
CO	93 (36)	48 (38)	45 (34)	0.584
LVEF	34 (13)	12 (9)	22 (17)	0.086
Arterial pressure	4 (1)	2 (2)	2 (1)	>0.99
<i>Maximal dose of dobutamine allowed</i>				
5 gamma/kg/min	23 (9)	10 (8)	13 (10)	0.577
10 gamma/kg/min	79 (31)	34 (27)	45 (34)	0.204
15 gamma/kg/min	71 (27)	34 (27)	37 (28)	0.820
20 gamma/kg/min	81 (31)	46 (36)	35 (26)	0.092
None	5 (2)	3 (2)	2 (1)	0.679
<i>Maximal heart rate allowed during dobutamine infusion</i>				
95	0 (0)	0 (0)	0 (0)	-
110	37 (14)	17 (13)	20 (15)	0.685
125	80 (31)	34 (27)	46 (35)	0.160
140	69 (27)	41 (32)	28 (21)	0.044
None	73 (28)	35 (28)	38 (29)	0.826
<i>Adverse event leading to dobutamine discontinuation (multiple answers allowed)</i>				
Ventricular arrhythmia	182 (70)	98 (77)	84 (64)	0.017

Supra-ventricular arrhythmia	160 (62)	86 (68)	74 (56)	0.054
Decrease in arterial pressure or increase in vasopressor dosage	114 (44)	52 (41)	62 (47)	0.329
Elevated heart rate	74 (29)	29 (23)	45 (34)	0.045
Decrease in vasopressor dose	43 (17)	19 (15)	24 (18)	0.486
Length of inotropic agent administration	21 (8)	14 (11)	7 (5)	0.092
Heart rate control to blunt excessive tachycardia	105 (41)	51 (40)	54 (41)	0.902
<i>Management to control heart rate</i>				
Fluid challenge	63 (60)	37 (68)	26 (51)	0.067
Specific drug agent	24 (23)	15 (30)	9 (17)	0.120
Control of body temperature	11 (10)	6 (12)	5 (9)	0.675
Increase of sedation	6 (6)	4 (8)	2 (4)	0.428
<i>Preferred drug agent used to control heart rate</i>				
Amiodarone	13 (52)	9 (60)	4 (40)	0.428
Beta-blocker	10 (42)	6 (40)	4 (44)	0.831
Ivabradine	4 (17)	3 (20)	1 (11)	>0.99
Digoxin	1 (4)	1 (7)	0 (0)	>0.99
Calcium blocker	1 (4)	0 (0)	1 (11)	0.375

Definition of abbreviations: LVEF=Left ventricle ejection fraction; CO=Cardiac output; LVEDP=Left ventricular end diastolic pressure; #Tissue hypoperfusion is defined as one of the following items: skin mottling, elevated lactate, and oliguria. *Pearson's chi-squared test or Fisher's exact test. *Data are expressed as n (%)*.

Dans notre enquête, nous avons confirmé que l'échocardiographie est l'outil principal de monitoring hémodynamique notamment parmi les jeunes réanimateurs. D'autres études faites en dehors de la France ont confirmé que l'échocardiographie est maintenant l'outil de monitoring principal en réanimation (Balzer et al. 2019; Garcia et al. 2017). Les réanimateurs sont plus attentifs à la dysfonction systolique VG qu'à la dysfonction diastolique VG ou encore la dysfonction ventriculaire droite. La dobutamine est l'inotrope utilisé majoritairement par les réanimateurs avec des critères d'initiation très variables, parfois éloignés des recommandations internationales (Evans et al. 2021). La définition et la prise en charge de la DMS est hétérogène parmi les réanimateurs, ce qui souligne la nécessité d'essais randomisés dans le domaine, pour des recommandations de haut niveau de preuve.

Article 7 :

Efficacité et tolérance hémodynamique de la dobutamine dans la dysfonction myocardique au cours du choc septique : une étude échocardiographique observationnelle prospective multicentrique.

Hemodynamic efficacy and tolerance of dobutamine for myocardial dysfunction during septic shock: an observational multicenter prospective echocardiographic study.

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Running Head : dobutamine for septic myocardial dysfunction

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List of abbreviations: LVEF (left ventricle ejection fraction); SAPS II (Simplified Acute Physiologic Score); SOFA (Sequential Organ Failure Assessment)

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Abstract (291 words)

Background: The role of dobutamine during septic shock resuscitation is still controversial.

Methods: The aim of this prospective multicentre study was to comprehensively characterize the hemodynamic response of septic shock patients with myocardial dysfunction to incremental doses of dobutamine (0, 5, 10, and 15 $\mu\text{g}/\text{kg}/\text{min}$) in terms of macrocirculation, cardiac function (including loading conditions, systolic and diastolic function), mottling and tissue hypoxia (indirect calorimetry and lactatemia).

Results: Thirty two patients (19 men and 13 women) were included in three centers. Dobutamine significantly increased contractility indices of both ventricles [crude and afterload-adjusted left ventricular (LV) ejection fraction, global LV longitudinal peak systolic strain, tissue Doppler peak systolic wave at mitral and tricuspid lateral annulus, and tricuspid annular plane excursion) as well as global function indices (stroke volume and cardiac index) and diastolic function (increased e' and decreased E/e' ratio at lateral mitral annulus). Dobutamine also induced a significant decrease in arterial pressure (diastolic and mean) and cardiac afterload indices (end-systolic arterial elastance, systemic vascular resistance and diastolic shock index). Oxygen transport, oxygen consumption and carbon dioxide production all increased with dobutamine, with no significant change in the respiratory quotient nor lactate. Dobutamine was discontinued (for worsening hypotension and/or severe tachycardia) in a majority of patients ($n=21$, 66%) at any dose and half of patients ($n=15$, 47%) at low-dose (5 $\mu\text{g}/\text{kg}/\text{min}$). Poor tolerance to low-dose dobutamine was enhanced by acidosis, mediated by worsened vasoplegic response and associated with lower vasopressor-free days and survival at day-14.

Conclusion: In patients with septic myocardial dysfunction, dobutamine induced an overall improvement of echocardiographic parameters of diastolic and systolic function, but was poorly tolerated in nearly two thirds of patients, with worsening vasoplegia. Patients with a poor tolerance to low-dose dobutamine seemed to have have a worse prognosis.

Keywords: septic shock; myocardial depression; dobutamine; mortality

INTRODUCTION (2576 words)

Circulatory failure is one of the hallmark alterations in septic shock and involves a variable combination of hypovolemia, vasoplegia and myocardial dysfunction. Septic myocardial dysfunction was first described by Parker *et al* in 1984.¹ In recent studies using echocardiography, systolic dysfunction was observed in one third (when assessed by left ventricle ejection fraction, LVEF) and more than two-thirds (when assessed by speckle tracking-derived LV longitudinal peak systolic strain) of patients during septic shock.² Diastolic dysfunction is also common and is a strong independent predictor of early mortality in septic shock.³

The surviving sepsis campaign recommends the use of dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.⁴ However, the role of dobutamine during septic shock resuscitation is still controversial since most clinical studies have been performed in an unselected population including patients with increased or decreased systolic function.^{5,6} Dobutamine failed to improve sublingual microcirculatory and hepatosplanchnic peripheral perfusion parameters or lactate levels in a randomized placebo crossover study.⁷ In addition, dobutamine may worsen cardiac diastolic function (via its tachycardic effect) and hypotension (via its vasoplegic effect) during septic shock and alter oxygen demand. We hypothesized that despite its beneficial effects on systolic function, dobutamine may alter diastolic function and worsen hypotension in patients with septic myocardial dysfunction.

The aim of this study was to comprehensively characterize the response of patients with septic myocardial dysfunction to incremental doses of dobutamine in terms of macrocirculation, cardiac function (including loading conditions, systolic and diastolic function), microcirculation (mottling), and tissue hypoxia (indirect calorimetry and lactatemia).

MATERIALS AND METHODS

Patients

Patients who met septic shock criteria (as defined according to the Sepsis-3 definition)⁸ were prospectively screened in three intensive care units (ICU) of Greater Paris in France. Norepinephrine was the first-choice vasopressor therapy (used to target a mean arterial pressure of 65 mmHg or more). Inclusion criteria were the presence of septic myocardial dysfunction [as defined by depressed LVEF (<45%) at echocardiography on the first or second day of septic shock onset] with ongoing signs of hypoperfusion despite adequate mean arterial pressure and correction of hypovolemia with absence of fluid responsiveness, mandating the introduction of dobutamine as per the physician decision. Non-inclusion criteria were chronic heart failure (defined as a baseline LVEF below 45%), severe valvulopathy, moribund state, tachycardia with heart rate >130 bpm, patients already receiving an inotropic agent, hemodynamic instability with mean arterial pressure <65 mmHg despite norepinephrine infusion, and unavailability of trained operators or echocardiography system.

Patient's severity was evaluated by the Mac Cabe and Jackson score for underlying diseases,⁹ the SAPS II (Simplified Acute Physiologic Score) for acute illness at ICU admission,¹⁰ and the SOFA (Sequential Organ Failure Assessment) score for organ dysfunction at septic shock onset.¹¹

Study procedure

An infusion of dobutamine was started at a rate of 5 µg/kg/min, and was sequentially increased to 10 µg/kg/min and 15 µg/kg/min after 30 minutes intervals, in case of good tolerance. Poor tolerance of dobutamine was defined as one of the following: i) worsening hypotension (mean arterial pressure <65 mmHg with a decrease of 10 mmHg or more as compared to baseline value or the need to increase norepinephrine infusion by at least 0.5 mg/hour to maintain a mean arterial pressure ≥65 mmHg); ii) severe tachycardia (new-onset atrial fibrillation or sinus tachycardia >130 beats per minutes with an increase of 10 beats per minute or more as compared to baseline value). Hemodynamic measurements were performed before dobutamine start and at the end of each step and included: arterial pressure and heart rate, mottling score, echocardiography, arterial blood gases with lactate, and indirect calorimetry [using CareScape R860 (General Electric Healthcare, USA), to assess oxygen consumption, carbon dioxide production, and energy expenditure].¹² Ventilatory settings, sedative and fluids infusions were

kept constant throughout the dobutamine titration protocol, as well as vasopressor dose (unless poor tolerance). The dobutamine titration was discontinued in case of poor tolerance as defined above.

Echocardiography

Serial transthoracic echocardiographies were performed by trained operators (competence in advanced critical care echocardiography) with a standard procedure.¹³ All measures were averaged over a minimum of three cardiac cycles (five to ten in case of non-sinus rhythm).

Assessment of contractility and loading conditions

Preload was assessed using estimates of LV filling pressures (E/A and E/e ratios from pulsed-wave Doppler early (E) and late (A) and tissue Doppler early (e') diastolic wave velocity at the lateral mitral valve annulus)¹⁴ and respiratory variations of inferior vena cava (as a surrogate of fluid responsiveness).¹⁵

Afterload was assessed using the following indices: i) diastolic arterial pressure (which is often used as a surrogate of LV afterload in clinical practice);¹⁶ ii) systemic vascular resistance (the most commonly used measure of vascular tone)¹⁷ = $\frac{80 * \text{mean arterial pressure (mm Hg)}}{\text{cardiac output (L.min}^{-1}\text{)}}$; iii) end-systolic arterial elastance (to reflect the pulsatile component of peripheral load)¹⁸ = $\frac{0.9 * \text{systolic arterial pressure (mm Hg)}}{\text{stroke volume (mL)}}$; and iv) diastolic shock index = $\frac{\text{heart rate (bpm)}}{\text{diastolic arterial pressure (mmHg)}}$ that could reflect the severity of circulatory dysfunction during vasodilatory conditions.¹⁹

LV systolic function was assessed using indices obtained by two-dimensional echocardiography (LVEF), tissue Doppler imaging (tissue Doppler peak systolic wave at the lateral mitral valve annulus), and speckle tracking imaging (global longitudinal peak systolic strain of the LV).² The ratio of mean arterial pressure to stroke volume was used as an estimate of effective arterial elastance. An afterload-adjusted LVEF was assessed as recently proposed,²⁰ using a simple nonlinear approach = $LVEF * \sqrt{\text{effective arterial elastance}}$. Ventriculoarterial coupling was defined as the ratio of arterial end-systolic elastance to left ventricular end-systolic elastance, which was estimated by using the single beat method of Chen et al.^{18,21}

We measured the velocity time integral in the LV outflow tract and the diameter of the aortic annulus, which allowed us to calculate LV stroke volume and cardiac index.

This study was approved by an Institutional Review Board (CPP Ile de France-V), as a

component of standard care. Written and oral information about the study was given to the patients or families as per French law.

Statistical Analysis

The data were analyzed using GraphPad Prism (Version 8.4.3) and IBM SPSS Statistics (Version 24). Normal distribution was checked using the Kolmogorov-Smirnov test. The global effect of dobutamine was assessed by the Friedman test followed by post-hoc paired Wilcoxon test with the Benjamini-Hochberg's correction. Continuous data were expressed as medians [25th-75th centiles] or mean (\pm standard deviation), as appropriate, and were compared using the non-parametric Kruskal-Wallis test followed by pairwise Mann-Whitney test. Categorical variables, expressed as percentages, were evaluated using the Chi-square test or Fisher exact test. Two-tailed p values <0.05 were considered significant. Using tissue Doppler early (e') diastolic wave velocity at the lateral mitral valve annulus as the primary measure of outcome focused on diastolic function, we calculated that a sample size of at least 33 patients would have a 90% power to detect a 20% decline in that variable with dobutamine titration, considering a baseline e' of 8 cm.s⁻¹ with a standard deviation of 2 cm.s⁻¹ in our previous cohort.²

RESULTS

Patient characteristics

Among 57 patients screened for myocardial dysfunction during septic shock, 24 were excluded because of one of the following reasons: chronic heart failure (n=1), already receiving an inotropic agent (levosimendan or adrenaline, n=2), moribund state (n=2), unavailability of trained operators or echocardiography system (n=5), heart rate >130 bpm (n=9), mean arterial pressure < 65 mm Hg despite norepinephrine infusion (n=1), and final diagnosis of cardiogenic shock without evidence of sepsis (n=5). Thus, the present study comprises 32 patients (19 men and 13 women). Clinical characteristics, comorbidities and organ failures are shown in Table 1. Dobutamine titration was performed after a median of 1 [0-1] day of septic shock onset. The doses of 5, 10 and 15 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine could be achieved in 32 (100%), 18 (56%) and 11 (34%) patients, respectively.

Hemodynamics

Table 2 summarizes the hemodynamic, echocardiographic, calorimetric and arterial blood gas responses to dobutamine.

Macrocirculation and cardiac function

Dobutamine induced a decrease in mean arterial pressure and an increase in heart rate. All contractility indices of both ventricles were increased with dobutamine (including crude LVEF, afterload-adjusted LVEF, global LV longitudinal peak systolic strain, tissue Doppler peak systolic wave at mitral and tricuspid lateral annulus, and tricuspid annular plane excursion), while all afterload parameters were decreased (including diastolic arterial pressure, end-systolic arterial elastance, systemic vascular resistance and diastolic shock index). Dobutamine also improved diastolic function (with increased e' and decreased E/e' ratio at lateral mitral annulus) and global cardiac function (with increased cardiac index), but non-significant change in ventricular–arterial coupling.

Mottling and tissue hypoxia

There was a trend towards decreased mottling score with dobutamine titration, but few patients had significant mottling. Arterial blood gases and lactate levels did not change during dobutamine titration, whereas oxygen transport, oxygen consumption and carbon dioxide production both increased, with a stable respiratory quotient. Energy expenditure increased with the maximal dose of dobutamine.

Clinical tolerance

During dobutamine titration, 21 (66%) patients had a poor tolerance leading to discontinuation in 15 patients at 5 $\mu\text{g}/\text{kg}/\text{min}$, four patients at 10 $\mu\text{g}/\text{kg}/\text{min}$, and two patients at 15 $\mu\text{g}/\text{kg}/\text{min}$. The reasons for discontinuation were worsening hypotension in the majority of patients ($n=18$, including 14 at 5 $\mu\text{g}/\text{kg}/\text{min}$, two at 10 $\mu\text{g}/\text{kg}/\text{min}$ and two at 15 $\mu\text{g}/\text{kg}/\text{min}$), severe sinus tachycardia in two patients (at 10 $\mu\text{g}/\text{kg}/\text{min}$), and worsening hypotension with new-onset atrial fibrillation in one patient (at 5 $\mu\text{g}/\text{kg}/\text{min}$).

After titration, dobutamine was maintained during septic shock treatment by the attending intensivist for a median of 2.5 [1-3] days, and continuation after titration was more frequent in patients with a good tolerance to low-dose dobutamine (5 $\mu\text{g}/\text{kg}/\text{min}$) than in their counterparts with poor tolerance [14/17 (82%) vs. 7/15 (47%), $p=0.03$]. Table 3 and 4 compare patients with good or poor tolerance to low-dose dobutamine in terms of baseline characteristics or percent change of circulatory parameters after dobutamine infusion, respectively. At baseline, clinical characteristics, hemodynamics, and echocardiographic parameters did not differ between patients with good or poor tolerance to low-dose dobutamine, except for a lower arterial blood pH in patients with poor tolerance (Table 3). Patients with a good tolerance to low-dose

dobutamine had a greater improvement in contractility indices whereas those with poor tolerance had a more severe deterioration of afterload indices (Table 4, Figure 1). At day-14, patients with a good tolerance to low-dose dobutamine had more vasopressor-free days (11 [0-13] vs. 0 [0-8] days, $p=0.01$) and a lower mortality [4 (24%) vs. 9 (60%), $p=0.04$] than their counterparts. However, ICU mortality was not significantly different between groups [6 (35%) vs. 9 (60%), $p=0.16$].

DISCUSSION

In this study of patients having septic myocardial dysfunction and severe septic shock, we have evidenced the following findings: i) dobutamine improved echocardiographic parameters of diastolic and biventricular systolic function, while it decreased afterload; ii) nearly half and two thirds of patients had a poor tolerance to low-dose and to any dose of dobutamine, respectively ; the inotropic effect was prominent in patients with good tolerance to low-dose dobutamine, while poor tolerance was enhanced by acidosis, and associated with worsened vasoplegic response and a worse short-term prognosis.

Systolic function

Dobutamine is a synthetic catecholamine that was developed as an inotrope for use in congestive heart failure. It consists of two composite enantiomers, which explains its mixed action on α_1 , α_2 , β_1 , and β_2 receptors.²² Variability in LVEF during septic shock may mainly reflect the influence of loading conditions.² Indeed, LVEF and other systolic indices reflect the ventriculo-arterial coupling between LV contractility and LV afterload. In our study, dobutamine decreased afterload, but LV contractility improvement was not only secondary to decrease of afterload. Indeed, among contractility parameters, global LV longitudinal peak systolic strain, tissue Doppler peak systolic wave at the lateral mitral valve annulus (which are less dependent from loading conditions) increased after dobutamine infusion. Moreover, dobutamine induced a significant increase in the afterload-adjusted LVEF.

Diastolic function

Dobutamine increases myocardial cyclic adenosine monophosphate (cAMP) by stimulating the β -adrenoreceptors. Raised cAMP concentrations causes intracellular calcium to increase, which could exacerbate diastolic dysfunction.²³ The tachycardic response to dobutamine could also favor diastolic dysfunction. However, cAMP also mediate the effect of β -adrenergic receptor stimulation to cause myocardial relaxation (i.e., positive lusitropic effect).²⁴ Studies in muscle

strips,²⁵ isolated hearts,²⁶ and intact animals,²⁷ have demonstrated that β -adrenergic receptor stimulation accelerates myocardial relaxation. Contrary to our hypothesis, we found that the net effect of dobutamine on diastolic function was an improved relaxation. These results are in accordance with those observed in patients with severe chronic heart failure.²⁴

Mottling and tissue hypoxia

Previous findings suggested beneficial effects of dobutamine on microcirculation.²⁸ We only found a trend towards a reduction in mottling score, but our results may be affected by the limited sample size and the low values of mottling score at baseline in our cohort. Some patients with significant microcirculatory alterations cannot be identified by visual assessment.²⁹ Moreover, both favorable and neutral effects of dobutamine on microcirculatory parameters have been reported.^{7,28}

Dobutamine tolerance and outcome

In our study, dobutamine was discontinued because of worsening hypotension or tachycardia in nearly two-thirds of patients at any dose (5 to 15 $\mu\text{g}/\text{kg}/\text{min}$) and in nearly half of patients at low-dose (5 $\mu\text{g}/\text{kg}/\text{min}$). This result is in accordance with a previous monocenter study with dobutamine incremental doses.⁶ Patients with poor tolerance to low-dose dobutamine had a mitigated inotropic response and an enhanced vasoplegic response to dobutamine. Baseline characteristics were not different between patients with good or poor tolerance to low-dose dobutamine, except for a deeper acidosis in the latter group. Acidosis has been shown to impair cardiac function. The drop in pH reduces the number of myocardial beta-adrenoreceptors,³⁰ and decreases the affinity of catecholamine for the beta-adrenoreceptor.³¹ Acidosis also induce vascular smooth muscle relaxation via the opening of ATP-sensitive potassium channels and vasodilatation secondary to overproduction of nitric oxide by inducible NO synthase.^{32,33} Acidosis may therefore impair the inotropic response and worsen the vasoplegic response to dobutamine, altering its tolerance.

In our study, a poor tolerance of dobutamine was associated with a worse outcome. A favorable response to dobutamine infusion (in terms of oxygen delivery to the tissues or whole body oxygen consumption) has been associated with a better outcome.³⁴ A recent meta-analysis suggested that the combination of norepinephrine and dobutamine is associated with a reduction in mortality at day-28 in patients with septic shock and low cardiac output.³⁵ Such results should be considered carefully since the heterogeneity of the studies included remains high.

Randomized controlled trial are ongoing to assess dobutamine in septic shock patients with myocardial dysfunction and low cardiac output.³⁶

Strengths and limitations

The strengths of our study include its prospective and multicentre design, the careful selection of patients with septic myocardial dysfunction, the comprehensive hemodynamic phenotyping of cardiac function (with evaluation of preload, contractility and afterload with advanced tools including strain imaging).

Our study has several limitations. The sample size was rather small and we explored patients within a short period. We cannot exclude that the statistical power and/or the limited period of observation were insufficient to detect subtle differences in some variables.

CONCLUSION

Dobutamine improved echocardiographic parameters of diastolic and biventricular systolic function, but further decreased LV afterload in human sepsis with myocardial dysfunction. Oxygen transport, oxygen consumption and carbon dioxide production both increased, with a stable respiratory quotient. Dobutamine titration was poorly tolerated in a majority of patients, with worsening hypotension. Poor tolerance to low-dose dobutamine was enhanced by acidosis, mediated by worsened vasoplegic response and associated with lower vasopressor-free days and survival at day-14.

Author Contributions Dr Razazi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Razazi, Dr Mekontso Dessap contributed to initial study design, analysis, interpretation of data, drafting of the submitted article, critical revisions for intellectual content, and providing final approval of the version to be published. Dr Vincent Labbé , Laurent Laine, Alexandre Bedet, Guillaume Carteaux, Nicolas de Prost, Florence Boissier, Francois Bagate contributed to study design and analysis, interpretation of data, drafting of the submitted article, critical revisions for intellectual content, and providing final approval of the version to be published.

Availability of data and material:

The datasets generated during and/or analysed during the current study are not publicly available as consent for publication of raw data was not obtained from study participants, but are available from the corresponding author on reasonable request.

Ethical approval

This study was approved by an Institutional Review Board (CPP Ile de France-V), as a component of standard care, and informed consent was waived. Written and oral information about the study was given to the patients or families.

Consent for publication

Not applicable

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Figure legend

Figure 1.

Data bars of median values of percent change in echocardiographic parameters after low-dose dobutamine infusion in septic shock patients with septic myocardial dysfunction, according to clinical tolerance to dobutamine; * denotes significant difference between good and poor tolerance

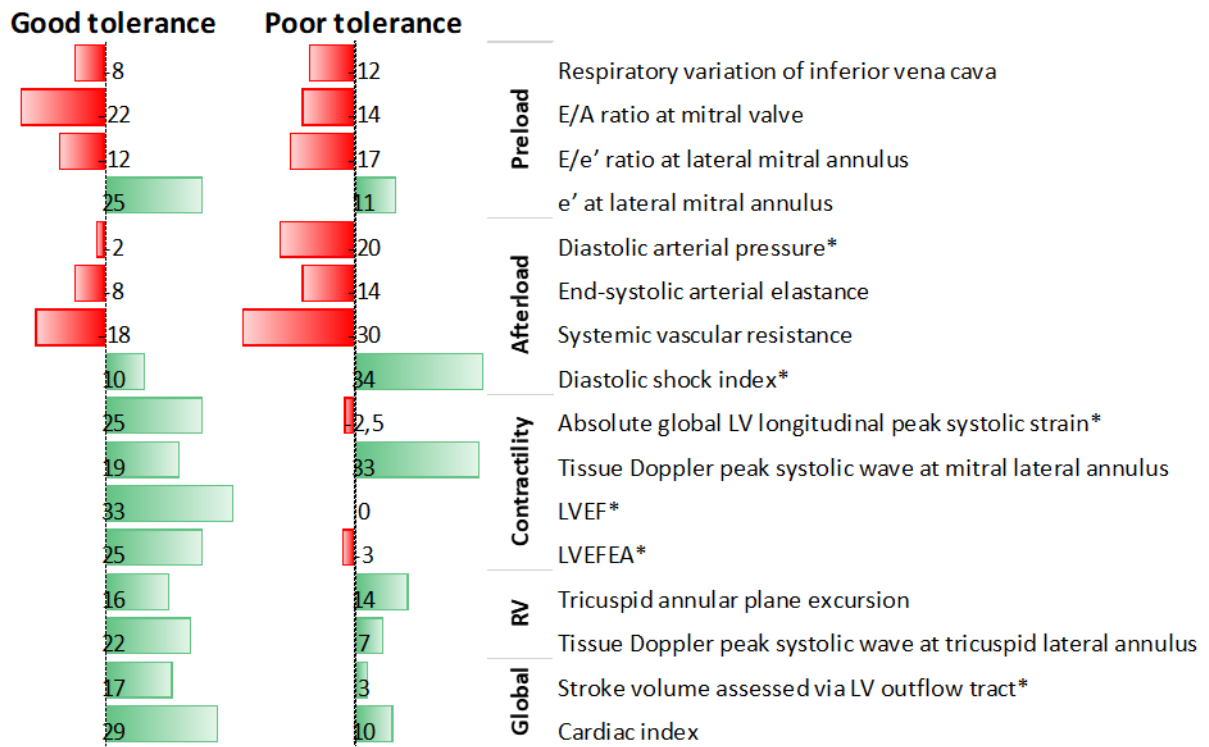


Table 1 Characteristics of patients with septic shock and myocardial dysfunction

Clinical characteristics and comorbidities	Patients n=32
Age, years	67 [57-76]
Male gender	19 (59%)
Body mass index, kg/m ²	23 [19-27]
SAPS II at ICU admission	64 [50-76]
Hypertension	4 (13%)
Chronic renal replacement therapy	1 (3%)
Chronic respiratory failure	1 (3%)
Cancer or hematological malignancy	7 (22%)
Cirrhosis	1 (3%)
Organ failures and hemodynamics	
SOFA score at ICU admission	11 [10-14]
Norepinephrine treatment	32 (100%)
Arterial blood lactate at admission, mmol/L	3.9 [3-6.4]
Infection source	
Pulmonary	18 (56%)
Abdominal	4 (13%)
Urinary	2 (6%)
Other origin	8 (25%)
Nosocomial infection	10 (31%)
Mechanical ventilation	31 (97%)
Tidal Volume, mL	375 [325-440]
Plateau pressure, cm H ₂ O	18 [16-22]
Positive end expiratory pressure, cm H ₂ O	8 [5-10]
Acute respiratory distress syndrome	25 (78%)
SOFA score at dobutamine initiation	12 [10-14]
Delay between shock onset and dobutamine initiation, days	1 [0-1]
Death in ICU	15 (47%)

Data are number (percentage) or median [1st-3rd quartile]

SAPS, simplified acute physiologic score; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment

Table 2. Hemodynamic and metabolic response during dobutamine titration in patients with shock and septic myocardial dysfunction.

	Dobutamine dose			P-value§
	0 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ (n=32)	5 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ (n=32)	Maximal dose§ (n=32)	
Macrocirculation				
Dose of norepinephrine, $\mu\text{g.kg}^{-1}.\text{min}^{-1}$	1.3 [0.5;2.3]	1.4 [0.6-2.4]	1.4 [0.6-2.4]	0.08
Dose of norepinephrine, mg/h	5.1 [1.6-9.0]	5.1 [2.2-9.0]	5.3 [2.4-9]	0.08
Mean arterial pressure, mmHg	73 [69-79]	68 [59-74] *	64 [56-74] *	<0.001
Heart rate, bpm	101 [81-119]	112 [88-122] *	117 [95-126] *	<0.001
Echocardiography				
<i>Preload</i>				
Respiratory variation of inferior vena cava, %	5 [0-11]	2 [0-17]	8 [0-20]	0.34
<i>Diastolic function</i>				
E/A ratio at mitral valve	0.89 [0.70-1.12]	0.83 [0.66-1.04]	0.82 [0.69-1.07]	0.67
e' at lateral mitral annulus	6.8 (± 3.7)	8.3 (± 4.4) *	8.2 (± 4.5) *	0.003
E/e' ratio at lateral mitral annulus	11.5 (± 8.5)	9.9 (± 7.0) *	10.0 (± 6.8) *	0.02
<i>Contractility</i>				
Global LV longitudinal peak systolic strain, %	-8.3 [-10.2 to -7.0]	-10.2 [-14.2 to -8.0]	-10.4 [-14.6 to -8.7] *	0.002
s' at mitral lateral annulus, cm.s^{-1}	8.0 [5.9-10.7]	9.7 [7.0-13.1]	10.0 [7.8-13.5] *	<0.001
LVEF, %	30 [25-40]	40 [30-50] *	45 [35-60] *	<0.001
Adjusted LVEF, %	41 [33-59]	47 [37-63] *	53 [42-67] *	0.006
LV end systolic elastance, mmHg.mL^{-1}	1.4 [0.97-2.0]	1.3 [1.8-3.0]	1.3 [1.2-2.7]	0.52
<i>Afterload</i>				
Diastolic arterial pressure, mmHg	58 [54-64]	51 [44-60] *	49 [44-59] *	<0.001
Diastolic shock index, bpm. mmHg^{-1}	1.7 [1.4- 2.0]	2.1 [1.7-2.7]*	2.1 [1.7-2.7] *	<0.001
Arterial end-systolic elastance, mmHg.mL^{-1}	2.6 [2.1-3.2]	2.1 [1.6-2.9] *	2.0 [1.5-2.7] *	<0.001
Systemic vascular resistance, $\text{mmHg.L}^{-1}.\text{min}$	1529 [1300-2088]	1087 [815-1473] *	999 [763-1387] *	<0.001
<i>RV function</i>				
Tricuspid annular plane excursion, mm	15 [13-17]	17 [12-19]	17 [14-22] *	<0.001
s' at tricuspid lateral annulus, cm/s	11.0 [8.0-12.0]	12.8 [11.1-15.7] *	15.0 [11.1-17.0] *	<0.001
RV dilatation (RV/LV area ratio)	0.6 [0.5-0.6]	0.6 [0.5-0.6]	0.6 [0.5-0.6]	0.29
<i>Global function</i>				
Stroke index, mL.m^{-2}	22 [17-27]	27 [19-30] *	28 [19-30] *	<0.001
Cardiac index, $\text{L.min}^{-1}.\text{m}^{-2}$	2.1 [1.7-2.7]	2.9 [2.0-3.6] *	3.1 [2.1-3.6] *	<0.001
Ventricular-arterial coupling	1.8 [1.3-2.3]	1.7 [1.1-2.4]	1.5 [1.1-2.4]	0.23
Mottling score				
	0 [0-2]	0 [0-1]	0 [0-1]	0.05
Arterial blood gases				
pH	7.26 [7.19-7.34]	7.29 [7.20-7.34]	7.29 [7.21-7.35]	0.91
PaCO ₂ , mmHg	37 [30-44]	37 [30-42]	37 [31-41]	0.99
PaO ₂ /FiO ₂ ratio, mmHg	209 [122-324]	209 [119-345]	214 [119-331]	0.56
SaO ₂ , %	97 [94-98]	97 [92-98]	97 [94-98]	0.56
Lactates, mmol/L	2.5 [1.5-3.7]	2.2 [1.6-3.5]	2.4 [1.6-3.5]	0.62
Oxygen metabolism				
TaO ₂ , $\text{ml/ min}^{-1}.\text{m}^{-2}$	310 [270-396]	393 [295-510] *	438 [295-546] *†	<0.001
VO ₂ , ml/min	243 [173-278]	247 [193-304]	265 [195-323] *	0.01
VCO ₂ , ml/min	178 [134-188]	176 [137-196]	183 [141-206] *	0.04
Respiratory quotient	0.70 [0.66-0.74]	0.70 [0.64-0.75]	0.69 [0.62-0.75]	0.66
Energy expenditure, kcal/day	1572 [1252-1767]	1547 [1346-1896]	1601 [1400-1999]*	0.005

Data are median [1st-3rd quartile] or mean (\pm standard deviation); §The maximal dose of dobutamine was 5, 10 and 15 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ in 32, 18, and 11 patients, respectively; §Friedman

test; * $p < 0.05$ as compared to baseline ($0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) by post hoc Wilcoxon paired test with Benjamini-Hochberg's correction; † $p < 0.05$ as compared to dobutamine $5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ by post hoc Wilcoxon paired test with Benjamini-Hochberg's correction; LV left ventricle; LVEF, left ventricle ejection fraction; RV, right ventricle; TaO_2 , oxygen transport, VO_2 oxygen consumption determined by indirect calorimetry, VCO_2 : carbon dioxide production determined by indirect calorimetry; E, blood Doppler early diastolic wave; A, blood Doppler late diastolic wave; e', tissue Doppler early diastolic wave; s', tissue Doppler peak systolic wave; see text for definitions.

Table 3. Baseline clinical, hemodynamic, echocardiographic, calorimetric and arterial blood gases data in patients with shock and septic myocardial dysfunction according to clinical tolerance at low-dose of dobutamine (5 γ /kg/min).

	Good tolerance (n=17)	Poor tolerance # (n=15)	P value
Age, years	64 [44-73]	69 [66-77]	0.17
Male gender	9 (53%)	10 (67%)	0.49
Body mass index, kg/m ²	24 [19-27]	23 [18-25]	0.56
SAPS II at ICU admission	57 [45-70]	73 [55-85]	0.052
SOFA on the day of dobutamine initiation	11 [10-13]	12 [11- 14]	0.11
Delay between ICU admission and dobutamine initiation, days	1.0 [0-1.5]	0 [0- 1]	0.06
Macrocirculation			
Dose of norepinephrine, $\mu\text{g.kg}^{-1}.\text{min}^{-1}$	0.9 [0.2-2.1]	1.6 [1.0- 2.4]	0.17
Dose of norepinephrine, mg/h	3.9 [1.1-8.5]	6.2 [3.2- 11.9]	0.29
Mean arterial blood pressure, mmHg	75 [73-80]	72 [67- 75]	0.13
Heart rate, bpm	100 [79-112]	105 [85- 121]	0.19
Echocardiography			
<i>Preload</i>			
Respiratory variation of inferior vena cava, %	6 [0-12]	0 [0-10]	0.32
<i>Diastolic function</i>			
E/A ratio at mitral valve	0.95 [0.61-1.13]	0.91 [0.73-1.22]	0.79
e' at lateral mitral annulus, cm. s ⁻¹	5.0 [4.0-9.0]	7.0 [4.3-9.7]	0.41
E/e' ratio at lateral mitral annulus	8.1 [5.9-13.1]	8.3 [6.9-14.8]	0.95
<i>Contractility</i>			
Global LV longitudinal peak systolic strain, %	-9.0 [-11.8 to -5.0]	-8.4 [-10.1 to -7.3]	0.99
s'at mitral lateral annulus, cm.s ⁻¹	8.0 [7.0-11.2]	7 [5.0-10.6]	0.39
LVEF, %	30 [25- 40]	30 [20-40]	0,79
Afterload-adjusted LVEF, %	43 [33-60]	39 [33- 51]	0.68
LV end-systolic elastance, mmHg.mL ⁻¹	1.8 [1.0-2.2]	1.4 [1.0-2.1]	0.38
<i>Afterload</i>			
Diastolic arterial pressure, mmHg	59 [56-65]	55 [50- 63]	0.20
Diastolic shock index, bpm. mmHg ⁻¹	1.6 [1.4-1.9]	1.9 [1.5- 2.3]	0.07
Arterial end-systolic elastance , mmHg.mL ⁻¹	2.2 [1.8-2.9]	2.6 [2.1- 3.3]	0.29
Systemic vascular resistance, mmHg.L ⁻¹ .min	1732 [1427-2115]	1448 [1036- 2137]	0.17
<i>RV function</i>			
Tricuspid annular plane excursion, mm	15 [12-17]	15 [14-17]	0.91
Tissue Doppler peak systolic wave at tricuspid lateral annulus, cm/s	10.1 [7.7-11.6]	11.3 [7.8-14.1]	0.53
RV dilatation (RV/LV area ratio)	0.6 [0.5-0.7]	0.6 [0.5-0.6]	0.77
<i>Global function</i>			
Stroke volume assessed via LV outflow tract, mL	37 [31-44]	37 [28- 48]	0.99
Cardiac output, L.min ⁻¹	3.6 [2.7-4.4]	4.0 [2.7-5.8]	0.55
Cardiac index, L.min ⁻¹ .m ²	2.0 [1.5-2.7]	2.2 [1.8-3.3]	0.39
Ventricular–arterial coupling	1.6 [1.2-2.1]	2.1 [1.6-2.4]	0.17
Mottling	3 (21%)	6 (40%)	0.14
Arterial blood gas			
pH	7.32 [7.27-7.39]	7.21 [7.18-7.26]	0.02
Bicarbonates, mmol/L	19 [16-22]	16 [14-21]	0.27
PaCO ₂ , mmHg	37 [30-39]	40 [29-46]	0.20
PaO ₂ /FiO ₂ ratio, mmHg	203 [125-314]	214 [120-350]	0.93

SaO ₂ , %	96 [94-98]	97 [94-98]	0.89
Lactates, mmol/L	2.3 [1.4-3.2]	3.3 [1.9-7.0]	0.15
Oxygen metabolism			
TaO ₂ , mL.min ⁻¹ .m ⁻²	319 [208-387]	309 [278-414]	0.68
VO ₂ , ml/min	252 [194-275]	163 [112-340]	0.38
VCO ₂ , ml/min	177 [138-188]	143 [98-187]	0.71
Respiratory quotient	0.70 [0.68-0.73]	0.71 [0.55-0.88]	0.99
Energy expenditure, kcal/day	1670 [1295-1806]	1478 [759-1572]	0.28
Outcome			
Days alive and free of norepinephrine at day 14	11 [0-13]	0 [0-8]	0.01
Death in intensive care unit	6 (35%)	9 (60%)	0.16

Data are number (percentage) or median [1st quartile – 3rd quartile]; #poor tolerance was defined as one of the following: i) worsening hypotension (mean arterial pressure < 65 mmHg with decrease of 10 mmHg or more as compared to baseline or the need to increase norepinephrine infusion to maintain a mean arterial pressure of 65 mmHg or more); ii) worsening tachycardia (increase of 10 beats per minute and sinus tachycardia > 130 mmHg or new-onset atrial fibrillation); SAPS, simplified acute physiologic score; SOFA, Sequential Organ Failure Assessment; LV, left ventricle ; RV, right ventricle; LVEF, left ventricle ejection fraction; TaO₂, Oxygen transport; VO₂ oxygen consumption determined by indirect calorimetry, VCO₂: carbon dioxide production determined by indirect calorimetry; E, blood Doppler early diastolic wave; A, blood Doppler late diastolic wave; e', tissue Doppler early diastolic wave; s', tissue Doppler peak systolic wave; see text for definitions.

Table 4. Percent change in hemodynamic parameters after low-dose dobutamine infusion (5 γ /kg/min) according to its clinical tolerance in patients with septic shock and myocardial dysfunction

	Good tolerance (n=17)	Poor tolerance (n=15)	P value
Macrocirculation			
Percent change in dose of norepinephrine	0 [0- 0]	0 [0 -14]	0.004
Percent change in dose of norepinephrine	0 [0- 0]	0 [0 -14]	0.004
Percent change in mean arterial blood pressure	1 [-7 to 12]	-19 [-25 to -15]	<0.001
Percent change in heart rate	7 [0-13]	5 [1-7]	0.62
Echocardiography			
<i>Preload</i>			
Percent change in respiratory variation of inferior vena cava	-8 [-14 to -2]	-12 [-29 to -2]	0.35
<i>Diastolic function</i>			
Percent change in E/A ratio at mitral valve	-22 [-43 to 10]	-14 [-30 to 13]	0.55
Percent change in E/e' ratio at lateral mitral annulus	-12 [-32 to 6]	-17 [-23 to 13]	0.63
Percent change e' at lateral mitral annulus	25 [0 to 59]	11 [-2 to 30]	0.23
<i>Contractility</i>			
Percent change in pulse pressure	20 [-1 to 29]	-20 [-31 to 4]	0.002
Percent change in absolute global LV longitudinal peak systolic strain	25 [16 to 41]	-2.5 [-10 to 16]	0.02
Percent change in tissue Doppler peak systolic wave at mitral lateral annulus	19 [-3 to 44]	33 [-7 to 66]	0.56
Percent change in LVEF	33 [24- 50]	0 [0- 35]	0.02
Percent change in afterload-adjusted LVEF	25 [16- 41]	-3 [-10 to 16]	0.001
Percent change in LV end-systolic elastance	16 [-18 to 37]	-12 [-41 to -7]	0.07
<i>Afterload</i>			
Percent change in diastolic arterial pressure	-2 [-8 to 4]	-20 [-24 to -15]	<0.001
Percent change in arterial end-systolic elastance	-8 [-23 to -3]	-14 [-27 to -5]	0.11
Percent change in systemic vascular resistance	-18 [-37 to -9]	-30 [-39 to -20]	0.17
Percent change in diastolic shock index	10 [1- 22]	34 [25-48]	<0.001
<i>RV function</i>			
Percent change in tricuspid annular plane excursion	16 [-8 to 27]	14 [-16 to 35]	0.09
Percent change in tissue Doppler peak systolic wave at tricuspid lateral annulus	22 [9- 61]	7 [1- 28]	0.06
Percent change in RV/LV area ratio	0 [0- 0]	0 [-9 to 0]	0.23
<i>Global function</i>			
Percent change in stroke volume assessed via LV outflow tract	14 [3- 35]	2 [0- 21]	0.08
Percent change in cardiac index	29 [6-50]	10 [5- 29]	0.21
Percent change in ventricular-arterial coupling	-12 [-28 to -9]	8 [-19 to 38]	0.15
Arterial blood gas			
Percent change in PaO ₂ /FiO ₂	-6 [-12- 5]	-2 [-15 to 10]	0.88
Percent change in SaO ₂	0 [-1 to 1]	0 [-3 to 1]	0.87
Percent change in arterial blood lactates	-3 [-8 to 3]	-3 [-11 to 6]	0.83
Oxygen metabolism			
Percent change in oxygen transport	29 [5-52]	8 [3-33]	0.21
Percent change in oxygen consumption	7 [3- 11]	-4 [-1 to -4]	0.01
Percent change in energy expenditure	7 [3; 9]	-1 [-4 to -1]	0.03
Percent change in carbon dioxide production	4 [-1 to 7]	3 [-8 to 3]	0.99

LV, left ventricle; RV, right ventricle; LVEF, left ventricle ejection fraction ; PaO₂, partial pressure of oxygen tension in arterial blood ; FiO₂, fraction of inspired oxygen ;TaO₂, oxygen transport.

Nous avons montré les effets sur la fonction systolique et la postcharge de la dobutamine. La dobutamine augmente la contraction myocardique quel que soit l'indice utilisé et cet effet semble persister si on ajuste sur la diminution de la postcharge que cette molécule entraîne. On peut remarquer que dans notre population de patients nécessitant de fortes doses de catécholamines, la mauvaise tolérance sur la pression artérielle ou la fréquence cardiaque est fréquente. Cette mauvaise tolérance est plus fréquente chez les patients avec une acidose métabolique marquée et est associée à un pronostic péjoratif. Une étude française (Geri et al. 2019) a récemment identifié dans une cohorte multicentrique cinq phénotypes cardiovasculaires de patients atteints de choc septique à partir des données cliniques et échocardiographiques. L'un de ces phénotypes regroupe les patients avec une dysfonction VG définie par une FEVG $\leq 40\%$ associée à une ITV (intégrale temps vitesse sous aortique) < 14 cm. Ce phénotype était associé à une surmortalité à J7 du début du choc septique.

L'étude multicentrique ADAPT (clinical trials.gov: NCT04166331; University Hospital, Limoges 2020) évalue actuellement la capacité de la dobutamine à réduire les défaillances d'organe chez les patients en choc septique ayant une cardiomyopathie septique et présentant une hypoperfusion tissulaire malgré une prise en charge adaptée. Dans cet essai, les patients devront présenter des signes d'hypoperfusion tissulaire associés à une FEVG $\leq 40\%$ et une ITV basse. L'étude espère montrer une diminution des dysfonctions d'organe à l'aide du score SOFA à J2 et J3 après introduction de la dobutamine.

D'autres inotropes comme le lévosimendan ou la milrinone ont été explorés au cours du sepsis. Le lévosimendan, un sensibilisateur au calcium avec des actions inotropes et vasodilatatrices était prometteur devant les résultats d'une méta-analyse montrant une baisse de la mortalité parmi 246 patients provenant de 7 études (Zangrillo et al. 2015). Cependant, une étude randomisée n'a pas montré de supériorité chez des patients en sepsis (Gordon et al. 2016). L'analyse du sous-groupe avec des biomarqueurs évocateurs de dysfonction myocardique (troponine I et NT-proBNP) n'a pas non plus montré de bénéfice du lévosimendan sur le pronostic (Antcliffe et al. 2019). La milrinone, un autre inotrope, est un inhibiteur sélectif de l'isoenzyme AMPc phosphodiesterase entraînant une augmentation des ions calcium intracellulaires et de la force contractile du myocarde où l'AMPc sert de second messenger. Cette molécule n'a pas montré de différence de pronostic en comparaison avec la dobutamine

dans la prise en charge des chocs cardiogéniques (Mathew et al. 2021). Sa supériorité, par rapport à la dobutamine, dans le choc septique semble peu probable.

La dysfonction myocardique extrêmement sévère de patients présentant un choc septique a justifié dans de très rares cas un support cardiovasculaire par ECMO veino-artérielle (Bréchet et al. 2013). Cette technique pourrait améliorer le pronostic de certains patients en choc septique (Bréchet et al. 2020; Ling et al. 2021), mais l'identification de cette population reste à mieux définir.

Les futures avancées sur le traitement de la DMS viendront probablement de la meilleure sélection des malades justifiant un support cardiaque par inotropes ou une éventuelle assistance par ECMO.

DISCUSSION GENERALE et PERSPECTIVE

L'ensemble de ces travaux de thèse a permis des avancées dans les domaines de la compréhension de la physiologie de la DMS (notamment le rôle des conditions de charge), de sa biopathologie (notamment des médiateurs du sepsis impliqués), de son diagnostic (notamment l'utilisation de nouveaux outils échocardiographiques pour mieux la caractériser), et de sa prise en charge thérapeutique (notamment l'utilisation des inotropes).

Physiopathologie de la DMS

Les mécanismes de la DMS sont nombreux et complexes. Nous avons montré dans ce travail que la DMS n'est pas une myocardite septique comme elle est parfois nommée par les réanimateurs. La DMS semble clairement associée aux médiateurs du sepsis, notamment les cytokines de l'immunité innée. L'effet semble médié par un groupe de médiateurs de l'immunité innée (avec un rôle associé de l'axe corticotrope) et non par un médiateur singulier. Des études supplémentaires sont nécessaires pour caractériser la voie de signalisation intracellulaire privilégiée par ce groupe de médiateurs de l'immunité innée dans la physiopathologie de la DMS.

L'orage cytokinique

Au vu de l'association entre l'élévation des cytokines et la DMS, on peut se demander si la déplétion des cytokines produites lors du choc septique pourrait améliorer ou prévenir la DMS. Les études dans le choc septique visant à moduler l'inflammation ou à capter les cytokines par absorption se sont révélées décevantes, sans effet sur la mortalité (Wendel Garcia et al. 2021; Livigni et al. 2014; Fujii et al. 2018), voire associées à une surmortalité (Garbero et al. 2021). Une des explications à ce résultat serait que ces techniques déplètent également les médiateurs pro-inflammatoires nécessaires à la guérison du patient et les médiateurs anti-inflammatoires sécrétés dès le début du choc septique (Angus et van der Poll 2013). Les études évaluant des anticorps anti-cytokines ont également été décevantes (Bernard et al. 2014; Opal et al. 1997). Le phénotypage des patients pourrait aider à sélectionner ceux pouvant bénéficier de ces thérapeutiques spécifiques (Shankar-Hari et al. 2021). De manière intéressante, l'inflammation joue un rôle dans le choc cardiogénique (Hochman 2003). L'IL-6 est impliquée également dans les lésions induites par l'ischémie reperfusion (Sawa et al. 1998). Sa concentration est

fortement associée à la mortalité (Ceglarek et al. 2021). Le tocilizumab, antagoniste des récepteurs de l'IL-6, pourrait diminuer la taille de l'infarctus (Broch et al. 2021). Une autre pathologie, le syndrome de relargage cytokiniques, qui apparaît après traitement par lymphocytes T dotés d'un récepteur à l'antigène chimérique (cellules CAR-T), peut se compliquer d'évènements cardiovasculaires (Qi et al. 2021). Ce syndrome de relargage cytokinique est également traité par du tocilizumab (Kotch, Barrett, et Teachey 2019). Des études sont nécessaires pour explorer de nouveau le rôle des anticorps anti-cytokines dans la physiopathologie du sepsis en général, et de la DMS en particulier.

Une place pour la corticothérapie à faibles doses ?

L'association que nous avons retrouvée entre DMS et ISR pose la question de la corticothérapie à faible doses dans cette indication. La corticothérapie a depuis longtemps été suggérée dans le traitement du choc septique. Les effets hémodynamiques de la corticothérapie sont selon les études (Sprung et al. 2008; Djillali Annane et al. 2002) plus ou moins associés à l'insuffisance surrénale relative. Les dernières grandes études ADRENAL (Venkatesh et al. 2018) et APROACCHS (Djillali Annane et al. 2018) ont permis d'éclaircir certaines incertitudes concernant la corticothérapie à faible doses au cours du choc septique. L'étude ADRENAL n'a pas montré de bénéfice de la corticothérapie sur la mortalité chez des patients sous ventilation mécanique en choc septique, mais a permis de confirmer qu'elle permettait une accélération du sevrage en catécholamines. L'essai APROACCHS (Djillali Annane et al. 2018) a démontré une baisse de la mortalité grâce à une corticothérapie à faibles doses associant l'hydrocortisone à la fludrocortisone chez des patients en choc septique avec au moins deux défaillances d'organe sévères. Les dernières recommandations internationales, sur la prise en charge du choc septique, par la *Surviving Sepsis Campaign* (Evans et al. 2021), proposent de réserver l'utilisation de la corticothérapie substitutive aux patients présentant un choc septique avec une nécessité de doses de noradrénaline ou d'adrénaline ≥ 0.25 mcg/kg/min.

Plusieurs études (Oppert et al. 2000; Schneider et Voerman 1991) ont démontré les effets vasculaires périphériques des corticoïdes à faibles doses au cours du choc septique avec notamment une augmentation de la pression artérielle grâce à la restauration des résistances vasculaires systémiques (Bollaert et al. 1998) et une augmentation de la réponse vasopressive à la noradrénaline. La

corticothérapie à tendance à augmenter la sensibilité aux vasopresseurs et donc la vasoconstriction chez les patients en choc septique probablement grâce à l'augmentation de l'affinité des récepteurs α 1-adrénergiques (D. Annane et al. 1998b; Bellissant et Annane 2000). La contractilité du VG étant inversement liée à la postcharge (Boissier et al. 2017), on pourrait théoriquement s'attendre à une baisse de la contractilité cardiaque et du débit cardiaque en réponse à cette intervention, comme observé dans certains essais physiologiques (Keh et al. 2003). Cependant, il semble que les stéroïdes possèdent aussi une activité inotrope positive propre (Tanz et Kerby 1961). En effet, une étude pharmacologique (Laviolle et al. 2010) a évalué l'effet hémodynamique d'une seule dose d'hémisuccinate d'hydrocortisone (HSHC 50 mg) et de fludrocortisone (50 μ g), administrés seuls ou en association, chez des volontaires sains, chez qui un hypoaldostéronisme fut induit par une charge de sodium intraveineuse (afin de mimer une ISR). Cette étude a permis de révéler une augmentation du débit cardiaque associée à une baisse des résistances vasculaires systémiques. L'hypothèse suggérée pour expliquer ces observations, est une régulation des récepteurs β 1 (effet inotrope positif direct sur le myocarde) et/ou β 2-adrénergiques (baisse des résistances vasculaires systémiques) (Fève et al. 1990; Kiely et al. 1994; Dangel et al. 1996). Par ailleurs, il a aussi été montré que des doses plus élevées de stéroïdes (autres que l'HSHC) améliorent l'index cardiaque chez des patients en choc ou non (Dietzman et Lillehei 1968; Shatney, Dietzman, et Lillehei 1980; Sambhi, Weil, et Udhoji 1965), en régulant les récepteurs β -adrénergiques du myocarde (Saito et al. 1995; 1996). Au vu de ses effets vasculaires et potentiellement cardiaques, nous évaluons actuellement à l'aide des nouveaux outils échocardiographiques l'effet de cette corticothérapie au cours de la DMS.

Nouveau outils échocardiographiques

Russel et al ont décrit une méthode non invasive de calcul du travail myocardique en utilisant des courbes pression-strain en échocardiographie avec une bonne corrélation avec les courbes pressions volumes (K. Russell et al. 2012). Cette technique serait indépendante ou moins dépendante des conditions de charge par rapport aux précédents indices et serait donc intéressante pour dépister ou suivre l'évolution au cours du choc septique de ces indices. Cette méthode estime le travail myocardique global mais aussi le travail myocardique global « constructif » et « gaspillé » (Billig et al. 2021). Son utilisation pour caractériser la DMS serait intéressante dans de futures études.

L'échographie cardiaque tri-dimensionnelle est un outil échographique au lit du patient permettant une meilleure évaluation des volumes ventriculaires que l'échographie 2D. Elle a été évaluée en comparaison avec l'IRM cardiaque, considérée comme étant la technique de référence (Jenkins, JACC, 2004 ; Mondelli, JASE, 2001 ; Gopal, Circulation, 1995 ; Hibberd, Am Heart J, 2000). Les études comparant l'évaluation de la FEVG, et des volumes télé-diastoliques et télé-systoliques en échographie 2D, 3D et IRM ont retrouvé une meilleure corrélation des volumes et de la FEVG entre le 3D et l'IRM (Hibberd et al. 2000). D'autre part, la variabilité inter et intra-observateur est faible (Gopal et al. 1995). L'échographie 3D permet également d'analyser la cinétique segmentaire et la mesure globale des volumes même en présence de troubles de la cinétique segmentaire avec une bonne corrélation par rapport à l'IRM (Pouleur et al. 2008). Les limites principales de l'échographie 3D sont l'acquisition du volume total pouvant être tronqué en cas de dilatation cardiaque importante, et la qualité de l'image qui est le facteur limitant principal notamment en réanimation, dépendant de la cadence image et de la densité des lignes de détection des volumes (la densité des lignes étant inversement proportionnelle à la largeur du secteur de détection: ainsi un ventricule dilaté nécessitera un secteur plus large et donc une moindre densité des lignes). L'échographie 3D présenterait donc un intérêt surtout dans la mesure séquentielle des volumes notamment pour préciser la possible dilatation adaptative décrite par Parker (M. M. Parker et al. 1984). Récemment, une méthode de speckle tracking 3D a permis de montrer également une très bonne évaluation et reproductibilité des volumes en comparaison à la méthode de référence de l'IRM (Nesser et al. 2009). Cette méthode permet également d'évaluer la rotation et la torsion du VG (Kormányos et al. 2019), phénomènes jusqu'ici peu explorés dans la DMS.

CONCLUSION GENERALE

Ce travail de thèse confirme le rôle des médiateurs circulants dans la genèse de la DMS, souligne l'interaction des conditions de charge dans sa détection, précise le rôle de l'échocardiographie dans sa gestion et les caractérise les effets de la dobutamine dans son traitement. Il pose les bases de futurs développements dans l'exploration et le traitement des malades avec DMS.

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