Etude de la mécanique ventriculaire en échographie : modélisation de l'asynchronisme mécanique

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Année 2010 **N°**

THESE

Pour le

DOCTORAT DE L'UNIVERSITE PARIS-EST-CRETEIL

Mention: Physiopathologie

Présentée et soutenue publiquement le
15 Décembre 2010
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ETUDE DE LA MECANIQUE VENTRICULAIRE EN ECHOCARDIOGRAPHIE

MODELISATION DE L'ASYNCHRONISME MECANIQUE

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Remerciements

Je remercie le **Professeur Benoit Diébold** qui me fait l'honneur de juger et d'être le rapporteur de cette thèse. Vous m'avez orienté vers la cardiologie et vos conseils ont guidé mes premiers pas. Je vous en suis profondément reconnaissant.

Je remercie le **Professeur Jean-Louis Vanoverschelde** qui me fait l'honneur de juger et d'être le rapporteur de cette thèse. Je vous remercie de m'avoir ouvert les portes de votre laboratoire qui est un exemple de rigueur et de créativité.

Je remercie le **Professeur Raymond Roudaut** qui me fait l'honneur de juger mon travail. Je garde une admiration renouvelée à chaque congrès d'échocardiographie face à votre dynamisme et votre esprit de synthèse.

Je remercie Le **Professeur Didier Carrié** qui me fait l'honneur de juger cette thèse et qui a tant contribué à tisser des liens étroits et amicaux entre nos deux équipes d'imagerie.

Je remercie le **Professeur Pascal Guéret** pour sa confiance, son aide et ses précieux conseils scientifiques et humains. Veuillez trouver en ces mots l'expression de ma profonde reconnaissance et de mon admiration.

Remerciements

Je remercie le **Docteur Jean-Luc Monin** pour son enseignement, son amitié et sa collaboration scientifique. La fédération de cardiologie et moi-même sommes marqués de ta personnalité.

Je remercie **le Professeur Jean-Luc Dubois-Randé** pour sa confiance et ses encouragements et soutien dans nos travaux de recherche en imagerie. Je vous remercie tout particulièrement de m'avoir ouvert les portes de la salle de cathétérisme pour nos travaux en imagerie. Veuillez trouver en ces mots l'expression de mon profond respect.

Je remercie **le Professeur Alain Berdeaux** pour m'avoir accueilli dans votre laboratoire et vos encouragements pour la recherche translationnelle entre nos deux équipes.

Je remercie **le Docteur Nicolas Lellouche** pour le plaisir de partager avec toi les idées et notre passion de la recherche clinique depuis notre clinicat. Trouve en ces mots l'expression de ma profonde amitié et admiration.

Je remercie mes amis, collègues et anciens internes, **les Docteurs Julien Mahum, Alexandre Bensalade et Laurent Macroute**. Votre dynamisme et votre créativité sont pour moi exemplaires. Veuillez trouver dans ces mots l'expression de quelques pintes de bières partagées.

A ma femme Marion pour sa patience et son intelligence humaine

A mon fils qui a bien voulu interrompre nos parties de foot pendant la rédaction de cette thèse

A mes parents, mes sœurs et mon frère adorés

RESUME

Introduction : La resynchronisation cardiaque améliore les patients insuffisants cardiaques présentant un élargissement du QRS>120ms et restant symptomatiques malgré un traitement médical optimal. Cependant, environ un tiers à 40% des patients ne tirent pas bénéfice de ce traitement. L'objet de cette thèse est d'identifier et de comprendre les mécanismes déterminant la réponse à la resynchronisation cardiaque. **Méthodes :** Dans un premier temps, nos travaux ont consisté à déterminer la précision des méthodes de quantification de contraction myocardique pour caractériser l'asynchronisme (Doppler Tissulaire et speckle tracking). Ensuite, nous avons évalué les facteurs liés à l'asynchronisme et à la réponse à la resynchronisation cardiaque (fibrose, nécrose myocardique, réserve contractile). Enfin, nous avons modélisé et validé un indice (strain delay index) permettant d'évaluer les conséquences « énergétiques » de l'asynchronisme sur la contraction myocardique **Résultats :** Nous avons démontré que le strain longitudinal en speckle tracking était supérieur au Doppler tissulaire pour l'évaluation de la déformation et de l'asynchronisme myocardique et mieux corrélé au pronostic des patients insuffisants cardiaques. Ensuite, nous avons démontré que le retard de contraction mécanique n'était pas seulement lié à un bloc de conduction électrique mais était constamment observé dans les segments myocardiques nécrosés. Par ailleurs, nous avons montré que ces zones de fibrose et de nécrose évaluées en échographie de stress par la réserve contractile influençaient la réponse à la resynchronisation cardiaque, suggérant l'importance de considérer le retard de contraction et la contractilité résiduelle pour prédire la réponse à la resynchronisation cardiaque. Partant de cette hypothèse, nous avons développé et validé un indice unique intégrant l'asynchronisme et la contractilité résiduelle pour évaluer la perte d'énergie contractile liée au retard de contraction. **Conclusion :** Les travaux réalisés ont permis de développer des outils pour mieux apprécier les conséquences de l'asynchronisme myocardique.

Mots clés : resynchronisation cardiaque, déformation myocardique, insuffisance cardiaque.

ABSTRACT

Background: Randomized studies demonstrated that Cardiac Resynchronization Therapy (CRT) improves symptoms and survival in heart failure patients with wide QRS duration that remains symptomatic despite optimal medical treatments. However, up to 40% of patients do not responde to CRT. The purpose of this work was to investigate the underlying mechanisms of mechanical cardiac dyssynchrony as to optimize the identification of responder to CRT. **Methods:** The first part of our study was to identify the accurate echocardiography method for quantifying of myocardial deformation and dyssynchrony (Tissue Doppler Imaging and Speckle tracking analysis). Next, we studied factors (myocardial scar and contractile reserve) interacting with myocardial dyssynchrony and response to CRT. Then, we developed and validated a mathematical model (strain delay index) to assess the wasted energy related to myocardial dyssynchrony **Results:** First we demonstrated that longitudinal strain computed from speckle tracking analysis was superior to tissue Doppler imaging in assessing myocardial dyssynchrony and function with a better correlation with outcome in heart failure patients. Next, we showed that mechanical dyssynchrony was not specific of electrical delay but was prevalent in scar segments. In addition, using dobutamine stress echocardiography, we demonstrated that contractile reserve in delayed segments greatly impacts on response to CRT. Then, we proposed and validated a mathematical model, the strain delay index, for assessing the wasted energy related to mechanical dyssynchrony. **Conclusion:** The mathematical model proposed in the present study to assess the impact of dyssynchrony on myocardial contractility allows a better identification of responder to CRT.

Key words: cardiac resynchronization therapy, myocardial deformation, heart failure.

SOMMAIRE

Introduction

Plusieurs études multicentriques, randomisées ont depuis plus de 20 ans validé la place de la resynchronisation cardiaque dans le traitement des insuffisants cardiaques. La stimulation triple chambre permet d'améliorer les symptômes et la survie des patients insuffisants cardiaques présentant un élargissement des QRS et restant symptomatiques malgré un traitement médical optimal. Cependant, le bénéfice de la resynchronisation sur le remodelage ventriculaire (réduction du volume télé-systolique >15%) n'est observé que chez 50 à 60% des patients bien que ces derniers présentent des QRS>120ms. Compte-tenu du surcoût et du risque d'implantation inutile, notre équipe et d'autres ont mené des travaux afin de mieux identifier les patients répondeurs. Parmi les causes permettant d'expliquer une réponse insuffisante à ce traitement figure l'hypothèse d'une absence d'asynchronisme mécanique malgré un asynchronisme électrique.

Cette thèse rapporte nos travaux portant sur l'asynchronisme mécanique dont l'objectif était d'améliorer l'identification des répondeurs à la resynchronisation cardiaque et de proposer une solution thérapeutique aux non-répondeurs. Dans la première partie de la thèse, nous rappellerons les bases et les conséquences physiopathologiques des blocs de conduction au cours de l'insuffisance cardiaque. Puis nous reverrons les résultats des études multicentriques validant la resynchronisation cardiaque et l'état de l'art sur le concept de l'asynchronisme mécanique. Enfin, nous décrirons les étapes de nos travaux qui nous ont permis de comprendre et de modéliser les conséquences de l'asynchronisme mécanique sur la contractilité myocardique.

Première Partie

Eléments généraux de physiologie

I. Mécanique ventriculaire gauche normale

1.1- Les cellules myocardiques

Au niveau des ventricules, les cardiomyocytes sont de larges cellules cylindriques. Ils représentent 75% du volume total du myocarde. Une fibre myocardique est une unité fonctionnelle contractile, constituée par un groupe de cardiomyocytes, maintenus entre eux par un réseau de fibres de collagène (**Figure 1**). Chaque myocyte est limité par un sarcolemme et contient des protéines contractiles, des mitochondries et des faisceaux de myofibrilles. Les mitochondries fournissent l'énergie nécessaire pour l'activité contractile cardiaque et les gradients ioniques transmembranaires, sous forme d'adénosine triphosphate.

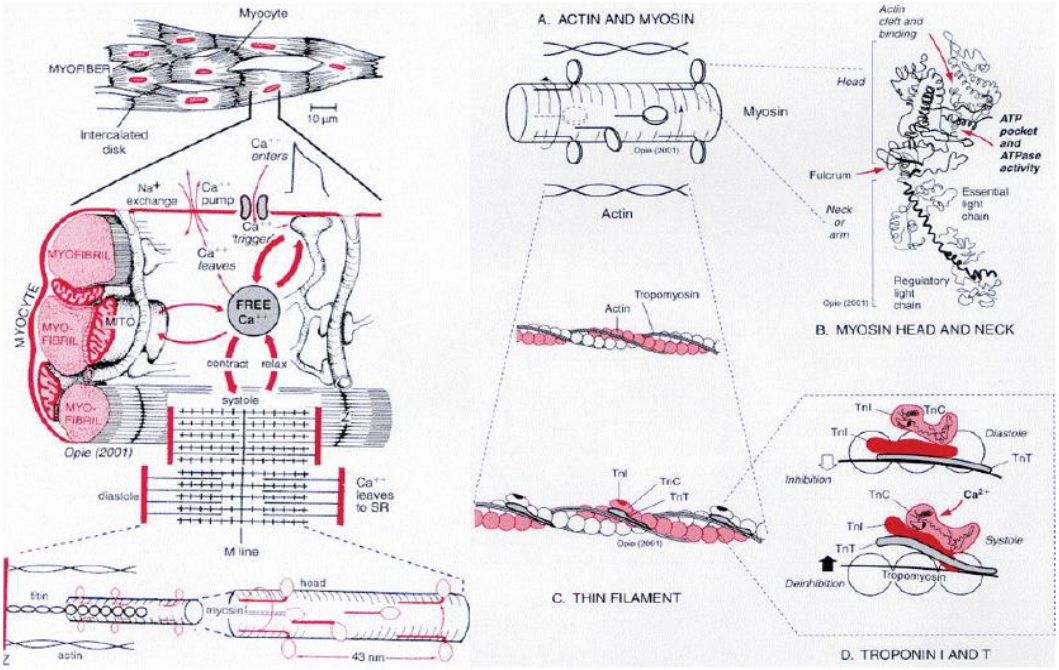


Figure 1 : Myocyte, fibre myocardique et protéines contractiles.
(Braunwald, Traité de Médecine Cardiovasculaire)

Le réticulum sarcoplasmique qui s'étend en un fin réseau à travers le myocyte, présente des renflements permettant les échanges calciques : le relargage du calcium dans le cytoplasme cellulaire permettant de déclencher la contraction cardiaque et son recaptage induisant la relaxation. Les concentrations calciques cytoplasmiques varient et contrôlent la contraction et la relaxation ventriculaire. La finalité de la contraction myocardique est d'assurer au cœur son rôle de pompe afin de maintenir un débit sanguin adéquat au besoin d'oxygène tissulaire. Cette contractilité est déclenchée par la stimulation électrique orchestrée par le nœud sinusal. L'activation électrique débute au nœud sinusal et se propage au nœud auriculo-ventriculaire puis dans le faisceau de His-Purkinje dont les fibres sont isolées du myocarde jusqu'à l'apex **(Figure 2)**[10].

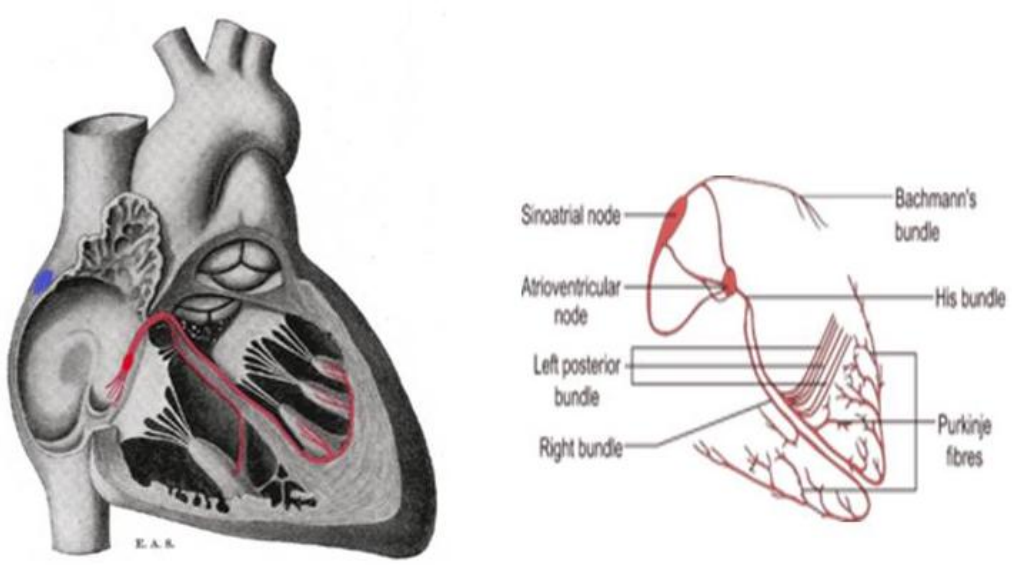


Figure 2: Représentation des faisceaux de conduction électrique: En rouge est représenté le nœud auriculo-ventriculaire, situé près du sinus coronaire. Le nœud auriculo-ventriculaire donne le faisceau de His qui se divise en fibres de Purkinje droit et gauche.

1.2- Activation électromécanique normale

La conduction électrique dans le myocarde est dite anisotrope (hétérogène) en raison de l'organisation architecturale des cellules myocardiques[11-14]. En effet, les cardiomyocytes sont organisés en myofibrilles. La propagation électrique est rapide et se transmet via les jonctions communicantes **(Figure 3)**. La vitesse de propagation dépend de la taille des cellules et du nombre et de la perméabilité des jonctions communicantes. Les fibres du faisceau de His-Purkinje possèdent des grandes cellules entourées de bandes de collagène avec de larges jonctions communicantes permettant une propagation rapide et linéaire du courant électrique. La dépolarisation cellulaire par les fibres du faisceau de His-Purkinje se fait au niveau de l'endocarde. Il n'y a pas de fibres de Purkinje dans les couches moyennes et épicardiques du myocarde. Au niveau du myocarde, les cellules myocardiques sont regroupées en lamelles avec grossièrement trois couches : sous-endocardique, moyenne et épicardique. L'orientation des couches est hélicoïdale avec une disposition longitudinale pour les couches les plus internes et externes et une disposition radiaire pour la couche moyenne. Les différentes couches sont connectées par des ponts cellulaires qui permettent la propagation de l'information électrique.

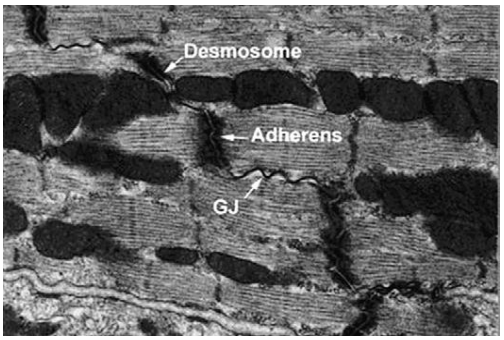


Figure 3: Microscopie électronique des zones de jonction.

Dépolarisation : Dans le myocarde normal, des modèles expérimentaux montrent que la dépolarisation débute en même temps sur les trois portions du septum[15]: sur la partie antéro-basale, sur la partie moyenne et postéro-apicale. L'ensemble de la couche sous-endocardique est dépolarisée par propagation de l'influx à travers les jonctions communicantes en 30ms. La paroi postéro-basale est la dernière à être dépolarisée **(Figure 4)**. Cependant, ce modèle n'est pas partagé par l'ensemble de la communauté scientifique et certains auteurs[16] pensent que la dépolarisation part du segment antéro-septo-basal et se propage vers la pointe. D'autres auteurs[17] montrent que le point de départ se situe au niveau de la région latéro-apicale et se termine à la base du ventricule gauche. La dépolarisation de l'endocarde vers l'épicarde se fait de couche en couche. Elle est plus lente car elle passe par des ponts cellulaires transversaux dont la propagation électrique dépend de l'angle d'orientation des cardiomyocytes.

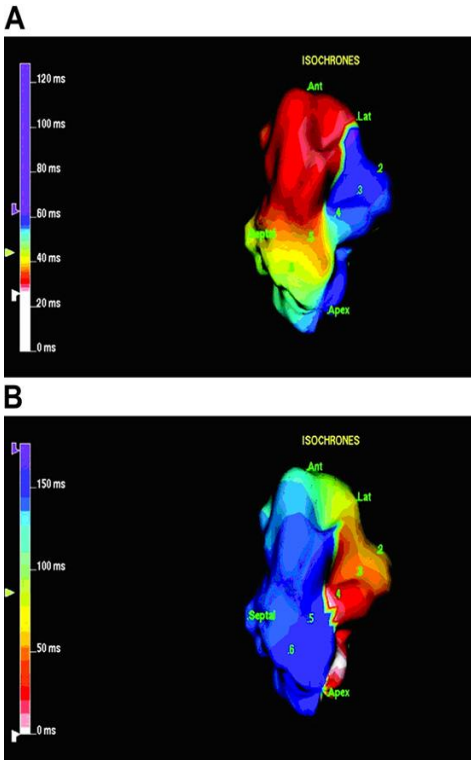


Figure 4: Cartographie des séquences de dépolarisation (A) et de repolarisation (B) de l'endocarde chez un sujet normal (adapté de Yue AM et al. Circulation 2005).

La repolarisation : les séquences de repolarisation restent peu connues et les résultats sont controversés. Pour certains, la repolarisation suit le chemin inverse de la dépolarisation avec une durée des potentiels d'action plus courte pour les couches les plus tardivement activées[10]. Pour d'autres, la repolarisation suit la même séquence d'activation avec un gradient base-apex.

Les séquences d'activation mécaniques : Les fibres myocardiques forment une structure hélicoïdale autour de la cavité ventriculaire gauche[4] **(Figure 5)**. Les fibres myocardiques partent du plan des anneaux valvulaires : les fibres les plus internes (endocarde) vont être orientées de façon parallèle à l'axe longitudinal (apex-base), puis tourner pour être radiales dans la couche moyenne et enfin se réorienter à environ 60° au niveau du sous-épicarde [3, 4, 18] **(Figure 6)**.

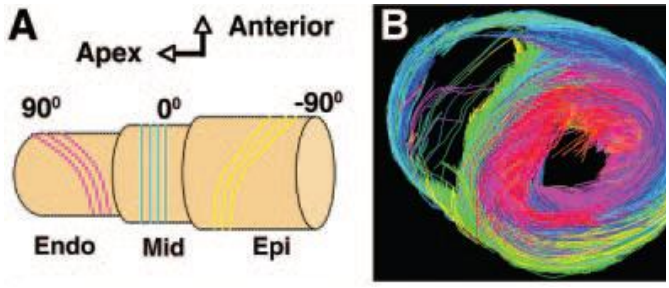


Figure 5 : modélisation de l'orientation des fibres myocardiaques en IRM de diffusion (d'après Sosnovik et al [3], Circ Cardiovasc Imaging 2009

Cette répartition hélicoïdale des fibres myocardiques permet de mieux comprendre la complexité des mouvements du myocarde qui peut se décomposer en raccourcissement longitudinal, épaississement radial et rotation. Le raccourcissement longitudinal assuré par la

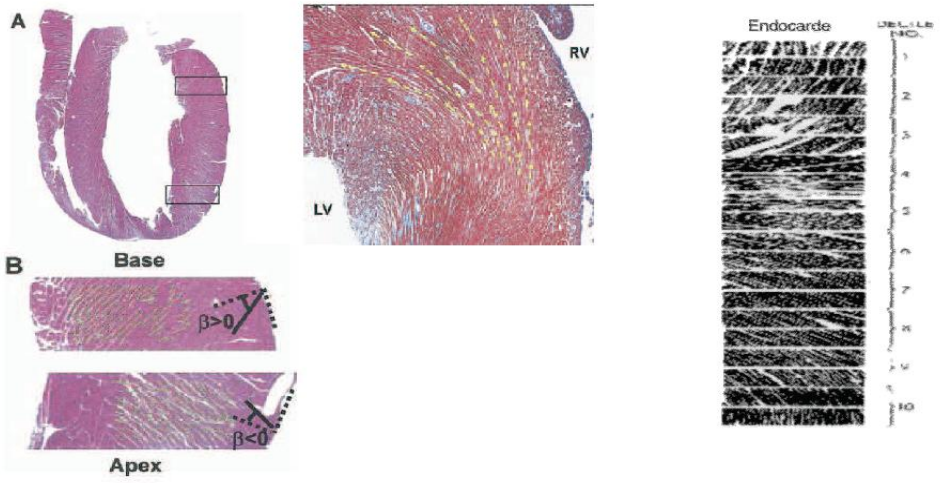


Figure 6: Représentations de l'architecture fibreuse ventriculaire gauche avec un changement d'orientation des fibres entre les différentes couches. (Streeter DD [4]. Circ Res 1969)

couche sous-endocardique est probablement l'une des composantes principales de la fonction pompe chez les grands mammifères [19] dont l'altération est la plus précoce dans l'insuffisance cardiaque [20]. L'épaississement radial est assuré par la couche médiane et la rotation par les fibres épicardiques. La disposition architecturale en couche hélicoïdale des fibres myocardiques et la distribution anatomique des fibres myocardiques sont responsables d'une anisotropie de conduction et de contraction myocardique. Cette anisotropie est supposée nécessaire pour assurer de façon optimale la fonction pompe.

La contraction isovolumétrique

débute de l'endocarde vers l'épicarde. La propagation transmurale mécanique est plus lente (0.25m/s) que la propagation électrique (0.49m/s). Il existe un gradient d'activation mécanique de l'endocarde vers l'épicarde **(Figure 7)**. Durant la contraction isovolumétrique, l'endocarde se contracte alors que l'épicarde s'étire. Cet asynchronisme mécanique endo-épicarde pourrait faciliter la propagation de l'influx électrique des couches externes en raison de la modification de l'orientation des fibres musculaires au cours de la systole ventriculaire[5, 6]. Les

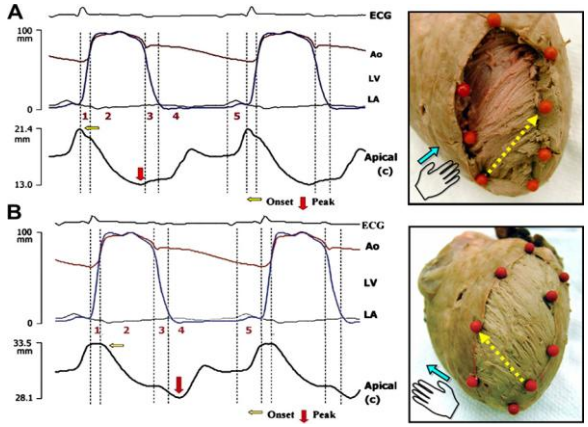


Figure 7: gradient d'activation mécanique endo-épicarde [6].

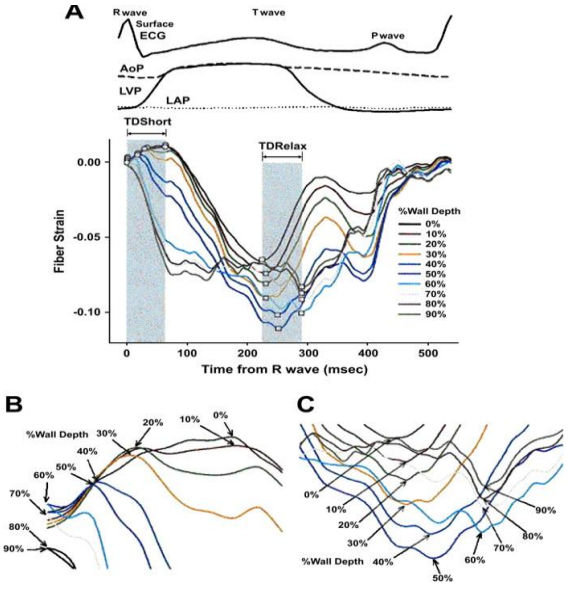


Figure 8: Anisotropie des amplitudes et délais de contraction de l'endocarde vers l'épicarde [5].

amplitudes de déformation sont plus importantes dans la couche sous-endocardique **(Figure 8)** et la déformation circonférentielle est plus importante que la déformation longitudinale quelque soit la couche étudiée. La déformation longitudinale survient plus tôt à la pointe qu'à la base. Il existe par ailleurs un gradient de déformation myocardique avec une déformation longitudinale et radiale plus importante à la pointe.

La relaxation est également hétérogène avec un gradient apex-base et endo- et épicarde. Ce gradient peut expliquer l'existence d'une déformation post-systolique chez les sujets normaux. Cet asynchronisme contribuerait à une relaxation plus rapide.

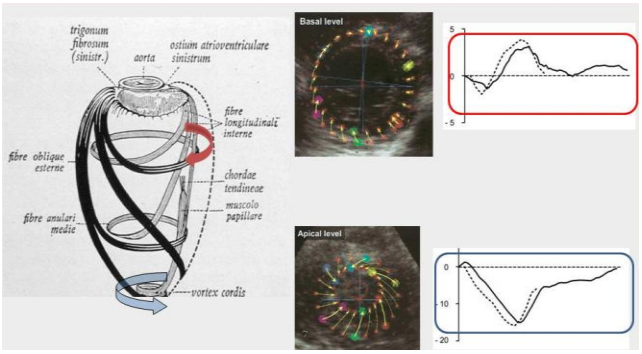


Figure 9: représentation de l'organisation des fibres myocardiques. La rotation horaire de la base et antihoraire de la pointe.

Mouvement de torsion : Le raccourcissement des fibres internes et externes longitudinales à orientation hélicoïdale participe au mouvement de rotation anti-horaire de l'apex et horaire de la base du ventricule gauche [21-24] **(Figure 9)**. Au niveau de l'apex, durant la contraction isovolumétrique, la couche longitudinale sous-endocardique se raccourcit en premier et entraîne une rotation horaire de faible amplitude (1-2°). Durant la systole, l'épicarde dont les fibres sont orientées dans le sens antihoraire se raccourcit et entraine une rotation anti-horaire (10-15°). Le mouvement global de la systole est dominé par la couche externe dont le moment des forces est plus important. Les mouvements de la base sont en miroir avec ceux de l'apex mais avec des angles de rotation plus faibles (**5**°). Le mouvement global du ventricule est celui de l'essorage d'une

serpillière. La détorsion se fait majoritairement durant la période de relaxation isovolumétrique.

II-Les modifications structurelles et fonctionnelles au cours de l'insuffisance cardiaque

2.1- De la fibrose aux troubles de conduction

Au cours de l'évolution de l'insuffisance cardiaque, un remodelage ventriculaire associant dilatation ventriculaire et hypertrophie excentrique est observé dans les cardiopathies ischémiques et non ischémiques. Ce remodelage ventriculaire semble être lié à l'activation répétée du système rénine-angiotensine-aldostérone, responsable de phénomènes d'apoptose cellulaire répétés. Sur le plan histologique, Beltrami[25] a observé sur des cœurs natifs de patients transplantés, que la réduction des cardiomyocytes était associée à une modification architecturale des cellules myocardiques. Ces cellules présentaient une hypertrophie prédominante dans le sens de la longueur et étaient réorientées dans le sens longitudinal. Ces changements morphologiques supposés réduire la contrainte pariétale contribuent à amincir la paroi et à favoriser la dilatation ventriculaire gauche. Ce remodelage va progressivement altérer la fonction contractile du myocarde mais peut entraîner par le biais de la fibrose des blocs de conduction électriques et entraîner un asynchronisme mécanique, des troubles du rythme par des phénomènes de réentrées électriques. Toutes les fibroses n'entraînent cependant pas des retards de conductions identiques. Tokuhiro Kawara[7] a

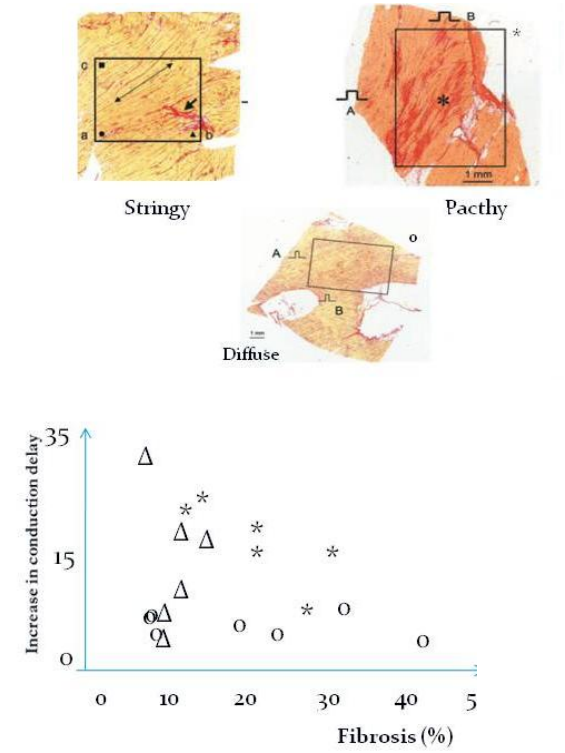


Figure 10: Relation entre fibrose et retard de conduction électrique [7]

démontré sur les cœurs de patients transplantés cardiaques que la fibrose diffuse entraînait peu de retard d'activation électrique, alors que les fibroses organisées pouvaient être responsables de lignes de bloc, indépendamment de leur extension transmurale **(Figure 10)**.

2.2- Epidémiologie des blocs de conduction

Sur les cohortes de suivi des patients insuffisants cardiaques, la majoration de la largeur du QRS est en moyenne de 5ms/an. Un élargissement du QRS≥120ms est retrouvé chez 30% (14-49%) des patients et la présence d'un bloc de branche gauche dans 15 à 27% des insuffisants cardiaques [26, 27]. La prévalence des blocs gauches augmente avec la sévérité de la dysfonction systolique et des symptômes [NYHA I (10%), II (32%) et III (53%)]. La présence d'un bloc de branche droit est plus rare (4-6%). L'élargissement des QRS>120ms expose les patients insuffisants cardiaques à des événements rythmiques plus fréquents [28] (tachycardie ventriculaire, mort subite). Le pronostic est encore plus défavorable dans le groupe de patients ayant un élargissement des QRS>120ms et une fraction d'éjection <35% [29] **(Figure 11).**

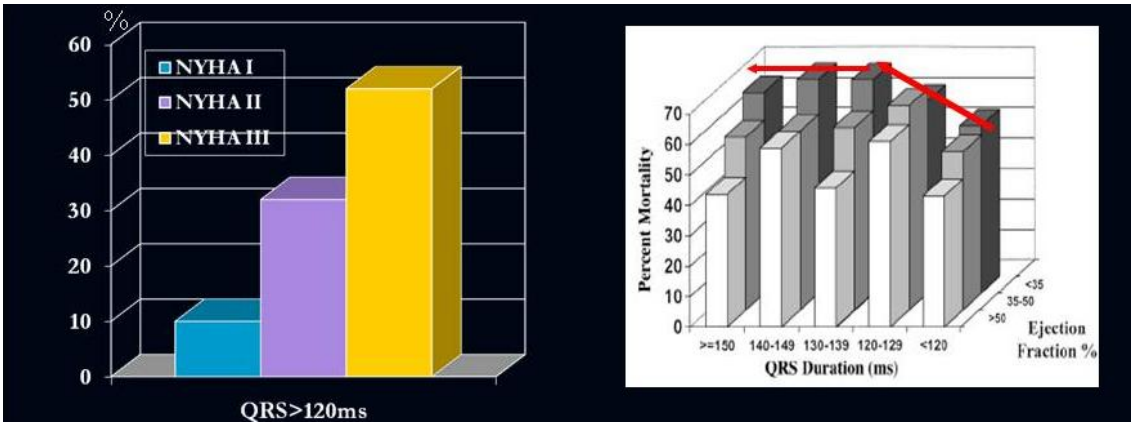
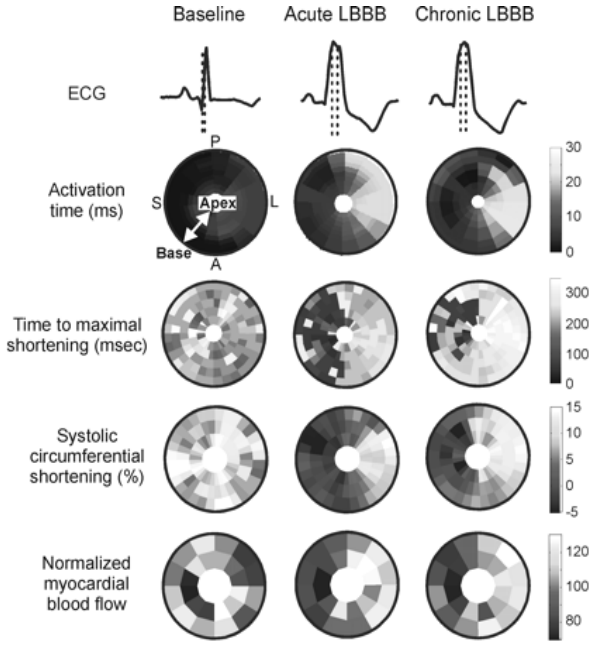


Figure 11: Prévalence de QRS larges selon la sévérité des symptômes (gauche) et pronostic en fonction de la largeur des QRS et de la fraction d'éjection ventriculaire gauche.

2.3- Conséquences de l'asynchronisme

a) Sur le plan électrique, un bloc de branche gauche entraîne une dépolarisation précoce du ventricule droit et du septum basal. Les autres parois sont dépolarisées par voie cellulaire. Cette dépolarisation de proche en proche est lente et se traduit par un retard marqué sur la paroi latérale et postéro-latérale[30] **(Figure 12)**.



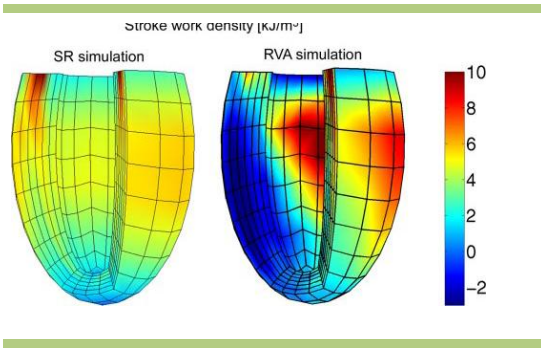


Figure 12: Distribution régionale du travail cardiaque en rythme sinusal (homogène) et en cas de bloc de branche gauche induit.

b) Sur le plan du rendement énergétique, les segments retardés ne vont pas pleinement contribuer à l'éjection systolique et sont responsables d'une réduction de la fonction systolique globale[31]. L'asynchronisme induit une augmentation régionale du stress pariétal et modifie l'interaction entre le ventricule droit et le ventricule gauche. La création d'un bloc de branche gauche par radiofréquence s'accompagne d'un déséquilibre métabolique et fonctionnel entre les parois du myocarde avec une réduction de la perfusion et de la contraction myocardique sur le septum[30]. A long terme, on observe une dégradation de la fonction ventriculaire gauche et un remodelage ventriculaire avec une augmentation des volumes ventriculaires et une hypertrophie excentrique. Sur le plan cellulaire et moléculaire

(Figure 13), il existe des modifications métaboliques et enzymatiques spécifiques[32-34] réversibles après resynchronisation cardiaque.

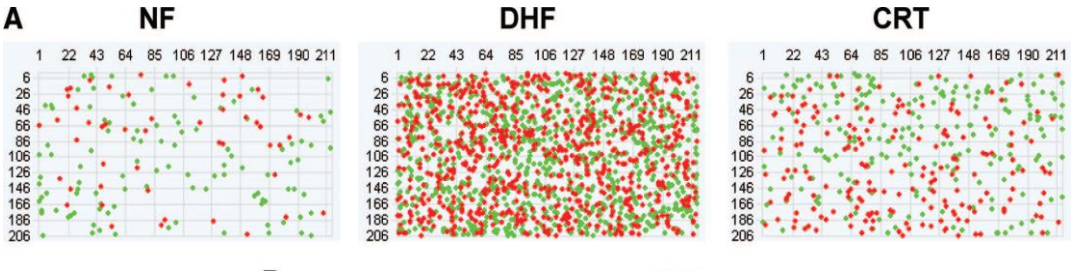


Figure 13: Représentation des résultats de microarrays montrant la modification de la transcription des gènes du métabolisme oxydatif de la paroi latérale avant (DHF) et après resynchronisation cardiaque (CRT). NF pour controle[35].

c) Sur le plan mécanique, le septum basal va se contracter très précocement durant la période de contraction isovolumétrique. Cette contraction est énergique (« septum flash ») car la pression dans le ventricule gauche est relativement faible[31]. Durant cette phase, la pointe du ventricule gauche et la paroi latérale encore au repos vont subir un étirement vers le septum basal. La propagation retardée de la dépolarisation va ensuite entraîner une contraction retardée de la paroi latérale qui va elle-même attirer vers la paroi latéro-basale la paroi septale. L'ensemble réalise un mouvement communément appelé le « rocking ». Cette désynchronisation des parois du myocarde contribue à altérer sa contractilité globale Ces phénomènes ont été reproduits sur un modèle animal dans un travail effectué à la Cleveland Clinic dans l'équipe du Professeur Don Wallick. L'objectif de ce travail était d'évaluer un algorithme de stimulation biventriculaire pour ralentir la fibrillation atriale. Au cours de ce travail, nous avons induit un bloc de branche gauche par stimulation du ventricule droit. Ce bloc de branche gauche expérimental était accompagné d'une majoration de l'asynchronisme mécanique et d'une réduction de la fraction d'éjection et des paramètres de déformation longitudinaux globaux. Ces anomalies étaient réversibles après resynchronisation cardiaque **(Figure 14).**

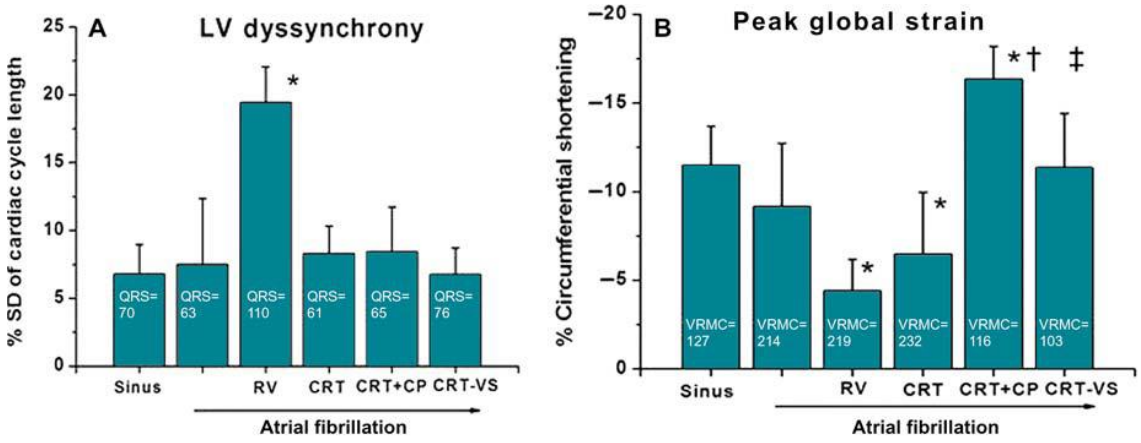


Figure 14 (A) Modification de l'asynchronisme mécanique, (B) et de la déformation longitudinale globale au cours de la stimulation ventriculaire droite (RV) et de la resynchronisation cardiaque.

d) Insuffisance mitrale : l'insuffisance mitrale fonctionnelle fréquemment observée chez les patients insuffisants cardiaques est un facteur de mauvais pronostic[35]. Dans cette population, le défaut de coaptation des feuillets mitraux est lié à une dilatation de l'anneau et un déséquilibre entre les forces de traction des cordages et la pression de fermeture des valves. La perte de coordination des piliers mitraux et la réduction de la contraction atriale et ventriculaire gauches liées à l'asynchronisme aggravent ce déséquilibre[8] et augmentent la sévérité de l'insuffisance mitrale surtout à l'effort [36-38] **(Figure 15)**.

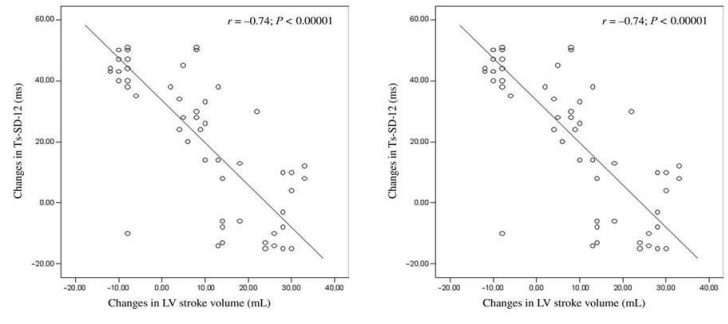


Figure 15: D'après D'Andrea[37]: L'augmentation de l'asynchronisme à l'effort est associée à la chute du volume d'éjection systolique et une augmentation de l'insuffisance mitrale.

Europace (2010) **12**, 430–436
doi:10.1093/europace/eup440

Coupled pacing improves left ventricular function during simulated atrial fibrillation without mechanical dyssynchrony

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Received 5 August 2009; accepted after revision 20 December 2009; online publish-ahead-of-print 29 January 2010

Aims Electrical stimulation [coupled pacing (CP)] applied near the end of the T-wave is able to create a retrograde activation of the atrioventricular (AV) node in turn to prevent rapid ventricular conduction during atrial fibrillation (AF). The impact of this pacing modality associated with cardiac resynchronization therapy (CRT) has been evaluated in the present experimental study.

Methods and results After inducing AF by rapid pacing in six dogs, we applied the following pacing modalities: rapid right ventricular (RV) pacing, rapid CRT, CRT with an additional RV paced beat (CP) at a specific delay (CRT + CP), and CRT with vagal stimulation (CRT-VS). Left ventricular (LV) pressure recordings and echocardiography for 2D strain analysis were performed. CRT + CP reduced the ventricular response rate and increased the LV systolic pressure and cardiac output compared with CRT alone (136 ± 6 vs. 86 ± 13 mmHg, $P < 0.05$ and 2.0 ± 0.4 vs.1.2 ± 0.1, $P < 0.05$ L/m, respectively). Compared with CRT-VS, CRT + CP increased the LV ejection fraction (LVEF = 51 ± 10 vs. 28 ± 4%, $P < 0.05$), peak global circumferential strain (−17 ± 2 vs. −11 ± 3%), and diastolic filling time (49 ± 6 vs. 28 ± 3%, $P < 0.02$) suggesting beneficial effects of CP beyond rate control. CRT + CP did not result in increased dyssynchrony [CRT (8.3 ± 2%) vs. CRTCP (8.4 ± 3%, P = NS)].

Conclusion CRT + CP effectively reduces ventricular contractile rate and leads to an increase in systolic and diastolic performance without inducing mechanical dyssynchrony.

Keywords Rate control • Cardiac resynchronization therapy • Atrial fibrillation

Introduction

Cardiac resynchronization therapy (CRT) has been shown to improve symptoms and survival in patients with systolic dysfunction and prolonged ventricular depolarization (wide QRS).[1–8] However, atrial fibrillation (AF) may cause significant problems in these patients, particularly when the ventricular rate exceeds the device programmable rate. Atrial fibrillation in heart failure patients is often clinically challenging,[9] and if poorly controlled, permanent atrioventricular (AV) nodal ablation when pharmacologic rate control is not possible may be required.[10] For the past 5 years, our laboratory has been studying the potential application of coupled pacing (CP) as a means of rate control when AF occurs.[11–14] Briefly, CP can be explained as follows: after sensing the intrinsic electrical activation of the ventricles which initiate mechanical contraction, an additional electrical stimulation (CP) is applied near the end of the T-wave. Coupled pacing is applied prior to the time that the ventricles are capable of fully contracting again. These critically timed retrograde activations of the AV node in turn prevent subsequent rapid ventricular activations that would have lead to weakened ventricular contractions. An additional advantage of CP in patients with AF and systolic dysfunction is that the CP beat increases contractility via the mechanism of post-extrasystolic potentiation.[15] Since premature stimulations have

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differential effects on Purkinje vs. ventricular muscle refractoriness,[16,17] there is some concern that CP may potentially alter the left ventricular (LV) electrical activation pattern during biventricular pacing. The goal of our study was therefore to better define the effects of CP during biventricular pacing (CRT + CP) on LV function and mechanical dyssynchrony.

Methods

The experimental protocol was approved by the Animal Research Committee of the Cleveland Clinic. All animals received humane care in compliance with the 'Guide for the Care and Use of Laboratory Animals'. The dogs ($n = 6$) were initially anesthetized with thiopental and maintained with isoflurane during positive pressure ventilation. A mid-sternotomy was performed and the heart was placed in a pericardial cradle. A quadrapolar plate electrode was sutured to the right atrium and was connected to a Grass stimulator for the induction of a pseudo AF. A second quadrapolar electrode was sutured on the right ventricular (RV) apex and was connected to the first channel of a Bloom stimulator for RV pacing as the protocol dictates. A third electrode was sutured on the lateral wall of the LV and connected to the second channel of our Bloom stimulator for LV pacing. The remaining two poles of these three quadrapolar electrodes were connected to our Ponemah™ system (Valley View, OH, USA) to record their corresponding electrograms: right atrial electrogram (RAE), right ventricular electrogram (RVE), and left ventricular electrogram (LVE). Finally, a bipolar plate electrode was sutured on the inferior vena cava–left atrial epicardial fat pad to stimulate the parasympathetic nerve that innervates the AV node to slow A–V nodal conduction.[18]

Pacing protocol

Five to ten minutes of each pacing paradigm was applied before obtaining the echocardiographic and invasive haemodynamic acquisitions. Step 1: With the animal in sinus rhythm (SR). Step 2: Subsequently, a simulated paroxysmal AF was induced by continuous rapid right atrial pacing (20 Hz, 1 ms, 3–5 V). Importantly, rapid atrial pacing was maintained continuously to ensure persistent AF for Steps 3–6.[11–13] Step 3: Application of rapid RV pacing (2 ms, 2–4 mA) at a ventricular rate greater than the resultant ventricular rate from rapid atrial pacing alone. The purpose of this rapid RV pacing was to prevent intrinsic ventricular activation over the AV node, thereby inducing dyssynchrony comparable with left bundle branch block (LBBB). Step 4: CRT: Rapid simultaneous biventricular pacing (both channels of the Bloom stimulator set at 2 ms, 2–4 mA) allowing capture by both ventricles in the presence of rapid simulated AF. Step 5: CRT + CP: Simultaneous biventricular pacing (both channels of the Bloom stimulator), followed by an additional stimulation of CP (first channel of the Bloom stimulator) which was applied only to the RV lead near the end of the T-wave. This was done by increasing the basic cycle length during biventricular pacing by ~50% above the length used in Step 4 (CRT alone). We subsequently added CP stimuli at a delay of 250 ms. This delay was then progressively shortened until we observed by both echocardiographic and LV pressure recordings that CP resulted in only minimal LV mechanical contractions (not leading to effective ejection). By adding CP, we were able to finally reduce the biventricular pacing rate to a rate close to SR. Step 6: vagal stimulation (CRT-VS): CRT capture enabled by reducing the ventricular rate response during rapid AF with selective stimulation of the parasympathetic nerves which innervate the AV node (pulses = 20 Hz, 0.1 ms, 10 mA). At this level of intensity, this selective and limited stimulation of the preganglionic parasympathetic fibres projection towards the AV node[18] slowed the rate of ventricular activation from the atria without negative inotropic effect. This allowed applying the CRT at a rate also similar to the SR. In this study, we chose not to apply CP to the LV for the following reasons: (1) The timing of retrograde activation of the AV node/His system would have been difficult to control if left ventricular CP had been applied in the presence of intrinsic LBBB. However, LBBB was not present in our study. (2) Since scar tissue would most likely be in the LV, applying CP close to scar tissue may theoretically increase the risk of fatal arrhythmias.[19] Thus for these reasons, we chose to evaluate the effects of CP when it was applied only from the RV.

Epicardial echocardiographic data

Echocardiographic acquisitions were performed with a Vivid 7 machine (GE Healthcare). During these periods, we turned off the aortic flow meter in order not to interfere with the Doppler measurements from the echocardiograph. The time intervals between two Doppler LV outflow peaks were used to determine the cardiac period. These integrated velocity profiles, times aortic cross-sectional area, were used to obtain an estimate of stroke volume (SV). Left ventricular contractile function was quantified by measuring (1) left ventricular ejection fraction (LVEF) and (2) the peak circumferential global LV strain by speckle tracking. Left ventricular ejection fraction was computed from standard apical views by using Simpson's biplane method. Global circumferential strain curve was derived from the 2D short axis view (basal segment) using 2D strain analysis (EchoPac, GE Healthcare). Peak circumferential global strain was defined as the minimal strain value during cardiac cycle. Left ventricular dyssynchrony was calculated as the standard deviation (SD) of the time (%) to peak circumferential strain of these six different segments with a larger SD indicating an increasing degree of dyssynchrony. Diastolic filling time [duration of the early diastolic filling wave (*E*) during AF or the sum of *E* and late diastolic filling wave (*A*) during SR] was normalized to cardiac cycle for variability in cycle length. All echocardiography parameters used were obtained by averaging five consecutive values.

Haemodynamic data

A Millar™ pressure transducer (Houston, TX, USA) was inserted into the LV in order to record pressure. In addition, we placed a Transonic™ flow probe (Ithaca, NY, USA) around the ascending aorta for cardiac output (CO) measurements. For CO measurement, SV was averaged over 15 cardiac cycles for each step. During the whole experiment, all dogs were invasively monitored to maintain haemodynamic parameters at similar levels.

Statistical analysis

Analysis of variance was used to determine if altering the pacing paradigms significantly changed any measurements. All continuous variables were expressed as means ± SE. We made paired comparisons between the first five steps. All statistical tests were two sided and a probability of <0.05 was considered significant.

Results

Representative experiment

Figure 1 shows representative tracings of the electrical activation sequences and haemodynamic responses. The first step was SR (*Figure 1A*). The response to rapid AF (Step 2) is illustrated in Panel B. In Step 3 (*Figure 1C*), we induced AF and then applied rapid RV pacing in addition to the AF. In Step 4 (*Figure 1D*), we

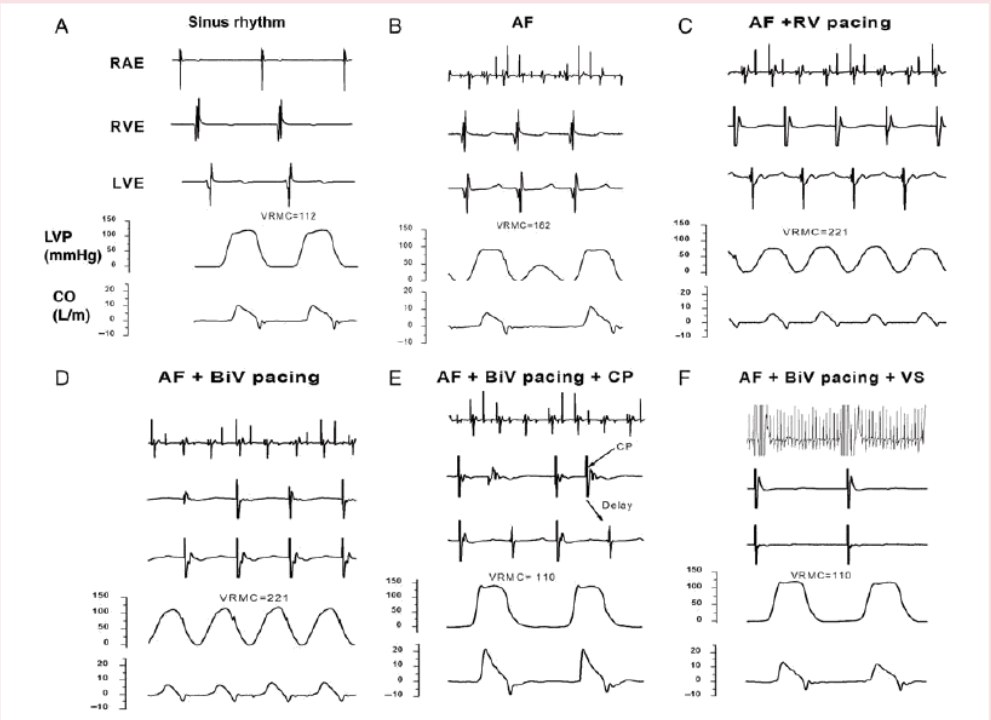

Figure 1 Representative tracings digitally extracted using the Ponemah system and then plotted with Origin graphic software. See Results section for further details.

applied CRT at a rate sufficient to provide ventricular pacing independent of supraventricular activation. In Step 5 (*Figure 1E*), we were able to apply CRT at a similar rate to SR despite the continual AF because we added the CP. Also, note that the activation of the LV is delayed following the CP because this paced beat is initiated from the RV electrode. Finally in Step 6 (*Figure 1F*), we were able to apply CRT at a rate similar to SR because the AV node was suppressed by the selective stimulation of the parasympathetic nerve. Video 1 (Supplementary material online) shows LV function during the pacing paradigms. The corresponding line diagrams below the video illustrate the circumferential strain curves with the dotted line representing the global strain. The left panel (Step 1) of this video shows the results obtained during SR. The next panel illustrates the effect of RV pacing on LV dyssynchrony after AF has been induced (Step 3). The middle panel shows the effect of rapid CRT (Step 4). In spite of CRT, a decrease can still be observed in the peak global strain. The next panel subsequently illustrates the effect of CRT + CP, resulting in a dramatic increase in the peak global strain (Step 5). Importantly, application of CP did not result in increased ventricular dyssynchrony. Finally (Step 6), we tried to differentiate the effects of CP from those of rate control alone achieved by selective parasympathetic nerve stimulation of AV nodal tissue (CRT-VS). Peak global strain is improved compared with rapid CRT, but not to the extent of CRT + CP.

Composite results

Impact of CRT + CP on LV mechanical dyssynchrony

The average LV dyssynchrony during SR and rapid AF was $\sim 7 \pm 2$ and $8 \pm 3\%$ (*Figure 2A*). Rapid RV pacing with AF increased LV dyssynchrony to an average of $19 \pm 3\%$ ($P < 0.0001$ vs. SR and AF), while the application of CRT reduced the extent of LV dyssynchrony, virtually back to the level of SR (SD = $8 \pm 3\%$). The application of CP (CRT + CP) from only the RV did not increase LV dyssynchrony (SD = $8 \pm 3\%$). The average time delay of CP from CRT for these six animals was 160 ± 11 ms. Finally, the CRT with parasympathetic nerve stimulation of the AV node (CRT-VS) did not change the extent of LV dyssynchrony compared with SR or CRT alone (SD = $7 \pm 2\%$, NS). The average corresponding QRS duration during each step is shown in the bars of *Figure 2A*.

Impact of CRT + CP on LV systolic function

During SR, the average peak global strain was $-12 \pm 2\%$ (*Figure 2B*) when the ventricular rate of mechanical contractions

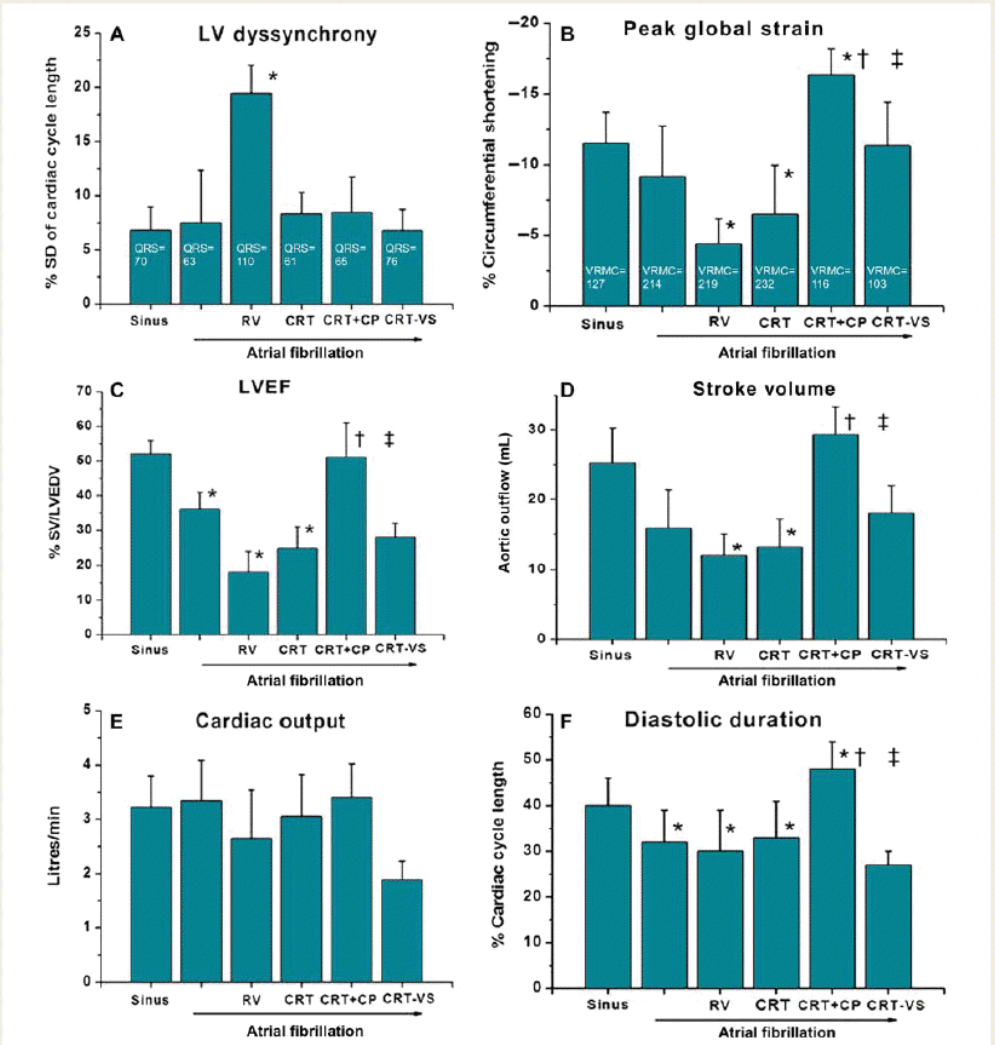

Figure 2 (*A*) Changes in LV dyssynchrony, (*B*) average strain, (*C*) LV ejection fraction, (*D*) stroke volume, (*E*) cardiac output, and (*F*) LV percentage of diastolic duration, during the six stages of this study. (*) for $P < 0.05$ vs. baseline, (†) for $P < 0.05$ vs. RV pacing, (‡) for $P < 0.05$ vs. CRT.

(VRMC) was 127 ± 17 c.p.m. With the induction of acute AF, the peak global strain decreased to −9 ± 6% and to −4 ± 2% when RV pacing was added to AF. The application of CRT during acute AF + RV pacing did not improve significantly the peak global strain (−6 ± 3%). The addition of the CP beat (CRT + CP) increased peak global strain to a level that was even greater than that found during SR (−17 ± 2%, $P < 0.05$). The average VRMC during CT + CP was 116 ± 17 c.p.m. The reduction in VRMC (103 ± 14 c.p.m.) during CRT-VS improved the peak global strain, until it approached values obtained in SR (−11 ± 3%).

Left ventricular ejection fraction closely followed the changes in global strain. Left ventricular ejection fraction decreased from 52 ± 4 to 36 ± 5% with rapid AF and to18 ± 6% (*Figure 2C*) with both AF and RV pacing. Although the resynchronization of the rapid contractions did not significantly improve the LVEF (25 ± 6%) compared with rapid RV pacing, a dramatic increase

Table 1 Measurements and derived parameters of the left ventricular pressure and aortic flow

	Sinus rhythm (Step 1)	AF (Step 2)	AF + RV pacing (Step 3)	AF + BV pacing (Step 4)	AF + BV pacing + CP (Step 5)
VRMC# (contractions/m)	122 ± 5	164 ± 14*§	211 ± 17*§	196 ± 24*§	115 ± 8
CCL# (ms)	494 ± 19	370 ± 30*§	302 ± 28*§	335 ± 47*§	535 ± 39
LVSP# (mmHg)	108 ± 7	102 ± 10§	86 ± 13§	102 ± 8§	136 ± 6
+dP/dt# (mmHg/s)	2228 ± 114	2490 ± 115	2088 ± 182§	2325 ± 121§	3719 ± 382*
−dP/dt# (mmHg/s)	2525 ± 164	2413 ± 698	1733 ± 291	2277 ± 332	3007 ± 664
Systolic time# (ms)	235 ± 5	186 ± 13*	165 ± 16*	180 ± 16*	194 ± 7
% Systole# (% diastole)	48 ± 1 (52)	50 ± 1 (50)	57 ± 4§ (43)	57 ± 5§ (43)	37 ± 2 (63)
Tau# (ms)	57 ± 11	67 ± 12	120 ± 34	75 ± 19	69 ± 13
SV# (mL/beat)	17 ± 4	11 ± 5	5.3 ± 1.4*§	6.6 ± 1.6*§	17 ± 3
CO# (L/min)	2.1 ± 0.4	1.7 ± 1	1.1 ± 0.2*§	1.2 ± 0.1*§	2.0 ± 0.4

VRMC, ventricular rate of mechanical contractions; CCL, cardiac cycle length; LVSP, left ventricular systolic pressure; dP/dt and −dP/dt, peak rate of rise and fall of LV pressure; ST, systolic time (time from LV end-diastolic pressure to peak −LV dP/dt); % Systole, [(ST/CCL) × 100]; % Diastole, remaining per cent of CCL; Tau, the time constant of isovolumic relaxation; CO, cardiac output; SV, stroke volume (SV = CO/VRMC). Changing overall the above pacing paradigms significantly alter the above parameters, #$P < 0.05$. Then we performed paired comparisons (*t*-test with Bonferroni correction). (*) for $P < 0.05$ vs. baseline, (§) for $P < 0.05$ vs. CRT + CP.

in LVEF was observed by adding CP to CRT (51 ± 10 vs. 25 ± 6%, $P < 0.05$). That is, the LVEF was virtually equal to SR ($P > 0.05$) despite the presence of AF. With parasympathetic nerve stimulation added, LVEF (28 ± 4%) was unchanged compared with CRT alone (25 ± 6%, $P > 0.05$).

During SR and AF, SV by the echocardiography method (*Figure 2D*) was 25 ± 5 and 16 ± 5 mL, respectively. With acute AF and rapid RV pacing, the SV decreased significantly ($P < 0.05$) to 12 ± 3 mL. The application of CRT during acute AF did not significantly improve the SV, which remained lower than SR (13 ± 4 vs. 25 ± 5 mL, $P < 0.05$). The addition of the CP beat (CRT + CP) increased SV (29 ± 4 mL) to a level slightly greater than that found during SR. The SV during CRT-VS was 18 ± 4 mL.

The echocardiographic measurements of CO (*Figure 2E*) did not significantly change, probably because of the variability of SV echocardiography measurement which may be challenging during epicardial echocardiography. In contrast, CO measurements via the transonic flow meter (Table *1*) showed that AF alone or with RV pacing and rapid CRT both significantly reduced CO. Interestingly, the changes in global circumferential strain by CRT + CP were concordant with similar increases observed in the invasively derived peak rate of LV pressure development (+LV dP/dt) and SV by the high-fidelity pressure transducer and flow probe (Table *1*).

Impact of CRT + CP on LV diastolic filling time and LV diastolic properties

Diastolic filling time was 40 ± 6% of cardiac cycle during SR (*Figure 2F*), decreasing to 32 ± 7 and 30 ± 9% during AF alone and with RV pacing, respectively. In spite of reducing LV dyssynchrony with rapid CRT, diastolic filling time remained unchanged with CRT (33 ± 8%). With CP, however, diastolic filling time increased significantly (48 ± 6%, $P < 0.05$ vs. CRT alone). A notable improvement in LV diastolic properties (−dP/dt, Tau, and invasively calculated duration of diastole shown in Table *1*) was equally observed. It should be noted, however, that contrary to echocardiography where diastolic filling time is limited to the inflow of blood into the LV, the invasively derived duration of diastole includes a portion of the isovolumic relaxation time. In spite of the reduction in rate by CRT + VS, no notable changes in diastolic filling time were noted with vagal AV node stimulation (27 ± 3%).

Discussion

Our study highlights the potential benefit role of right ventricular CP for providing ventricular rate control during simulated paroxysmal AF. This rate control leads to a significant improvement in both LV systolic and diastolic function as documented by both invasive and echocardiographic methods. This study did not address changes in atrial electrical or mechanical properties that would change with the development of AF. In addition, contrary to previous concern,[16,17] these effects were achieved without causing mechanical dyssynchrony.

While the beneficial effects of CRT have been well documented in previous studies,[1–8] rapid AF often occurs in heart failure population and results in acute clinical deterioration of the functional status.[9] Routine biventricular pacing usually does not allow rapid tracking of the atrial rate in acute AF because of the potential for inducing ventricular tachycardia. Although conventional methods of slowing AV nodal conduction may be sufficient to normalize LV function in rapid AF, these clinical strategies of rate reduction by pharmacological agents may not, in some cases, be well tolerated. In case of drug-refractory atrial tachycardia, AV nodal ablation with permanent pacemaker implantation or pulmonary vein isolation is sometimes necessary, procedures that each carry significant risks.[9,10] On the basis of our results of global strain, ejection fraction, and SV, the acute effects of the ventricular tachycardia as the result of acute AF appear to be the major cause for the acute reduction of systolic function. The application of CP to the right ventricle permitted a reduced rate of biventricular pacing needed for synchronized contractions in the presence of acute AF. Our findings show that CP has considerable

potential as a new pacing paradigm by reducing the rate of ventricular contractions, increasing systolic function, and maintaining CO. We therefore believe that the concept of CP deserves further attention, and the most reasonable initial application would be the implementation of CP in patients who already have a biventricular device. Modern and elaborate algorithms associating electrical and mechanical (*dP/dt* measurement) sensing could be used to appropriately apply CP when AF occurs. Instead of switching into pacing mode of ventricular inhibited pacing with rate modulation (VVIR) when the atrial rate exceeds a prescribed limit, CP would then theoretically allow further application of CRT at a rate similar to that prior to the induction of supraventricular tachycardia. The addition of CP to biventricular pacing effectively reduces the ventricular rate by approximately one-half in the presence rapid AF. The electrical wave front from the coupled beat would travel retrogradely into the AV node and block approximately half of the supraventricular activations of the heart. This mode of pacing permits the biventricular pacing to be maintained at a rate similar to that prior to the AF. Particularly, patients with advanced systolic dysfunction may benefit from CP as the supplemental beat will increase contractility by the mechanism of 'post-extrasystolic potentiation' due to an increased intracellular release of calcium.[15] This concept is not entirely novel as 'paired stimulation' was first proposed as a heart failure therapy more than 40 years ago.[20–22] However, in these previous studies, paired stimulation was achieved by continuously applying two closely paced stimuli to the RV. It is now well known that continuous RV pacing may eventually lead to adverse effects because of chronic LV mechanical dyssynchrony.[23] Our findings suggest, however, that when added to CRT, right ventricular CP does not induce significant LV mechanical dyssynchrony assessed by 2D strain echocardiography. Since stimuli are applied near the end of the T-wave; there is a theoretical risk that these stimuli could induce ventricular tachycardia, which might lead to ventricular fibrillation. However, extending the delay of coupled stimuli still maintains improved global cardiac function, while reducing the risk of ventricular arrhythmias as shown earlier by our group.[13] In addition, Mischke *et al.* [24] have recently demonstrated that paired ventricular stimulation can be safely delivered during ventricular tachycardia in patients with predominantly ischaemic LV dysfunction. We do believe, however, that the first clinical application of this pacing concept should best be reserved for patients with an internal cardiac defibrillator system, allowing immediate termination of any ventricular tachycardia if it would occur.

Limitations

Our study was performed in the acute heart failure model with systolic LV dysfunction induced by rapid AF and RV pacing and not during chronic heart failure with AF and left branch block. Thus, we acknowledge that our experimental model of pacing-induced LV dysfunction has significant limitations mimicking the complexity of human heart failure. First, RV pacing cannot be assimilated to a LBBB occurring in fibrosis myocardial tissue despite similar mechanical impact with LV dyssynchrony and myocardial dysfunction. Safety and efficiency of CRT + CP may differ in chronic heart failure with less gain in contractility and a higher risk of ventricular tachycardia expected. Therefore, a specific algorithm to determine optimal delay to deliver CP has to be addressed in future study in this setting. However, we believe that the use of this oversimplified model has been helpful in assessing the feasibility and the efficiency of this new pacing algorithm.

Conclusion

The application of CP to CRT during rapid AF in this experimental model of LV systolic dysfunction allows effective ventricular rate control without inducing LV dyssynchrony. In addition, this new pacing modality increases myocardial contractile performance and diastolic properties to a greater extent than observed by simply slowing AV nodal conduction.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: R.A.G. has received consulting fees from GE Healthcare, Medtronic, and St. Jude Medical, honoraria from GE Healthcare and Medtronic, and grant support from Medtronic. The other authors report no conflicts of interest.

Funding

This study was supported by the Ohio Valley Affiliate grant-in-aid of the AHA and a Product Development Fund Grant of the Cleveland Clinic.

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IMAGES IN ELECTROPHYSIOLOGY

doi:10.1093/europace/eup439
Online publish-ahead-of-print 26 January 2010

Interventricular septum haematoma following CRT-D implant

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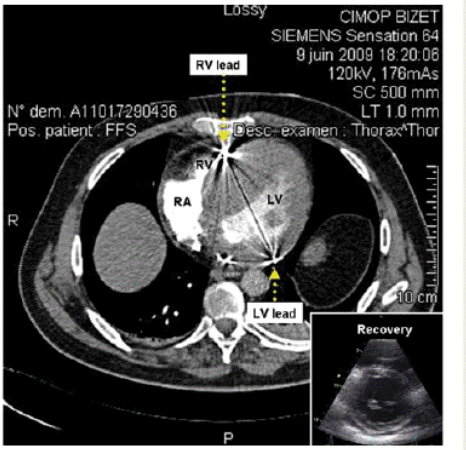
After CRT-D implant, the patient complained of chest pain and presented with frequent polymorphic premature ventricular contractions. Echocardiogram, and subsequent CT-scan (*Figure*), demonstrated a large interventricular septum haematoma (septal thickness 4 cm), probably related to a damaged coronary subsidiary caused by the right ventricular screw-in lead, although no coronary angiogram was performed due to patient instability. The patient status improved and the haematoma spontaneously resolved over 6 weeks with a normal septum on post-recovery echocardiography (*Figure*, inset). RV/LV, right ventricle/left ventricle; RA, right atrium.

Conflict of interest: none declared.



Deuxième Partie

Essais cliniques et recommandations de l'ESC

I- Validation et Recommandations pour les patients en stade NYHA III-IV

La resynchronisation cardiaque est un concept ancien, rapporté depuis les années 1970[39-41]. Son développement technique et les premiers essais de validation clinique ne débutent qu'au début des années 90 sous l'impulsion de groupes français[42, 43]. Depuis, plusieurs études randomisées multicentriques ont été menées[43-49]. Les résultats ont été résumés dans le **Tableau 1**. Ces études ont été menées dans un premier temps sur des patients symptomatiques (stade III-IV), en rythme sinusal avec des QRS larges (>120ms). Elles ont montré un effet bénéfique sur le plan clinique et sur le remodelage ventriculaire gauche.

Trial	n	NYHA	LVEF	SR/AF	QRS	ICD	End points	Design	Findings
MUSTIC-SR	58	III	≤35	SR	≥150	NO	6'WT, V02, Hosp	Single blinded, cross over 6 month FU	improved 6MWT, V02, reduced Hosp
MIRACLE	453	III-IV	≤35	SR	≥130	NO	NYHA, V02	Double blinded, 6 month FU	Improved NYHA, V02,
MUSTIC AF	43	III	≤35	AF	≥200	NO	6'WT, V02, Hosp	Single blinded, cross over 6 month FU	improved 6MWT, V02, reduced Hosp
PATH-CHF	41	III-IV	≤35	SR	≥120	NO	6'WT, V02	Single blinded, cross over 12 month FU	improved 6MWT, V02
MIRACLE ICD	369	III-IV	≤35	SR	≥130	YES	6'WT, Hosp	Double blinded, ICD vs. CRT-ICD 6 month FU	CRT-ICD improved from baseline Not ICD alone
CONTAK ICD	227	II-IV	≤35	SR	≥120	YES	6'WT, V02, death, LVEF, EDV	Double blinded, ICD vs. CRT-ICD 6 month FU	CRT-D Improved V02, 6'WT, LEVF, EDV, no mortality reduction
MIRACLE ICD II	186	II	≤35	SR	≥130	YES	6'WT, V02, LVEF, LV volumes	Double blinded, ICD vs. CRT-ICD 6 month FU	CRT-D improved LV volumes, LVEF
COMPANION	1520	III- IV	≤35	SR	≥120	YES/NO	All death/Hosp	Double blinded, OMT vs. CRT-D vs. CRT-P /15 months	CRT-D/CRT-P reduced mortality and hospitalisation
CARE-HF	814	III- IV	≤35	SR	≥120	NO	Death and MACE	Double blinded, OMT vs. CRT-P 29 months	Reduced death and MACE
REVERSE	610	I-II	≤40	SR	≥120	YES/NO	ESV, hosp and death	Doubled blinded, OMT vs. [CRT-P or CRT-D]-12months	Primary end point not reach Reduced ESV and hosptitalisation
MADIT CRT	1800	I-II	≤30	SR	≥130	YES	HF or death/ESV	DAI vs. CRT-D 2.4 years	CRT-D reduced HF event or death but not death alone. Reduced ESV

Table I : *Résumé des études multicentriques randomisées validant la resynchronisation cardiaque chez les patients ayant des QRS≥120ms.*

Recommandations[50, 51]**:** Aux vues de ces données, le comité d'experts de l'ESC recommande l'implantation soit d'un défibrillateur triple chambre soit d'un stimulateur triple chambre chez les patients symptomatiques (NYHA III-IV) avec un traitement optimal, une FEVG≤35%, en rythme sinusal et un élargissement du QRS≥120ms (niveau de recommandation grade I, niveau de preuve A). Les experts recommandent une resynchronisation cardiaque pour les patients en stade NYHA IV, uniquement chez ceux dont l'espérance de vie est supérieure à 6 mois. Par ailleurs, ces patients doivent être ambulatoires, c'est-à-dire ne pas avoir été hospitalisés dans le mois avant resynchronisation cardiaque. Chez les patients en stade NYHA III-IV, nécessitant une stimulation permanente pour un bloc de conduction de haut degré, une stimulation triple chambre est recommandée pour éviter l'effet délétère de la stimulation ventriculaire droite (niveau de recommandation II-a, niveau de preuve C).

Les bénéfices cliniques : La resynchronisation cardiaque permet d'améliorer les symptômes, la distance de marche et le pic de consommation d'oxygène (+15 à 20%). La réduction des hospitalisations pour récidive d'insuffisance cardiaque est importante (-52% dans CARE-HF, -76% dans COMPANION[48]). La réduction de la mortalité a été démontrée dans l'étude CARE-HF[1]. Le bénéfice sur la mortalité avait cependant été très discuté dans l'étude COMPANION[48] **(Figure 16).** Cette étude comprenait trois groupes : un groupe

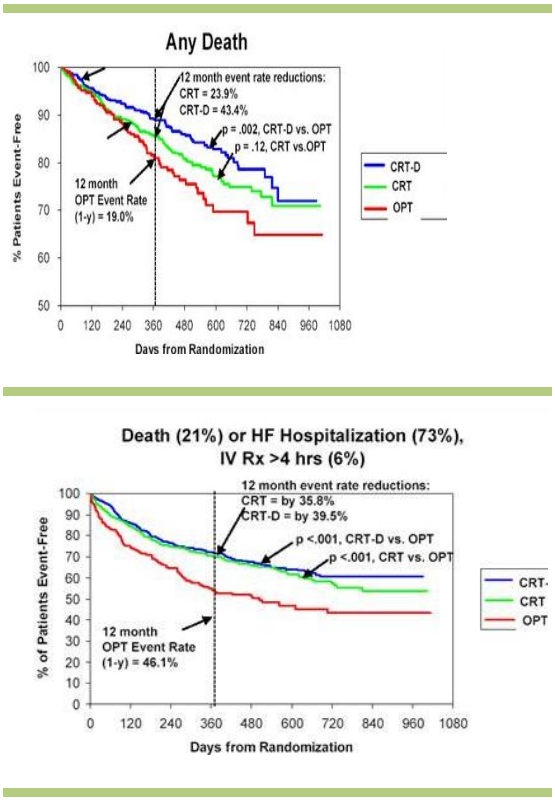


Figure 16 : Résultats de l'étude COMPANION montrant une réduction de la mortalité non significative dans le groupe CRT sans DAI

contrôle, un groupe CRT avec défibrillateur et un groupe CRT sans défibrillateur. Dans le groupe CRT avec défibrillateur, la réduction de la mortalité était de 36% (p=0.0003 *vs*. traitement médical optimal) contre 24% dans le groupe CRT sans défibrillateur (p=0.059 *vs*. traitement médical optimal). Cette analyse de sous-groupe non planifiée n'exclut pas un manque de puissance.

Dans l'étude CARE-HF[1] évaluant le bénéfice de la resynchronisation cardiaque sans défibrillateur, la réduction relative de la mortalité était de 36% (p<0.0002 *vs*. traitement médical optimal) après 29 mois de suivi. Il est important de souligner la nette réduction des morts subites (-46%) dans le groupe resynchronisé **(Figure 17).**

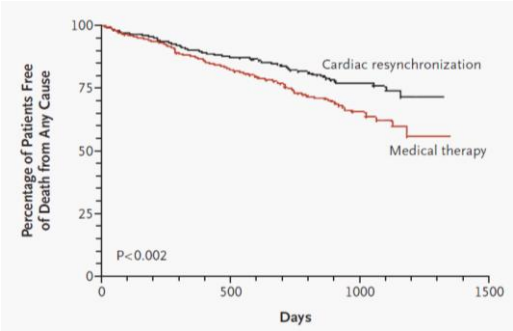


Figure17: Résultats de CARE-HF[1] montrant +36% de survie dans le groupe CRT

Remodelage inverse : Le bénéfice clinique est associé à un remodelage inverse observé à 6 mois de la resynchronisation cardiaque. Dans l'étude CARE-HF, la réduction du volume télé-systolique est de 18% à 3 mois et de 26% à 18 mois. Ce remodelage inverse est associé à un gain de contractilité avec une amélioration de la fraction d'éjection de 3,7% à 3 mois et de

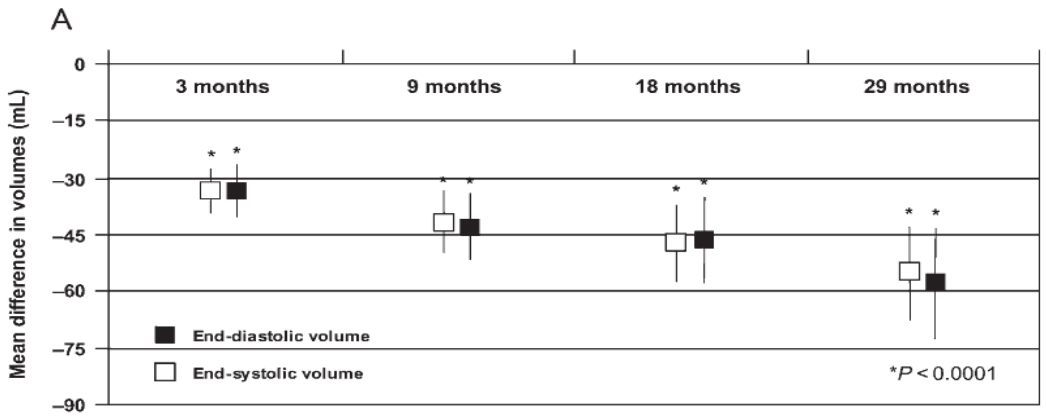


Figure18: Remodelage inverse après resynchronisation, données d'après CARE-HF.

6,9% à 18 mois.

Insuffisance mitrale : Une réduction de l'insuffisante mitrale peut être observée immédiatement après la resynchronisation cardiaque chez 43% des patients. Cette amélioration rapide semble être liée à une resynchronisation des parois ventriculaires et de l'appareil sous-valvulaire mitral. A distance de la resynchronisation cardiaque, la réduction du volume ventriculaire gauche entraîne une réduction de la fuite mitrale chez 20% des patients resynchronisés[8]. Cette réduction est associée à une augmentation de la contraction de l'anneau et à une diminution de l'aire sous la tente mitrale et de la hauteur de coaptation **(Figure 19)**. Cette réduction de la fuite mitrale a été rapportée sur les résultats de l'étude COMPANION [52].

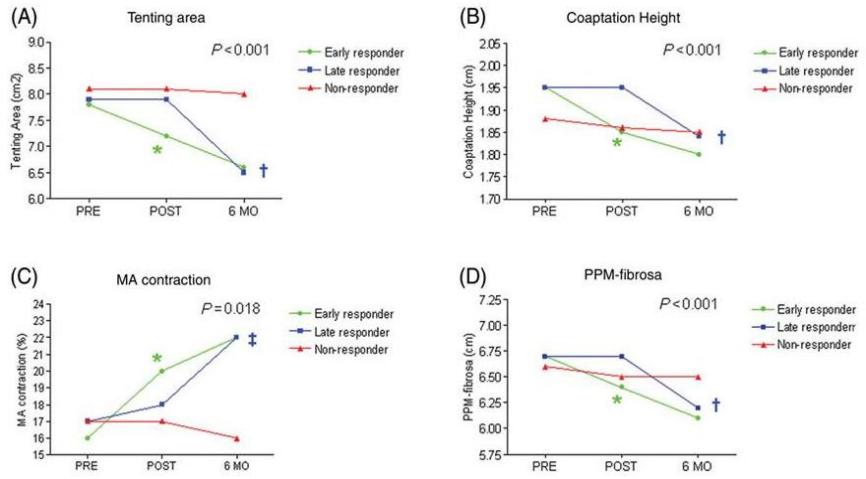


Figure19: d'après C. Ypenburg et al[8]., « Early responder », « late » et « non responder » correspondent respectivement aux patients dont la fuite mitrale s'est immédiatement corrigée après la resynchronisation cardiaque, à 6 mois et non modifiée. MA pour anneau mitral et PPM-fibrosa pour la distance entre la tête du pilier posterieur et l'anneau mitral.

La présence d'une insuffisance mitrale ne permet pas de prédire la réponse à la resynchronisation cardiaque et sa présence dans l'étude CARE-HF[35] apparaît comme un facteur de mauvais pronostic indépendamment de la resynchronisation cardiaque.

Rapport coût-bénéfice : L'insuffisance cardiaque est un problème majeur de santé publique avec un coût pour les hospitalisations >50% des dépenses. La resynchronisation cardiaque permet d'améliorer les patients au prix d'un surcoût estimé à 29400 euros par année de vie gagnée pour un stimulateur triple chambre simple et le double pour un défibrillateur triple chambre. Ce surcoût du défibrillateur doit être pris en compte par rapport à l'âge du patient.

II- Validations et Recommandations pour les patients en stade I-II :

La majorité des patients inclus dans les premiers essais cliniques étaient en classe III-IV de la classification NYHA. Deux études récentes ont été réalisées chez des patients en stade I-II (l'étude REVERSE[53] et l'étude MADIT-CRT). MADIT-CRT[54] a inclus 1820 patients en classe I (15%) et classe II (84%) avec une FEVG≤30% et un élargissement des QRS≥130ms. Les patients ont été randomisés en deux groupes (2:3), l'un recevant un défibrillateur seul (n=731), l'autre un défibrillateur avec resynchronisation cardiaque (n=1089). Après 2,4 ans de suivi, le critère primaire (décès de toute cause et insuffisance cardiaque, **Figure 20**) était réduit de 34% dans le groupe des patients resynchronisés, surtout attribuable à la réduction de l'insuffisance cardiaque (-41%, p<0.0001).

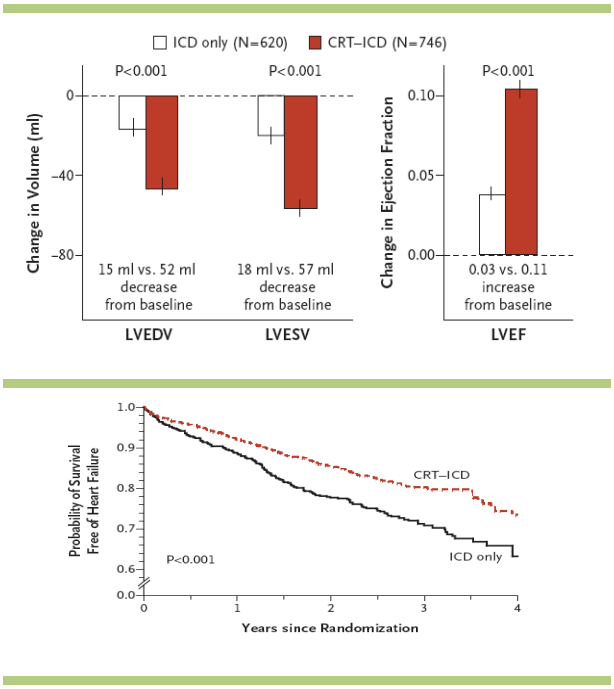
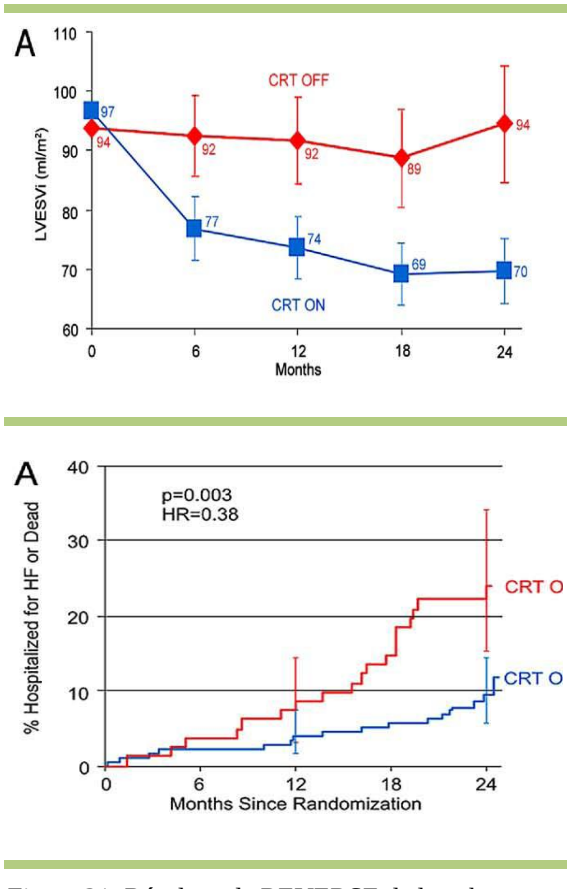


Figure 20: résultats de MADIT-CRT montrant un

L'étude REVERSE a inclus 610 patients insuffisants cardiaques ayant un traitement médical optimal, en classe NYHA I (18%) ou II, dont la FEVG était ≤40%, le diamètre télédiastolique

≥55mm et l'ECG montrant un rythme sinusal avec des QRS≥120ms. Les investigateurs étaient libres d'implanter un défibrillateur ou un stimulateur triple chambre (15%). Les patients ont ensuite été randomisés en « resynchronisé » ou « non resynchronisé ». Après 12 mois de suivi, le critère primaire (décès et insuffisance cardiaque) n'était pas différent entre les deux groupes. En revanche, le critère secondaire (réduction des volumes ventriculaires et augmentation de la fraction d'éjection ventriculaire gauche) était plus important dans le groupe resynchronisé. Dans le sous-groupe Européen de l'étude REVERSE[55], le bénéfice de la resynchronisation a pu être démontré avec un suivi prolongé à deux ans **(Figure 21)**. Dans ces deux études, une sous-analyse planifiée met en évidence un bénéfice surtout chez les patients ayant des QRS≥150ms.



Recommandations[50, 51]: Aux vues des résultats de ces deux études, le comité d'experts recommande l'implantation d'un défibrillateur triple chambre aux patients en stade NYHA II avec un rythme sinusal, un traitement médical optimal, une FEVG≤35% et un élargissement des QRS≥150ms (niveau de recommandation I, niveau de preuve A).

Troisième Partie

Identification des non-répondeurs

I-Introduction

Les résultats de ces études cachent cependant des disparités de réponse. Environ 30% à 40% des patients ne sont pas cliniquement améliorés et seulement la moitié bénéficie d'une réponse en terme de remodelage ventriculaire (56% dans PROSPECT[56] et 49% dans l'étude CARE-HF). Compte-tenu du coût de la procédure et des risques liés à l'implantation (2.4%)[57], l'identification des causes de non-réponse à la resynchronisation cardiaque préoccupe particulièrement la communauté scientifique. Les hypothèses expliquant l'absence de réponse adéquate incluent[58] :

- 1) Les problèmes techniques de positionnement des sondes de stimulation
- 2) Le réglage des délais ventriculaires et auriculo-ventriculaires
- 3) Le passage en fibrillation atriale
- 4) Et l'absence d'asynchronisme mécanique malgré des QRS larges

II-Effet de la position de la sonde VG

En pratique, la sonde ventriculaire gauche est placée en position latérale ou postéro-latérale. Certains auteurs ont suggéré de placer la sonde ventriculaire gauche dans les segments les plus désynchronisés[59] **(Figure 22 et 23)** afin d'améliorer la réponse à la resynchronisation cardiaque. Cette attitude n'a cependant pas été confirmée dans la sous-étude de PROSPECT[60]. En effet, les auteurs ne retrouvent pas de lien entre la position de la sonde ventriculaire gauche et la réponse à la resynchronisation cardiaque. En revanche, l'équipe de Bordeaux[61] a montré que le site optimal était très variable d'un patient à l'autre, ne correspondant pas toujours forcément à la paroi la plus retardée. Ces résultats surprenants peuvent être liés à des

lignes de bloc de conduction sur les segments les plus retardés qui peuvent empêcher la propagation de l'influx électrique. Le même groupe a donc proposé d'augmenter les chances de la resynchronisation cardiaque par la mise en place de plusieurs sondes ventriculaires gauches[62].

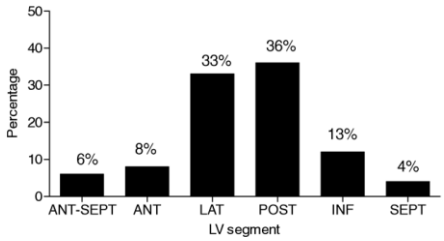


Figure 22: Distribution des segments les plus retardés

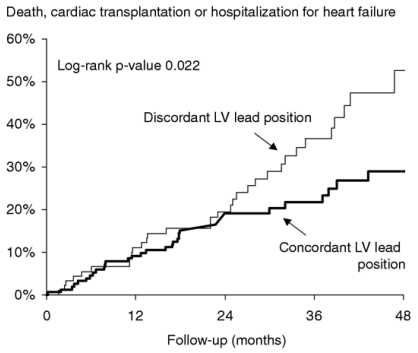


Figure 23: Impact pronostique de la position de la sonde

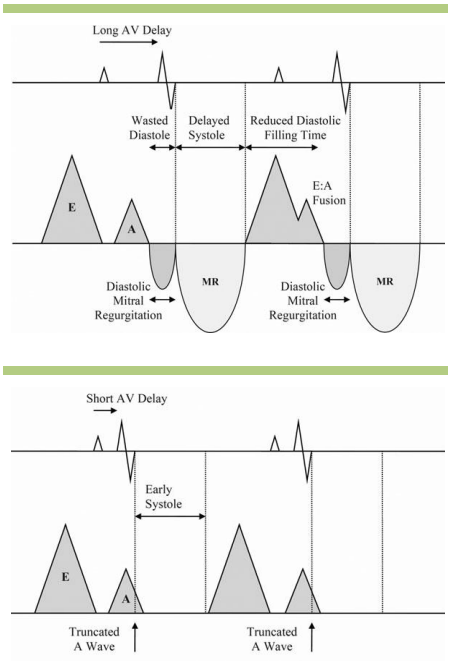
III-Optimisation du stimulateur

Le bénéfice de la resynchronisation pourrait être amélioré par une optimisation du délai inter-ventriculaire (délai VV) et auriculo-ventriculaire (DAV). L'optimisation des délais était inconstante dans les études multicentriques randomisées validant la CRT[63].

3.1- Réglage du délai VV : Certains auteurs[63-66] ont rapporté dans des études mono-centriques non randomisées qu'une amélioration des symptômes et des paramètres de fonction ventriculaire pouvait être observée lorsque le délai VV était ajusté au volume d'éjection systolique, à la dP/dt, à la synchronicité des ventricules ou au remplissage diastolique. Cependant, deux études randomisées incluant au total plus de 400 patients ne montrent pas de bénéfice sur l'amélioration fonctionnelle. Dans l'étude RHYTHM II ICD[67] (n=121 patients, randomisation 1/3), le délai VV réglé sur le volume d'éjection systolique n'avait d'impact ni sur le test de 6 minutes de marche ni sur la symptomatologie fonctionnelle. Dans l'étude DECREASE-HF (n=306)[68], le délai VV réglé de façon automatique sur un algorithme de calcul (délai optimal=-0.33 x (délai électrique VD-VG)-20ms) n'avait pas montré non plus de bénéfice sur les paramètres fonctionnels. Le réglage du délai VV est une procédure longue et

doit être réservée aux patients non-répondeurs compte-tenu de l'absence de preuve formelle sur le bénéfice clinique.

3.2- Le réglage du délai AV : Le réglage du délai AV repose sur l'optimisation du temps de remplissage diastolique. En effet, un délai AV trop long entraine un retard de l'onde E (évènement physiologiquement dépendant de la systole) qui va empiéter sur l'onde A. Par ailleurs, la fin prématurée de l'onde A par rapport au début de la systole peut être responsable d'une insuffisance mitrale diastolique. A l'inverse, un DAV trop court entraîne une troncature de l'onde A par la systole ventriculaire. Plusieurs méthodes ont été proposées pour optimiser le DAV. Le DAV optimal se situe entre 90 et 150ms, pour la majorité des patients à 120ms. La méthode la plus simple est de partir de 120ms et de diminuer de 20ms jusqu'à l'obtention d'une troncature de l'onde A puis d'augmenter de 10ms jusqu'à l'obtention d'une durée maximale du remplissage diastolique. Le DAV ne devra pas être trop long pour éviter l'échappement en rythme spontané. Il est conseillé de conserver un DAV<80% du DAV spontané. Il est possible de calculer le DAV optimal avec la méthode de Ritter[69] validée chez les patients ayant un stimulateur double chambre. Cette méthode consiste à appliquer un DAV très long (200ms) et un DAV très court (30ms) et de calculer pour chacun des réglages l'intervalle de temps qui sépare la fin de l'onde A et le début de l'onde Q. Le DAV optimal est égal à $AV_{op}= DAV_{long} – (QA_{court}-QA_{long})$. D'autres auteurs ont proposé l'optimisation du DAV sur le volume d'éjection systolique[63], la dP/t ou l'indice de



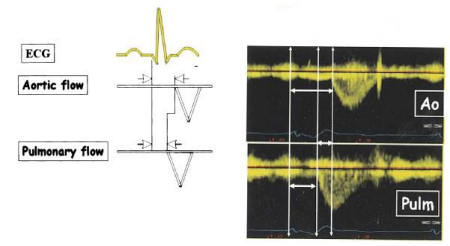
performance myocardique (indice de Tei). Les nouveaux algorithmes de réglage automatique embarqués sur les stimulateurs sont basés sur la mesure de la dP/dt ou de la contractilité myocardique. Ils n'ont pas encore clairement démontré un bénéfice clinique. La seule étude randomisée positive sur les paramètres hémodynamiques utilisait un réglage de DAV sur une optimisation du volume d'éjection systolique mesuré en échocardiographie[70]. Il est actuellement recommandé d'effectuer un réglage du DAV chez les patients resynchronisés surtout lorsque la réponse à la resynchronisation cardiaque reste sub-optimale. Par ailleurs, ce réglage devrait être répété compte-tenu de l'évolution du remodelage induit par la stimulation bi-ventriculaire.

IV- Fibrillation atriale

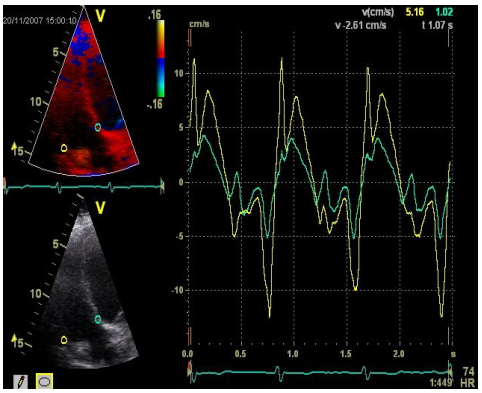
La présence d'une fibrillation atriale est un facteur de mauvais pronostic (OR=1.18, p=0.01) chez l'insuffisant cardiaque bénéficiant d'une resynchronisation cardiaque[71]. L'alternance de cycle court et cycle long au cours de la fibrillation atriale peut diminuer les périodes effectives de stimulation bi-ventriculaire et réduire le bénéfice de la resynchronisation cardiaque[72]. Dans ce contexte, l'ablation du nœud auriculo-ventriculaire semble être supérieure à l'approche pharmacologique ralentisseur sur l'amélioration des symptômes, le remodelage ventriculaire inverse et la survie[73]. Ce bénéfice doit cependant être confirmé par des études randomisées. Cette stratégie reste peu utilisée en pratique en raison du risque de bloc complet en cas de dysfonction du stimulateur ou en cas d'anomalies des sondes de stimulation.

V-Asynchronisme mécanique

Parmi les hypothèses suggérées expliquant l'absence de réponse à la resynchronisation cardiaque, certains auteurs ont suggéré l'existence d'une discordance entre l'asynchronisme mécanique et électrique[58]. En effet, chez les insuffisants cardiaques à QRS larges, il n'existe pas de corrélation linéaire entre la réponse à la resynchronisation et la largeur des QRS. Par ailleurs, de nombreuses études monocentriques rapportent un bénéfice de la resynchronisation cardiaque chez les patients ayant des QRS fins[74]. Ces données suggèrent que l'asynchronisme électrique ne permet pas de prédire le bénéfice de la resynchronisation cardiaque. Sur le plan conceptuel, l'asynchronisme mécanique peut être catégorisé en trois niveaux: inter-ventriculaire, intra-ventriculaire et auriculo-ventriculaire.



Mesure de l'asynchronisme inter-ventriculaire en Doppler pulsé par la différence des délais pré-éjectionnels droit et gauche



Calcul par échantillonnage en Doppler tissulaire.

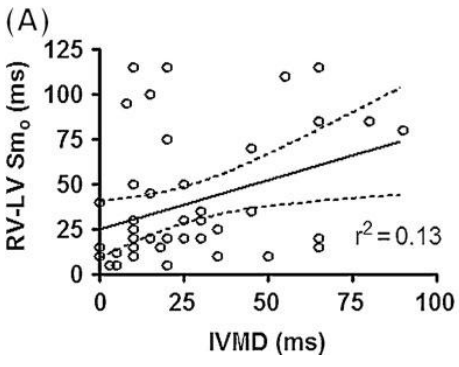
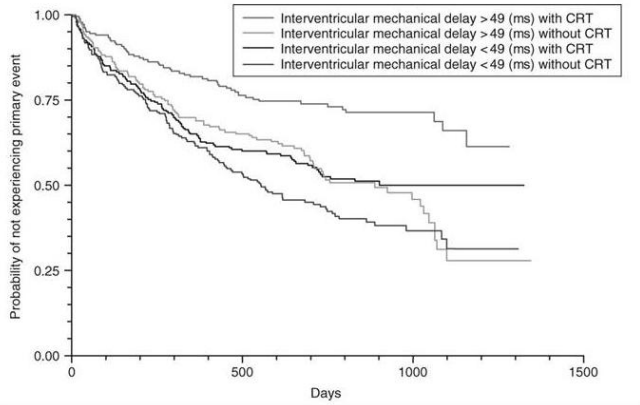


Figure 24 [9] : Corrélation entre l'asynchronisme inter-ventriculaire dérivé du Doppler pulsé conventionnelle (x) et tissulaire (y)

5.1-L'asynchronisme inter-ventriculaire

Cet asynchronisme est défini comme l'intervalle de temps séparant l'activité mécanique du ventricule droit et gauche. Cet asynchronisme peut être quantifié en scintigraphie de phase[75] ou plus habituellement en

échographie cardiaque par le Doppler pulsé conventionnel, en échantillonnant le flux pulmonaire et le flux aortique. La différence des délais pré-éjectionnels gauche et droit définit l'asynchronisme inter-ventriculaire. La valeur normale dans une population témoin est <40ms. L'asynchronisme inter-ventriculaire peut également être quantifié grâce à la méthode du Doppler tissulaire en échantillonnant une vitesse de déplacement myocardique au niveau de l'anneau tricuspide et mitral[76]. Cependant, les mesures en DTI et en Doppler pulsé conventionnel ne sont pas bien corrélées [9] (r^2=0.13, **Figure 24**). L'intérêt de mesurer cet indice pour identifier les répondeurs à la resynchronisation cardiaque reste controversé. Les premières études retrouvaient une bonne corrélation entre l'importance de cet asynchronisme et la réponse à la resynchronisation cardiaque[77]. Par la suite, d'autres équipes ont montré que l'asynchronisme inter-ventriculaire était bien corrélé à la largeur des QRS mais ne permettait pas de prédire la réponse à la CRT. Dans l'étude CARE-HF[78], les patients ayant un asynchronisme inter-ventriculaire>40ms étaient inclus lorsque la durée des QRS était comprise entre 120 et 150ms. Dans cette étude, l'asynchronisme inter-ventriculaire augmentait avec la largeur des QRS (r=0.11), l'altération de la fraction d'éjection et était plus important en cas de cardiopathie dilatée non ischémique. Après resynchronisation cardiaque, l'asynchronisme inter-ventriculaire diminuait de 21ms (IC 95% -26 à -16ms) 29 mois après la resynchronisation cardiaque. Un asynchronisme inter-ventriculaire >40ms était présent chez 62% des patients et était modérément prédictif du remodelage ventriculaire inverse[79] (OR=1.012/ms [1.005-1.020]) et des évènements cliniques[35] après CRT (décès et hospitalisation pour insuffisance cardiaque, **Figure 25**).



Number at risk interventricular mechanical delay (IVMD)				
IVMD	1 month	3 months	6 months	12 months
<49 ms without CRT	202	179	164	130
<49 ms with CRT	213	194	179	145
>49 ms without CRT	181	165	151	128
>49 ms with CRT	176	169	159	147

Figure 25: D'après Richardson et al [35]. Impact de l'asynchronisme inter-ventriculaire sur la réponse à la resynchronisation cardiaque (n=813, 404 sans CRT, 409 avec CRT) Les évènements sont définis par le décès et les hospitalisations pour insuffisance cardiaque).

Dans PROSPECT, l'asynchronisme inter-ventriculaire >40ms avait une faible valeur diagnostique (AUC=0.59, p=0.0009) pour identifier les répondeurs à la resynchronisation cardiaque (sensibilité=60%, spécificité=54%).

5.2- Asynchronisme auriculo-ventriculaire

L'asynchronisme auriculo-ventriculaire est défini par la durée relative de la diastole (durée de l'onde E et A) par rapport au RR. Il existe un asynchronisme AV significatif lorsque la durée du remplissage est inférieure à 40% du cycle cardiaque. En l'absence de bloc auriculo-ventriculaire du premier degré, le raccourcissement de la diastole est la conséquence d'une systole ventriculaire gauche retardée. Cet indice permet donc d'évaluer les conséquences globales de l'asynchronisme mécanique sur le remplissage diastolique. Cependant, sa valeur n'est pas spécifique: le remplissage peut être raccourci en cas de tachycardie, lorsque les pressions de remplissages sont augmentées ou lorsqu'il existe une augmentation de l'espace PR. Dans l'étude PROSPECT, cet indice était évaluable chez 85% des patients et avait une précision diagnostique limitée pour identifier les patients répondeurs (AUC=0.6, p=0.007). La sensibilité n'était que de 41% et la spécificité de 74%. Son

évaluation prend en revanche une grande importance pour l'optimisation du délai auriculo-ventriculaire (DAV) au décours de la resynchronisation cardiaque.

5.3- Asynchronisme myocardique intra-ventriculaire:

L'asynchronisme intra-ventriculaire se définit comme un retard de contraction d'un ou plusieurs segments du myocarde entre eux. L'asynchronisme intra-ventriculaire peut être évalué en scintigraphie myocardique par l'analyse de Fourier ou en IRM cardiaque par l'étude de la déformation du myocarde ou de vélocimétrie. Cependant, les études utilisant ces méthodes ont inclus un nombre limité de patients. Nous reporterons principalement les données issues de l'échographie cardiaque dont la résolution spatiale et temporelle est supérieure. L'analyse en échographie cardiaque de l'asynchronisme mécanique peut être réalisée par des outils simples comme le mode temps-mouvement (TM) ou par une analyse plus sophistiquée de la déformation myocardique en 2D (Doppler tissulaire et speckle tracking).

5.3.1- Le mode TM est la méthode la plus simple permettant d'étudier les délais d'activation d'une paroi ou de deux parois du myocarde. Le mode TM couplé au Doppler tissulaire peut être utilisé pour sensibiliser l'analyse des phases de contraction. Plusieurs indices d'asynchronisme mécanique ont été proposés à partir de ce mode : l'identification de la contraction précoce du septum (septum flash) et le retard de contraction entre la paroi latérale et septale.

a) Le « septum flash » correspond à une contraction précoce du septum durant la contraction isovolumétrique **(Figure 26)**. Cette contraction est rapide et très énergique compte-tenu du faible régime de pression durant cette période précoce de la systole. Dans une cohorte multicentrique publiée par Parsai et al[2]. (n=161), la présence d'un septum flash était observée chez 54% (87/161) des patients. La sensibilité et spécificité étaient respectivement de 64% et 55%, soit une valeur prédictive positive et négative respectivement de 81% et 33%. Les auteurs soulignent cependant que tous les patients qui avaient une résolution du septum flash étaient tous des répondeurs (77/87). Les dix patients ayant un septum flash persistant avaient dans la majorité des cas une sonde ventriculaire gauche mal positionnée (n=6).

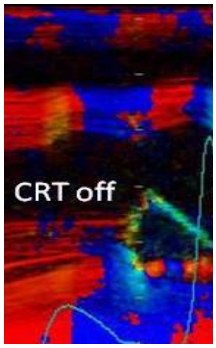
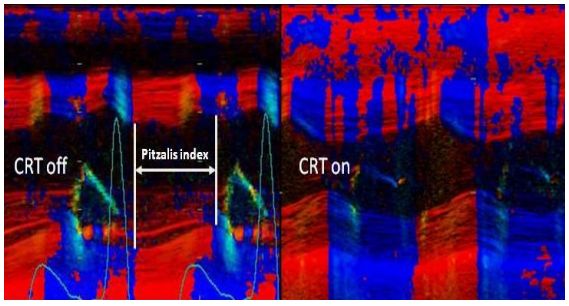


Figure 26 : Exemple d'un septum flash, correspondant à une contraction précoce et rapide du septum basal en période de contraction iso-volumique.

b) Le retard latéral-septal en TM a été proposé par l'équipe de Vittoria Pitzalis (**Figure 27**). Le principe repose sur la mesure de l'intervalle de temps qui sépare le pic de contraction radiale de la paroi septale et latérale. La première étude



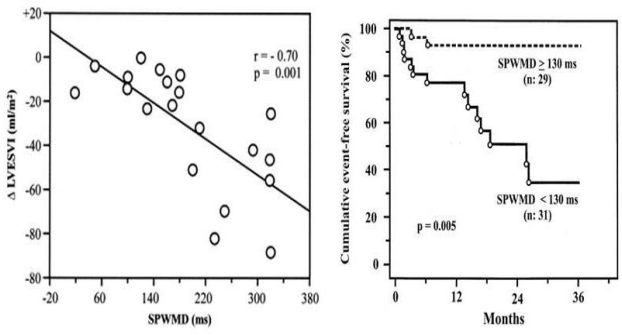


Figure 27 : Retard latéral septal ou indice de Pitzalis

publiée [80] en 2002 (n=20) avait montré que cet intervalle de temps était corrélé au remodelage inverse après resynchronisation cardiaque. Un intervalle de temps >130ms permettait d'identifier 80% des répondeurs à la resynchronisation et était associé à un pronostic favorable après resynchronisation[81]. La valeur prédictive de cet indice reste controversée en raison de la difficulté de mesure lorsque l'une des parois est akinétique [82]. Dans l'étude PROSPECT [56], la faisabilité n'était que de 72% et la variabilité de 72% avec un taux de concordance de 35%. La précision diagnostique était assez faible (AUC=0.62, p=0.0003). Une différence septal-latéral >130ms avait une sensibilité et spécificité de 64% et 52%, soit une valeur prédictive positive et négative respective de 65% et 51%.

5.3.2- Analyse des déformations myocardiques en 2D : Deux méthodes sont disponibles pour étudier la déformation myocardique et l'asynchronisme: le Doppler tissulaire et la poursuite acoustique de l'image ou speckle tracking. Nous avons rappelé en annexe les principes des deux méthodes. L'avantage de ces méthodes par rapport au TM est la possibilité d'étudier la déformation myocardique dans plusieurs segments du myocarde et d'appréhender la déformation dans plusieurs directions de l'espace.

a) Analyse de l'asynchronisme en DTI : le DTI permet de mesurer les vitesses de déformation dans le sens longitudinal (par la vue apicale, **Figure 28**) et radial (en petit axe). La quantification de l'asynchronisme mécanique entre les parois du myocarde a été étudiée par plusieurs équipes. Les travaux les plus aboutis viennent de l'équipe de Jeroen Bax qui, en 2004, [83] a montré que le délai maximal entre les pics de vitesse systolique longitudinale séparant les quatre parois opposées du myocarde (latérale, septale, antérieure et inférieure) était corrélé au remodelage ventriculaire après CRT (r^2=0.7,

p<0.0001, **Figure 29**). Un seuil de 65ms permettait d'identifier avec une sensibilité et une spécificité de 92% les répondeurs à la resynchronisation cardiaque.

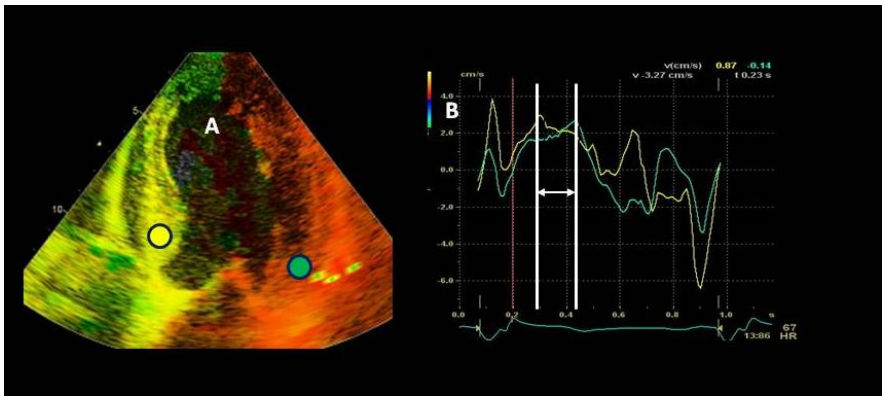


Figure 28: Mesure de l'asynchronisme entre le septum et la paroi latérale sur les courbes de l'imagerie BD en Doppler couleur.

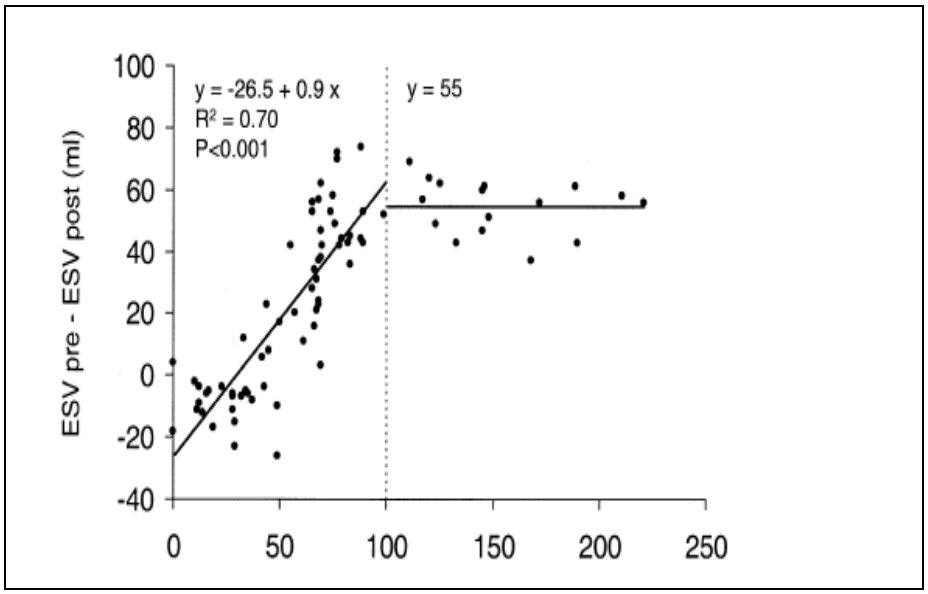


Figure 29: Corrélation entre le remodelage inverse et l'opposing wall delay ou retard maximal entre les parois du myocarde

La même année, le groupe de Yu CM [76] a proposé de mesurer l'asynchronisme mécanique en quantifiant la déviation standard du temps au pic systolique de vélocités sur 12 segments du myocarde (12SD-TDI, **Figure 30**). Cette équipe montre que le 12SD-TDI était mieux corrélé au remodelage inverse que le délai entre deux parois (indice de Bax). Un seuil du 12SD-TDI> 33ms permettait d'identifier les répondeurs avec une sensibilité de 96% et une spécificité de 78%. La robustesse de ces deux indices dérivés du Doppler

tissulaire ne s'est cependant pas confirmée dans l'étude PROSPECT[56]. En effet, l'intervalle de temps entre deux parois en DTI n'était mesurable que chez 64% des patients et la précision diagnostique était assez faible (AUC=0.61, p=0.01). La sensibilité était de 53% et la spécificité de 69%, soit une valeur prédictive positive et négative respectivement de 68% et 55%. La reproductibilité était de 32% avec une concordance de 25%. Pour l'indice de Yu (12SD-TDI), la faisabilité (50%), la concordance (15%) et la précision (AUC=0.55, ns) étaient moins bonnes. Les valeurs prédictives positive et négative n'étaient respectivement que de 56% et 54%.

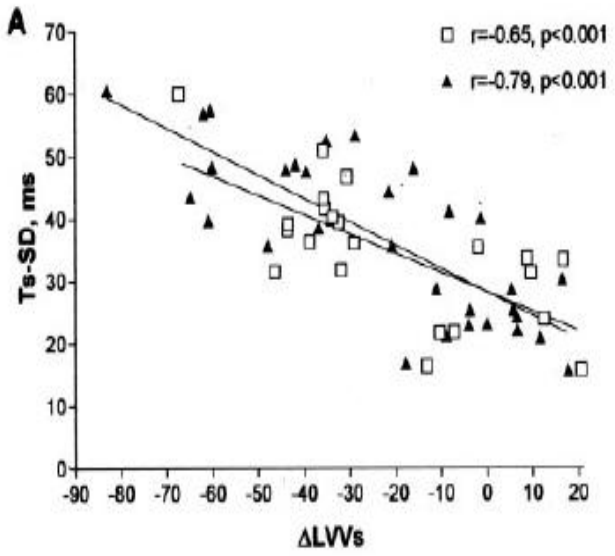


Figure 30: Corrélation entre la déviation standard du temps au pic systolique des vitesses myocardiques sur 12 segments et le remodelage inverse.

b) Asynchronisme en « speckle tracking » : Les études de l'asynchronisme à l'aide du « speckle tracking » ont fait suite aux résultats négatifs de l'étude PROSPECT pour répondre aux limites du DTI. L'équipe de John Gorcsan III[84] a montré que la quantification de l'asynchronisme par la déformation radiale en speckle tracking donnait d'excellents résultats avec une sensibilité de 89% et une spécificité de 83% lorsque la

déformation radiale de la paroi postérieure avait un retard de plus de 130ms par rapport à la paroi septale **(Figure 31)**. Une étude intéressante de l'équipe de Jeroen Bax [85] a comparé la précision diagnostique à prédire la réponse à la resynchronisation, de la quantification de l'asynchronisme mécanique provenant de la déformation longitudinale, radiale et circonférentielle en speckle tracking.. Les auteurs retrouvent les mêmes résultats que Gorcan III et montrent que seul l'asynchronisme issu de la déformation radiale permettait d'identifier les répondeurs à la resynchronisation cardiaque. Ces résultats sont cependant en désaccord avec la publication récente du groupe de Jae Oh de la Mayo Clinic [86] qui montre qu'aucun paramètre d'asynchronisme mécanique issu du speckle tracking n'est assez précis pour prédire la réponse à la resynchronisation cardiaque. L'asynchronisme mécanique calculé à partir du strain radial en speckle tracking selon les mêmes logiciels que l'équipe de Gorscan III et de Bax n'a aucune précision diagnostique (AUC=0.53) pour identifier le remodelage inverse.

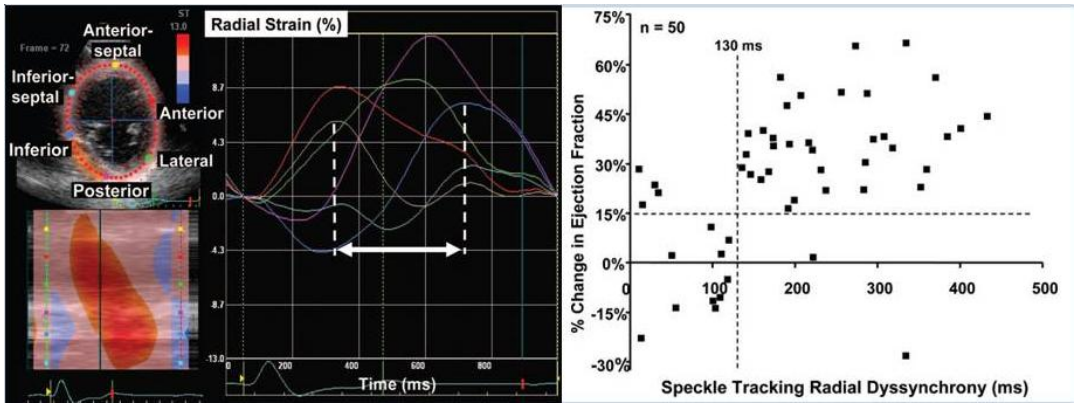


Figure 31: D'après Gorcsan et al : Asynchronisme inter-ventriculaire dérivé du strain radial en speckle tracking et corrélation avec l'augmentation de la fraction d'éjection après resynchronisation cardiaque.

c) **La rotation et la torsion:** Dans un cœur sain, la rotation de la pointe plus importante à l'apex se fait dans le sens inverse de la base (9.4±3.2 *vs*. -6.1±2.4°). L'ensemble réalise un mouvement de torsion d'environ 15±3.6°. Chez les patients insuffisants cardiaques

désynchronisés, l'équipe de Sade[87] a montré que les amplitudes de rotation étaient altérées et qu'il existait une rotation plus précoce de la base et une rotation plus retardée de la pointe. Il est intéressant de noter que chez environ 15% des patients, la rotation de la base et de la pointe peuvent changer de sens. L'asynchronisme de rotation et la réduction des amplitudes contribuent à diminuer les valeurs de torsion, notamment lors de la systole. Dans ce travail, la valeur de la torsion au moment de la fermeture de la valve aortique était bien corrélée à la sévérité de la dysfonction ventriculaire gauche, à l'importance de l'asynchronisme mécanique et à la réponse à la resynchronisation cardiaque. La valeur prédictive du pic de torsion avant la CRT pour identifier les répondeurs n'est pas retrouvée par l'équipe de Bax : ils montrent que seule l'augmentation de torsion sous stimulation biventriculaire est corrélée au gain de contractilité et à la correction de l'asynchronisme sous CRT **(Figure 32)**.

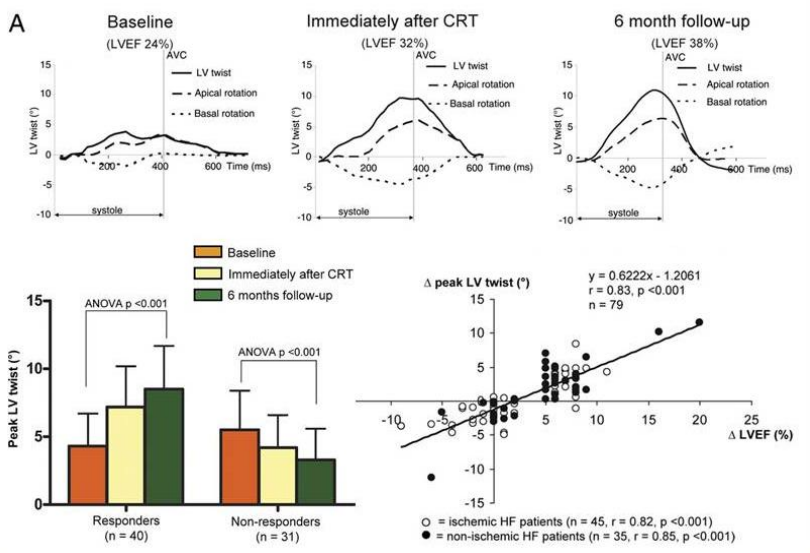


Figure 32: adapté de Bertini et al. Modification des valeurs de rotation au cours de la resynchronisation cardiaque. La restauration des paramètres de rotation est corrélée à l'amélioration de la fraction d'éjection ventriculaire gauche.

5.3.3- L'asynchronisme en 3D : L'étude de l'asynchronisme en 3D repose sur la possibilité d'évaluer sur l'ensemble du myocarde les zones désynchronisées. Cependant, cette

approche est limitée par la résolution spatiale et temporelle de l'imagerie 3D. Dans une étude publiée dans Circulation, l'équipe de Kapetanakis[88] avait montré que l'asynchronisme évalué en 3D par la mesure de la dispersion du temps au pic de volume rapportée à l'intervalle RR (SDI%) et exprimé en pourcentage était bien corrélé à la sévérité de la dysfonction ventriculaire gauche **(Figure 33)**. Chez les patients resynchronisés (n=23), cet indice était plus important chez les répondeurs que les non-répondeurs (16.1±5.1% *vs*. 7.1±3.6%, p<0.0001). Ces données n'ont cependant pas été confirmées par la sous-population de l'étude PROSPECT ayant eu une échographie 3D, ni dans l'étude de la Mayo Clinic récemment publiée[86].

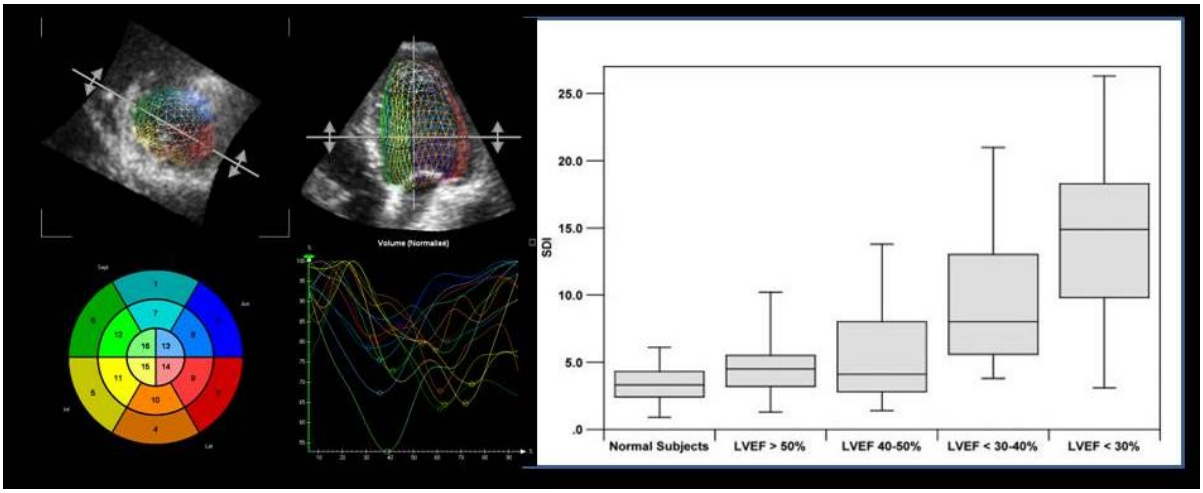


Figure 33: d'après Kapetanakis[88]. Corrélation entre l'asynchronisme en 3D et l'altération de la fraction d'éjection ventriculaire gauche.

5.4-Approche multiparamétrique et mécanistique

Cette approche a été proposée par plusieurs auteurs, principalement après les résultats décevants de l'étude PROSPECT [56]. Le concept repose sur l'idée de combiner la présence de plusieurs signes positifs pour augmenter la valeur prédictive positive des indices d'asynchronisme mécanique afin d'identifier les répondeurs à la resynchronisation cardiaque. Dans une étude multicentrique, Stéphane Lafitte [89] de l'équipe de Bordeaux a proposé de combiner les paramètres d'asynchronisme inter-, intra- et auriculo-ventriculaire afin

d'améliorer la valeur prédictive positive de la réponse à la resynchronisation cardiaque. Cette étude montre que la présence de plus de 3 critères d'asynchronisme permet d'avoir une spécificité de 90% avec une valeur prédictive positive >65%. Cependant, la présence de trois critères faisait chuter dramatiquement la sensibilité à 10% **(Figure 34)**.

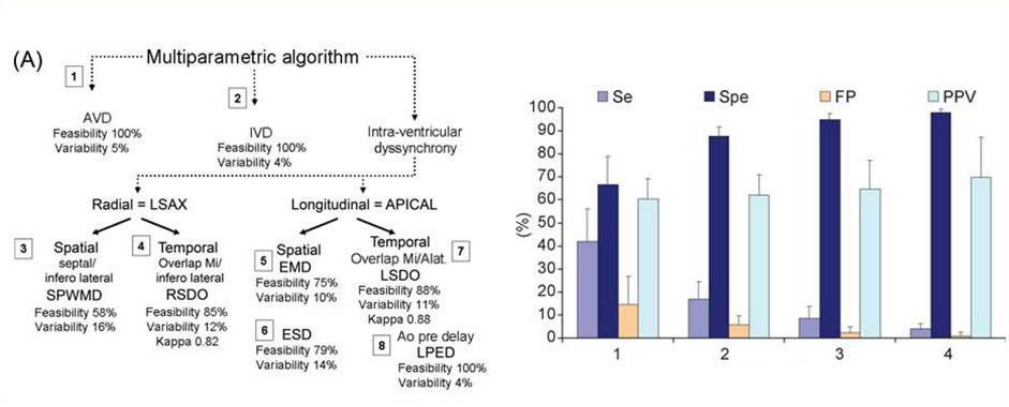
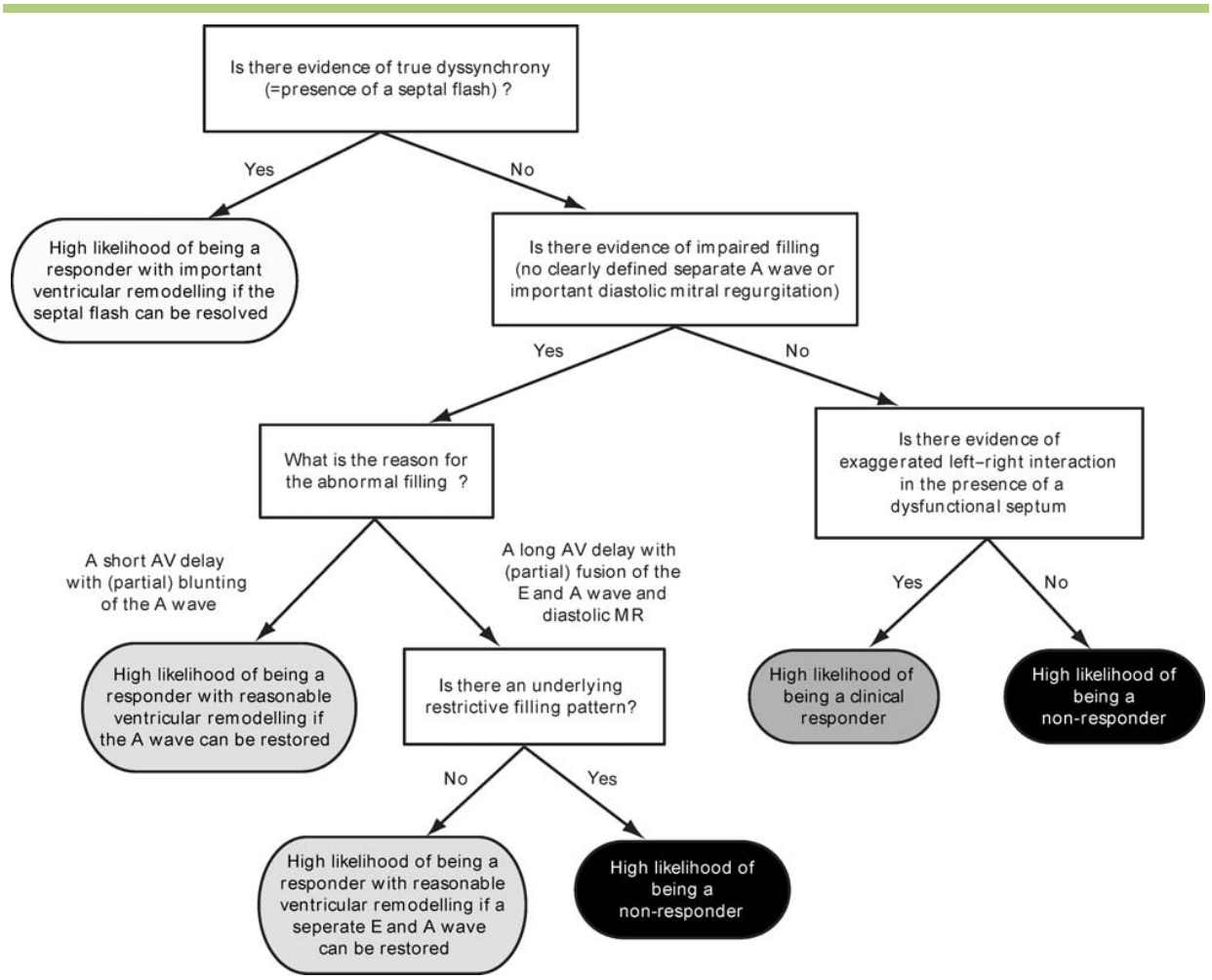
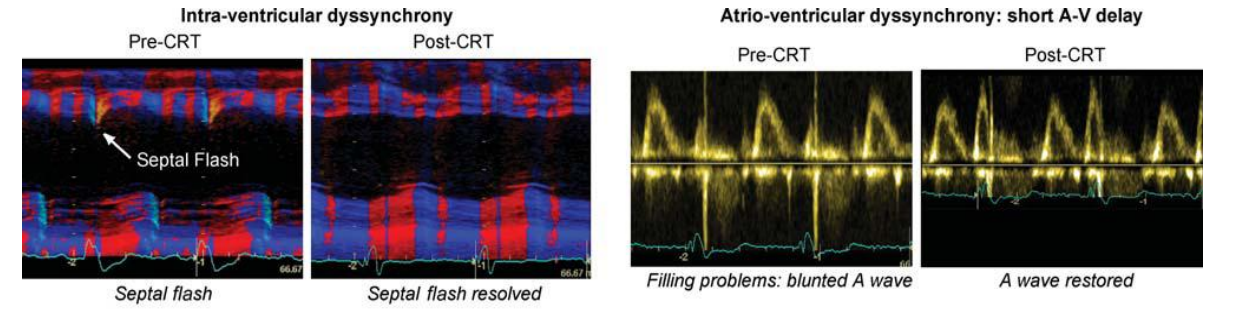


Figure 34: D'après Lafitte et al[89]. Approche multiparamétrique consistant à combiner plusieurs paramètres pour augmenter la spécificité au prix d'une réduction de la sensibilité.

Une approche multiparamétrique incluant une approche mécanistique a été proposée dans l'étude multicentrique de Parsai[2] **(Figure 35)**. Cette étude étudiait la présence de trois critères : un septum flash, un asynchronisme auriculo-ventriculaire et inter-ventriculaire. L'absence des trois critères rendait peu probable la réponse à la resynchronisation cardiaque. Par contre, la présence d'un ***septum flash réversible*** après resynchronisation cardiaque permettait de classer le patient dans une haute probabilité de réponse à la resynchronisation cardiaque. En l'absence de septum flash, la présence d'un asynchronisme inter-ventriculaire ou d'une diastole raccourcie ***corrigibles*** après resynchronisation cardiaque est prédictive d'une réponse à la CRT. Cette approche est intéressante sur le plan physiopathologique car elle démontre que l'asynchronisme mécanique doit être imputable au trouble de la conduction électrique pour être prédictive de la réponse à la resynchronisation cardiaque. Son utilisation en pratique clinique n'est cependant pas possible car elle nécessite une connaissance à priori de l'évolution après resynchronisation cardiaque.

Figure 35: Approche mécanistique proposée par Parsai.





Troisième Partie

Relation fibrose et asynchronisme

I-Introduction

Aux vues des différents indices et méthodes utilisés pour tenter d'identifier les répondeurs à la resynchronisation cardiaque, les données de la littérature sont donc très controversées. Pour mieux comprendre les discordances, il est important d'identifier les déterminants de l'asynchronisme mécanique.

II- Relation fibrose et asynchronisme mécanique

Certaines fibroses myocardiques localisées sur le trajet des fibres de conduction peuvent être responsables de troubles de la conduction électrique et entraîner le retard de contraction de certaines parois du myocarde. Les conséquences mécaniques de ce retard peuvent être reproduites sur des modèles de bloc de branche gauche expérimentaux par radiofréquence ou par stimulation ventriculaire droite induite.

Cependant, une contraction retardée peut être présente malgré l'absence de bloc de conduction électrique, notamment chez les sujets normaux et chez les patients ayant une cardiopathie ischémique. Ces retards de contraction, lorsque la contraction survient après la fermeture de la valve aortique sont dits « contraction post-systolique ». Dans la cardiopathie ischémique, la déformation post-systolique observée au cours de l'ischémie myocardique est réversible après rétablissement du flux coronaire. Ces observations ont longtemps laissé penser que la contraction post-systolique était un marqueur de viabilité myocardique.

Nos travaux et ceux d'autres équipes ont remis en cause ce concept. Grâce à une approche multi-modalité combinant l'échographie cardiaque et l'imagerie de résonance magnétique, nous avons corrélé les données de l'asynchronisme mécanique à l'extension

transmurale de la nécrose myocardique. Dans ce travail mené dans le laboratoire du Professeur Jean-Louis Vanoverschelde[90], nous avons démontré que, chez les patients ayant une altération chronique de la fonction ventriculaire gauche d'origine ischémique, la contraction post-systolique n'était un marqueur spécifique de viabilité. Elle était présente dans 96% des segments présentant une nécrose transmurale et 50% des segments ayant une nécrose non-transmurale. Par ailleurs, l'importance du retard post-systolique était corrélée à la transmuralité de la nécrose **(Figure 36)**.

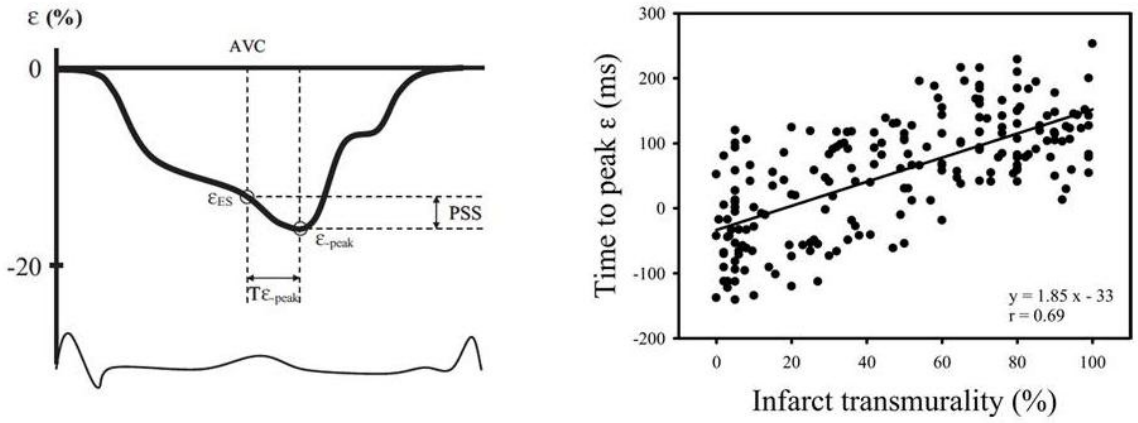


Figure 36 : A gauche : déformation longitudinale post-systolique et à droite, corrélation entre le retard post-systolique et la transmuralité de la nécrose myocardique.

Ces données sont concordantes avec les travaux expérimentaux de l'équipe de Skulstad [91] qui retrouvait une contraction post-systolique dans les segments ischémiques et infarcis **(Figure 37),** se majorant avec l'augmentation de la post-charge. La variation de l'asynchronisme mécanique en fonction des conditions de charge a été démontrée chez l'homme par l'équipe de Park[92] qui retrouve une majoration de l'asynchronisme mécanique en cas d'augmentation de la contrainte pariétale du ventricule gauche **(Figure 37-C)**. Les modifications de l'asynchronisme sont aussi observées au cours de l'effort. En effet,

D'Andrea[37] et Stéphane Lafitte[38] ont montré que la majoration de l'asynchronisme observée chez un certain nombre de patients insuffisants cardiaques était corrélée à l'augmentation de l'insuffisance mitrale et à une réduction du débit cardiaque à l'effort.

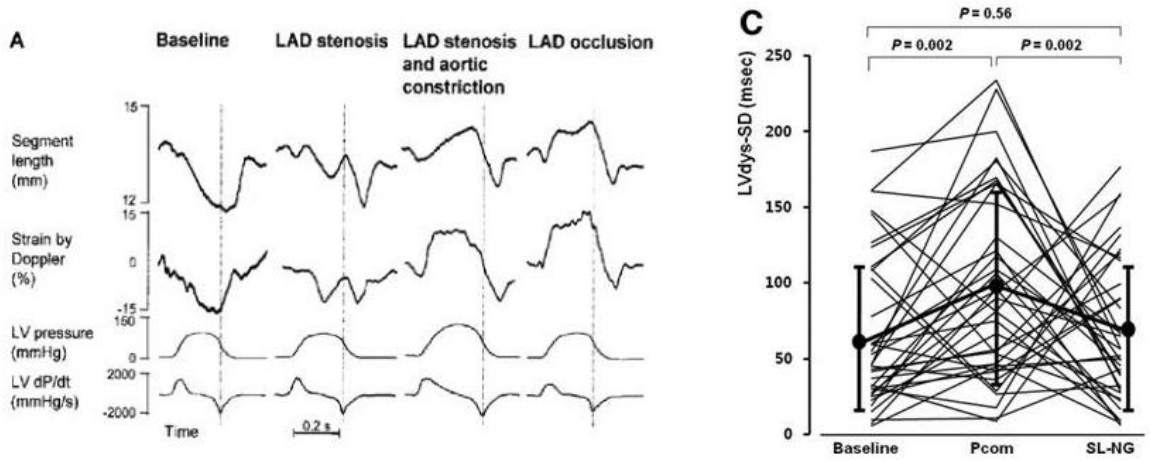


Figure 37: A gauche : Retard de contraction induit par ischémie et nécrose myocardique induite expérimentalement. L'augmentation de la post-charge par constriction de l'aorte exagère la contraction post-systolique. A droite, le graphique montre la variation des paramètres d'asynchronisme selon les conditions de charge chez l'homme.

Is Postsystolic Shortening a Marker of Viability in Chronic Left Ventricular Ischemic Dysfunction? Comparison with Late Enhancement Contrast Magnetic Resonance Imaging

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Background: During acute myocardial ischemia, myocardial postsystolic shortening (PSS) is considered as a sign of viability. In chronic left ventricular (LV) ischemic dysfunction, the value of PSS is less well established. In this study, PSS was compared with transmural extent of necrosis and contractile reserve in patients with chronic LV ischemic dysfunction.

Methods: A total of 25 patients (20 men, mean age: 63 ± 8 years) with LV dysfunction (mean ejection fraction: 32 ± 10%, range: 14%-47%) and stable coronary artery disease underwent rest color Doppler myocardial imaging, low-dose dobutamine echocardiography, and late enhancement gadolinium-magnetic resonance imaging. Strain (ε) curves were computed in 16 segments from color Doppler myocardial imaging sequences and were compared with transmural extent of necrosis and with contractile reserve. End-systolic ε was defined as ε value at aortic valve closure, peak ε (ε-peak) as maximal ε value during cardiac cycle, and time to ε-peak as time interval between aortic valve closure and ε-peak. PSS was considered when ε-peak occurred after aortic valve closure.

Results: Of 348 analyzable segments, 212 (61%) were graded as abnormal. In dysfunctional segments, PSS was more prevalent in transmural than in nontransmural infarcted segments (96% vs 50%, $P < .001$) and time to ε-peak was correlated to transmural extent of necrosis ($r = 0.69$, $P < .0001$). In nontransmurally infarcted segments, prevalence of PSS was similar in segments with or without contractile reserve (37% vs 45%, respectively).

Conclusion: In chronic LV dysfunction, PSS is not a specific marker of viability. These results suggest strongly that delayed myocardial shortening may be associated to scarred segments.

Risk stratification in patients with left ventricular (LV) ischemic dysfunction typically includes a combination of clinical, hemodynamic, and angiographic parameters.[1] During the past 10 years, several different studies have indicated that assessment of myocardial viability, ie, the ability of dysfunctional myocardium to improve in contraction after revascularization, also provides useful prognostic information in these patients,[2-6] with an effect additive to that of the usual clinical assessment.[2] Although a variety of different imaging modalities have been used to assess myocardial viability, these approaches are often limited by their availability, their cost, their technical difficulty, their subjective character, or a combination of these factors.

It has been recently proposed that postejection or postsystolic shortening (PSS) may serve as a marker of actively contracting and, therefore, viable myocardium.[7] PSS is defined as a myocardial deformation that occurs after aortic valve closure (AVC). It is typically seen in the early phases of acute myocardial ischemia, where its spatial distribution is consistent with that of the myocardium at risk. Several experimental and clinical studies have recently suggested that PSS could be a marker of residual myocardial viability.[7-10] Yet, results of several other studies suggest that it is a purely passive phenomenon that results from the interaction of ischemic with surrounding nonischemic segments.[11]

In view of these conflicting results, we designed the current study to evaluate the spatial and temporal relationships among PSS, derived from color Doppler myocardial imaging (CDMI) strain (ε) curves[12,13]; the transmural extent of necrosis, as delineated by late-enhancement gadolinium cardiac magnetic resonance (MR)[14-16]; and contractile reserve, as evaluated by low-dose dobutamine echocardiography (DbE).[17]

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Dr Lim was supported by a grant from the Société Française de Cardiologie, Paris, France. Dr Gerber was supported by a grant from the Fondation de la Recherche Scientifique, Brussels, Belgium.

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0894-7317/$34.00

doi:10.1016/j.echo.2007.09.004

METHODS

Study Population

The population consisted of 25 patients (20 men, mean age: 63 ± 8 years) with angiographic coronary artery disease and both regional and global LV dysfunction (mean ejection fraction: 32 ± 10%, range: 14%-47%). A total of 21 patients had experienced a previous myocardial infarction (16 anterior, 1 inferior, and 4 lateral). Five patients were diabetic, 11 had a history of hypertension, and two had a history of coronary artery bypass graft surgery. All patients gave written, informed consent to participate in the study, which had been approved by the ethical committee of our institution.

All patients underwent rest CDMI, contrast-enhanced (CE) low-dose DbE, and CE MR during the same hospital stay.

Cardiac Catheterization

Selective coronary arteriography and contrast left ventriculography were performed from the femoral approach, before the echocardiographic and CE MR studies. The presence and severity of coronary artery disease was assessed visually. Significant coronary disease was defined as a greater than 70% luminal diameter stenosis in any major coronary branch. Six patients had single-vessel disease, 6 others had 2-vessel disease, and 13 had 3-vessel disease.

CDMI

All CDMI studies were performed with the patients in a supine position. Data were acquired using a Sonos 7500 system, Philips Medical Systems, Andover, Mass) equipped with the broadband phased-array S3 transducer (1-3 MHz). CDMI myocardial velocity data were acquired at a frame rate of 80 ± 19 frames/s, using an imaging sector angle of 45 degrees. CDMI data from 3 consecutive cardiac cycles were acquired at rest in the apical 4-, 3-, and 2-chamber views and transferred onto a remote microcomputer for subsequent offline analysis.

CE DbE

For DbE, the patients were allowed to take their prescribed medications with an exception for β-blockers, which were withdrawn for at least 48 hours before the investigation. Before the test was started, a clinical history was recorded, a rest electrocardiogram (ECG) and echocardiogram were obtained, and a venous line was secured. To optimize LV contour delineation, a continuous intravenous infusion of PESDA (Perfluorocarbon-enhanced Sonicated Dextrose Albumin), a second-generation ultrasonic contrast agent, was then started. The rate of infusion was progressively adjusted to obtain homogenous cavity opacification during real-time scanning. Once an adequate LV opacification was obtained, dobutamine was infused in 3-minute dose increments from 5 to 40 μg/kg/min, under continuous ECG and echocardiographic monitoring. The test was concluded after achievement of the peak dose or earlier if the patient developed severe ischemia (either angina or impairment of LV function) or experienced intolerable side effects, as previously described.[17] Clinical signs, the ECG, and echocardiographic images were recorded at the beginning of the study and every 3 minutes thereafter until completion of the stress.

CE MR

MR imaging was performed in a 1.5-T magnet (Integra CV, Philips, Eindhoven, The Netherlands) using a phased-array coil wrapped around the chest. After localization of the heart, patients received an intravenous bolus of 0.2 mmol/kg of gadodiamide. Fifteen minutes later, delayed images were acquired in the apical 4-, 3-, and 2-chamber orientations using an inversion-recovery prepared gated fast gradient echo pulse sequence. Imaging was performed with the following parameters: repetition time, 4.6 milliseconds; echo time, 2.3 milliseconds; image matrix, 256 × 192; flip angle, 20 degrees; and inversion pulse of 180 degrees with an inversion time of 250 to 300 milliseconds. All image prescriptions had the same orientation as the echocardiographic images.

Data Analysis

The CDMI, CE DbE, and late-enhancement MR imaging data were analyzed using the American Society of Echocardiography 16-segment model.

CDMI

Longitudinal ε was computed from CDMI data using a prototype version of the Qlab software package (Philips Medical Systems). The software automatically tracks wall displacement and maintains the region in which measurements are made in midwall position. For ε computation, end diastole was chosen as the reference time point. This was defined to occur at the R-top on the ECG trace. The timing of end systole (AVC) was derived from M-mode echocardiographic recordings. End-systolic ε (ε-ES) was defined as the magnitude of deformation at the time of AVC. When further deformation occurred after AVC, this was measured as the peak ε (ε-peak). The difference between ε-ES and ε-peak was calculated as the PSS and, from this, the postsystolic index, expressed as a percentage, was derived from the equation; ([PSS/ε-peak]*100). The time delay from AVC to ε-peak was also calculated (Figure 1).

CE DbE

Images were interpreted qualitatively in accordance with previous guidelines by experienced observers who had no knowledge of the angiographic and clinical data. Regional function was defined as normal (1), hypokinetic (2), or akinetic (3).[17] Normal wall motion was defined as greater than or equal to 5 mm of endocardial excursion and obvious systolic wall thickening. Hypokinesis was defined as less than 5 mm of endocardial excursion and reduced wall thickening. Akinesis was defined as near absence of endocardial excursion or thickening.

A normal segmental response to dobutamine was defined as a progressive enhancement in contractility during stress. Ischemia was identified by a stress-induced wall-motion abnormality. Dysfunctional myocardium at baseline was considered as exhibiting contractile reserve if wall-motion score improved by at least one full grade with low-dose (5-10 μg/kg/min) dobutamine.

CE MR

Assessment of the transmural extent of delayed hyperenhancement was performed on the late (15-minute) gadolinium-DTPA–enhanced MR images as previously described.[16] Briefly, the images were binarized to a threshold of 2 SD above the mean value obtained in remote normal segments without hyperenhancement. The transmural extent of hyperenhancement was computed within each segment on these thresholded images and reported as the percentage of the segmental area that was hyperenhanced. Transmural necrosis was defined as greater than 50% hyperenhancement and nontransmural necrosis as less than or equal to 50% hyperenhancement.

Statistical Analysis

Continuous values were expressed as mean ± SD. Dichotomous data were presented as percentages. Linear regression was used to

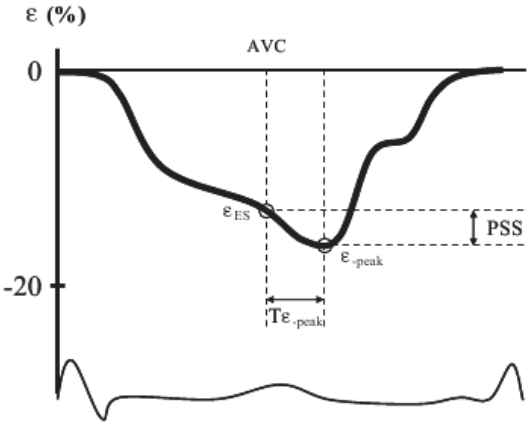

Figure 1 Parameters derived from strain (ε) profiles. Schematic representation of longitudinal ε profiles. End-systolic ε (*εES*) and peak ε (*ε-peak*) were measured at end systole and peak deformation, respectively. *Te-peak* is time from aortic valve closure (*AVC*) to ε-peak. Postsystolic ε was calculated as ε-peak if it occurred after AVC. Postsystolic shortening (*PSS*) was calculated as difference between εES and εpeak.

assess the relationship between the transmural extent of necrosis and time to ε-peak. The χ^2 test or the Fisher's exact test was applied for dichotomous and categorical data. Unpaired *t* test was used to compare two continuous variables. Two-tailed *P* values less than .05 were considered as indicative of a statistically significant difference.

RESULTS

Patient characteristics are summarized in Table 1.

CDMI

Of the possible 400 segments, 52 (13%) could either not be adequately visualized at baseline (n = 30) or generated noisy, uninterpretable ε curves (n = 22) and were, therefore, excluded from the analysis. Most of these segments (83%) were considered dysfunctional on rest CE echocardiographic images. The remaining 348 (87%) segments were analyzed both qualitatively and quantitatively. Of these, 96 (28%) were supplied by arteries with less than 50% stenosis, 28 (8%) by arteries with 50% to 70% stenosis, 150 (43%) by arteries with 70% to 90% stenosis, and 74 (21%) by arteries with greater than 90% stenosis.

PSS and Rest Contractility

Of the 348 analyzable segments, 136 (39%) were graded as normal and 212 (61%) as dysfunctional (80 hypokinetic, 132 akinetic) (Figure 2). PSS was observed in 45/136 (33%) normal segments and in 152/212 (72%) dysfunctional segments (36 hypokinetic and 97 akinetic) (Figure 2).

ε-Peak, PSS, and Transmural Extent of Necrosis

According to CE MR, 112/212 (53%) dysfunctional segments exhibited less than 50% transmural hyperenhancement, whereas the

Table 1 Patient characteristics

Age, y	63 ± 8
Sex	20 M, 5 F
Anginal class I + II	23/25 (92%)
III + IV	2/25 (8%)
NYHA class I + II	9/25 (44%)
III + IV	14/25 (56%)
Previous Q-wave MI	19/25 (76%)
Diseased vessels	
LAD	24/25 (96%)
Cx or RCA	19/25 (76%)
LAD + Cx	16/25 (64%)
LAD + RCA	15/25 (60%)
Cx + RCA	14/25 (56%)
LAD + Cx + RCA	13/25 (56%)
End-diastolic volume, mL	138 ± 38
End-systolic volume, mL	92 ± 36
Ejection fraction, %	32 ± 10
WMS	32 ± 5

Cx, Circumflex coronary artery; *F*, female; *LAD*, left anterior descending coronary artery; *M*, male; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *RCA*, right coronary artery; *WMS*, global wall motion score.

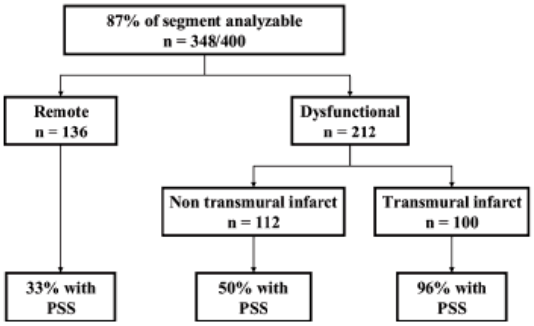

Figure 2 Prevalence of postsystolic shortening (*PSS*) among all analyzable segments.

remaining 100 (47%) dysfunctional segments showed greater than 50% transmural hyperenhancement. In the latter segments, systolic ε was negative in 83 (83%, ε-peak = −8.7 ± 5.2%) and biphasic in 17 (17%, ε-peak = −1.8 ± 5.2%). PSS was observed in 96/100 (96%) of the segments with greater than 50% transmural hyperenhancement and in 56/112 (50%) of the segments with less than 50% transmural hyperenhancement ($P < .0001$). As shown in Table 2, the amplitude of ε-ES was less and the time to ε-peak was longer in segments with greater than 50% than in those with less than 50% transmural hyperenhancement. Furthermore, a significant correlation was found between the time delay from AVC to ε-peak and the percentage of transmural hyperenhancement ($r = 0.69$, $P < .0001$) (Figure 3).

PSS and Contractile Reserve

As expected, contractile reserve was observed more frequently in segments with less than 50% than in those with greater than 50% transmural hyperenhancement (68/112 vs 8/100, $P < .001$). Interestingly, in segments exhibiting less than 50% transmural hyperen-

Table 2 Parameters of longitudinal deformation in normal and dysfunctional segments

	Remote (n = 136)	<50% Hyperenhancement (n = 112)	>50% Hyperenhancement (n = 100)
ε-ES, %	−10.0 ± 6.2	−6.7 ± 7.0†	−4.6 ± 4.9*†
ε-peak, %	−10.0 ± 5.9	−7.8 ± 7.3†	−7.5 ± 5.6
T ε-peak, ms	−10.5 ± 67	2.94 ± 76	108 ± 61*†
PSS, %	−0.5 ± 1.4	−1.0 ± 1.6	−2.8 ± 2.8*†
PSI, %	9 ± 10	18 ± 41%	56 ± 73%*†
Timing of ε-peak			
<AVC	90/136 (66%)	56/112 (50%)	4/100 (4%)
>AVC, <MVO	25/136 (18%)	27/112 (24%)	21/100 (21%)
>MVO	21/136 (15%)	29/112 (29%)	75/100 (75%)

AVC, Aortic valve closure; *ε-ES*, end-systolic strain; *MVO*, mitral valve opening; *ε-peak*, peak strain; *PSI*, postsystolic index; *PSS*, postsystolic shortening; *T ε-peak*, time from AVC to ε-peak.
*$P < .01$ vs <50% hyperhancement.
†$P < .01$ vs remote.

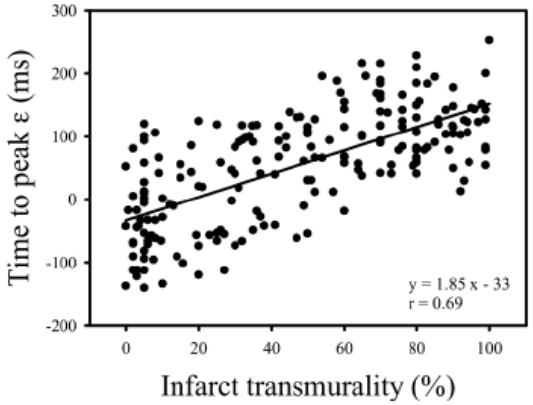

Figure 3 Scatterplot showing correlation between transmural extent of hyperenhancement and time delay from aortic valve closure to peak strain (ε) in all dysfunctional segments.

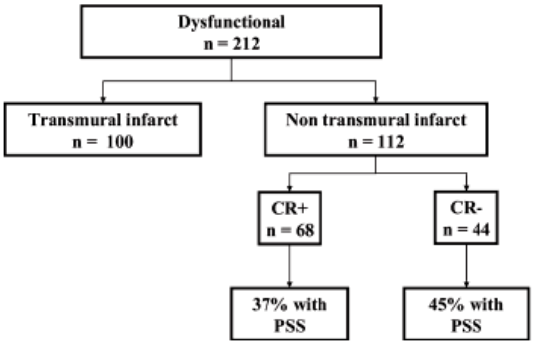

Figure 4 Prevalence of postsystolic shortening (*PSS*) in segments with less than 50% transmural hyperenhancement according to presence or absence of contractile reserve (*CR*).

hancement, the occurrence of PSS was similar whether contractile reserve was present or not (Figure 4). Similarly, no differences in ε-peak and in time delay from AVC to ε-peak were found among segments with or without contractile reserve (Table 3).

Table 3 Parameters of longitudinal deformation in dysfunctional segments with less than 50% hyperenhancement according to contractile reserve

	CR (+) (n = 68)	CR (−) (n = 44)	*P* value
ε-ES, %	−7.8 ± 7.1	−5.1 ± 6.6	.04
ε-peak, %	−8.8 ± 7.3	−6.1 ± 7.0	.06
T ε-peak, ms	−4 ± 73	11 ± 84	.3
PSS, %	−1.0 ± 1.8	−1.0 ± 1.4	.9
PSI, %	16 ± 34	22 ± 51	.4

CR, Contractile reserve; *ε-ES*, end-systolic strain; *ε-peak*, peak strain; *PSI*, postsystolic index; *PSS*, postsystolic shortening; *T ε-peak*, time from aortic valve closure to ε-peak.

DISCUSSION

In an attempt to overcome the limitations inherent in the visual scoring of wall motion in hearts with regional dysfunction, several noninvasive quantitative imaging methods have been developed. Motion-based techniques, such as Doppler myocardial velocity measurements, are influenced by tethering effects and, thus, may not represent regional function. In contrast, ultrasonic ε rate imaging provides several advantages for the quantification of rest or stress-induced ischemia[1,2]: it quantifies regional myocardial deformation with a high temporal resolution; it can quantify regional longitudinal deformation for all LV and right ventricular segments; changes in systolic ε and ε rate have been shown to parallel changes in global contractility and to be relatively heart rate independent; and systolic ε is related to global ejection performance as assessed by either stroke volume or ejection fraction. In the current study, we used this new approach to evaluate whether PSS, ie, myocardial deformation that occurs after AVC, may serve as a valid index of myocardial viability. Our results can be summarized as follows.

PSS is a universal feature of transmurally infarcted segments, in which it almost exclusively occurs after mitral valve opening.

PSS can also been seen, albeit less frequently, in nontransmurally infarcted segments. In this case, it equally occurs before and after mitral valve opening.

There is no relationship between the occurrence of PSS or its timing and the presence of contractile reserve.

Together with the positive correlation between the time to ε-peak and the transmural extent of hyperenhancement, our data, thus, suggest that PSS is not a marker of viability in patients with chronic LV ischemic dysfunction.

Postsystolic Deformation During Acute Myocardial Ischemia

PSS was first observed during acute coronary occlusion in experimental animals.[18,19] Immediately upon cessation of coronary flow, several mechanical events were found to occur simultaneously in these experiments, including a rapid decrease in the amplitude of ε-ES, a progressive delay of the onset of systolic contraction toward mid to end systole, and continuation of wall thickening after AVC. Shortly thereafter, systolic contraction is progressively being replaced by systolic lengthening. As a consequence, during early diastole, when LV pressure decreases, the dyskinetic segment shortens. This is a dominantly passive phenomenon, much like a spring that is stretched and shortens passively when the stretching force is removed.[11] As ischemia goes on, the ischemic myocardium becomes stiffer. Initially, this is a result of the development of ischemic contracture. Later on, however, tissue edema and fibrosis contribute as well. This increase in segmental stiffness mollifies the amplitude of both systolic lengthening and PSS.

Postsystolic Deformation and Myocardial Viability

Because release of coronary occlusion soon after the onset of ischemia results in a rapid normalization of all deformation indices, several authors have claimed that PSS represents actively contracting and, therefore, potentially viable myocardium. In a chronic animal model, Takayama et al[7] reported that the magnitude of PSS, measured by sonomicrometry, was a good predictor of the late return of regional myocardial function, thus, suggesting that PSS was an active process reflecting myocardial viability. Subsequently, Hosokawa et al[20] analyzed the cineventriculograms of 35 patients recovering from a first anterior myocardial infarction and found that PSS at baseline correlated closely with the recovery of wall motion at 3 months. More recently, Yang et al[21] reported significantly faster PSS velocities in viable compared with nonviable segments and proposed a threshold of 2 cm/s to identify viable myocardium with a sensitivity of 61% and a specificity of 97%.

The results of the current study are, thus, clearly at variance with those of these previous studies. Indeed, in our study, we found that the presence, timing, and amplitude of PSS were correlated with the transmural extent of scar in the infarcted region, the segments with the least amount of necrosis displaying the lowest occurrence of PSS, whereas those with transmural necrosis almost universally exhibited PSS. Our findings are nonetheless in agreement with those of Weidemann et al.[22] In a swine model of myocardial infarction, these authors also used ε rate imaging to study the regional deformation characteristics of both chronic nontransmural and transmural infarctions and found that transmural scar extent correlated closely with postsystolic ε and ε-ES at baseline. Our results are also in agreement with those of Hanekom et al[23] who found no significant differences in systolic and postsystolic ε-peak between viable and nonviable segments.

Study Limitations

Despite improvements, ε imaging is still limited by signal noise, and remains angle dependent. We have tried to minimize these problems by acquiring tissue velocity data with adequate temporal and spatial resolution, as well as by taking care that the ventricular walls were aligned with the ultrasound beam within 10 degrees during image acquisition. In addition, we did not attempt to quantify deformation in the different myocardial layers because of the concern that lateral resolution was insufficient to acquire this at 16-cm depth in the adult heart. Our data, therefore, reflect average longitudinal deformation across the entire wall and cannot assess the role of the different myocardial layers in the prediction of myocardial viability.

CONCLUSION

In chronic LV ischemic dysfunction, the high prevalence of PSS in scarred segments and its association with the transmural extent of necrosis indicates that PSS is not an accurate marker of myocardial viability.

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III- Relation entre fibrose et réponse à la resynchronisation cardiaque

Ces données permettent de comprendre qu'un retard de contraction mécanique n'est pas spécifique d'un retard d'activation électrique mais peut également être la conséquence d'une déformation passive d'une paroi fibreuse. Les deux mécanismes peuvent coexister notamment chez les patients insuffisants cardiaques ayant un bloc de branche gauche. Cette compréhension est importante pour l'identification des répondeurs à la resynchronisation cardiaque. En effet, il est théoriquement peu probable qu'une amélioration de la fonction ventriculaire gauche puisse être obtenue en resynchronisant une zone akinétique, retardée, dénuée de muscle viable.

Il nous est donc apparu important de confirmer cette hypothèse en caractérisant la réserve contractile de la paroi désynchronisée. Cette investigation[93] a été réalisée sur une cohorte de 19 patients insuffisants cardiaques adressés pour une resynchronisation biventriculaire. La viabilité myocardique dans les segments retardés était évaluée par la présence d'une réserve contractile en échographie de stress sous dobutamine. La présence d'une réserve contractile sur la paroi stimulée (latérale ou postéro-latérale)

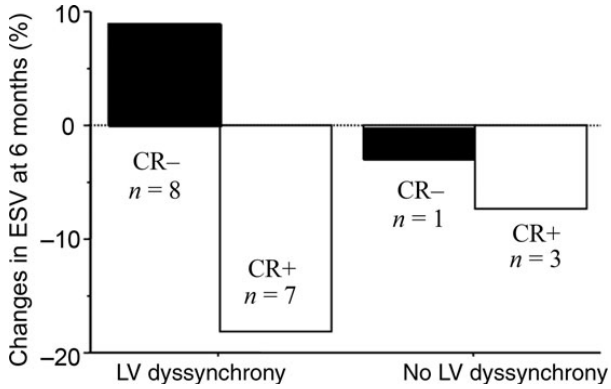

Figure 38: En l'absence de réserve contractile, l'asynchronisme persiste après resynchronisation alors que la présence d'une réserve contractile est associée à une réduction de l'asynchronisme après resynchronisation cardiaque

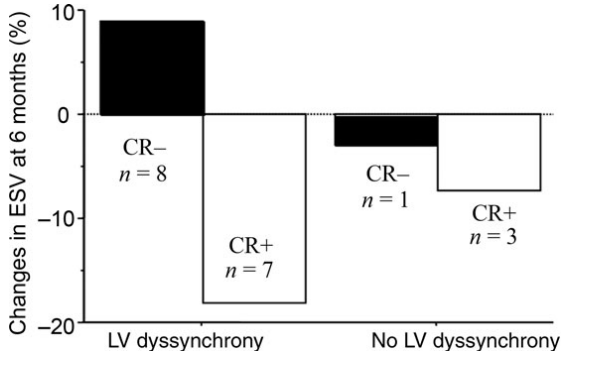

Figure 39 : la présence d'une réserve contractile et d'un

était associée à une correction de l'asynchronisme après resynchronisation alors que son absence ne modifiait pas le retard de contraction **(Figure 38)**. Par ailleurs, un remodelage bénéfique à 6 mois n'était observé que chez les patients ayant une réserve contractile sur la paroi stimulée **(Figure 39)**. Ce papier a été publié dans le journal Europace[93] et les résultats sont concordants avec d'autres études [94, 95, 96].

Europace (2007) 9, 739–743
doi:10.1093/europace/eum117

Importance of contractile reserve for CRT

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Received 1 March 2007; accepted after revision 3 May 2007; online publish-ahead-of-print 14 June 2007

KEYWORDS
Dyssynchrony;
Cardiac resynchronization therapy;
Contractile reserve;
Viability

Aims To assess whether response to cardiac resynchronization therapy (CRT) is related to myocardial viability in the paced left ventricular (LV) region, evaluated by contractile reserve (CR). Non-response to CRT may partly be due to inefficient pacing by the LV lead located in a fibrotic area.

Methods and results Nineteen patients (64 ± 13 years, 14 men, 9 ischaemic) with severe heart failure (EF = 27 ± 8%, QRS = 154 ± 25 ms) were included in the week after device implantation. Stroke volume (SV) and LV dyssynchrony (by Tissue Doppler Imaging) were successively assessed with CRT on and CRT off. Afterwards, CRT device was maintained off during dobutamine infusion to assess CR in the LV-pacing region. LV end-systolic volume (ESV) was assessed after 6 months to quantify reverse remodelling. CR in the paced LV region ($n = 10$, 5/9 ischaemic and 5/10 non-ischaemic) was correlated to a reduction in LV dyssynchrony under CRT (120 ± 76 vs. 78 ± 64 ms, $P = 0.02$). Conversely, LV dyssynchrony was unchanged (161 ± 100 vs. 163 ± 80 ms) without CR. In desynchronized patients (>65 ms, $n = 15$), increase in SV under CRT and changes in ESV at 6 months were +22 and −18%, respectively, when CR was present and 0% and +9%, respectively, when absent.

Conclusion Acute haemodynamic response and reverse remodelling under CRT require viability in the target region of LV lead.

Introduction

Cardiac resynchronization therapy (CRT) is an additional treatment option in the management of end-stage drug-refractory heart failure. Large clinical trials[1–9] have reported the sustained benefit of CRT in patients with severe heart failure (NYHA III/IV), impaired left ventricular ejection fraction (LVEF ≤35%), and a wide QRS complex (>120 ms). Beneficial effects of CRT include improvement of symptoms, stroke volume (SV), ejection fraction, mitral regurgitation, left ventricular (LV) remodelling, and survival. In spite of these encouraging results, ~20 to 30% of patients selected according to QRS duration criteria do not respond to CRT. Several observational studies have demonstrated that the main predictor of responsiveness to CRT is mechanical[10–19] rather than electrical dyssynchrony.[20] Among available techniques, echocardiographic assessment of LV dyssynchrony [mainly by M mode and Tissue Doppler Imaging (TDI)] seems to provide additional selection criteria for potential candidates to CRT. However, despite the presence of LV dyssynchrony, several patients still do not respond to CRT. It has been suggested[21] that LV lead positioning in scar tissue may be a determining factor for poor response to CRT on the basis of anecdotal report[22] and recently published trials,[23–25] assessing myocardial viability before device implantation. Indeed, LV pacing is likely to be less efficient because advanced tissue fibrosis may have severely altered local myocardial contractility and conduction properties.[26,27] The presence of myocardial viability can be evidenced by several validated non-invasive techniques such as nuclear imaging, low-dose dobutamine echocardiography, and contrast magnetic resonance imaging (MRI).[28] Contractile reserve (CR) using low-dose dobutamine correlated with the extent of fibrosis[29,30] and was a largely available method with high sensitivity and excellent specificity,[31] useful for ischaemic and non-ischaemic cardiomyopathy. We sought to assess whether CRT efficiency was related to the presence of CR in the target region of the LV lead, in patients with severe ischaemic or idiopathic cardiomyopathy.

Methods

Population

The study was performed in 19 stable patients, in the week (4 ± 1 days) after successful ventricular lead implantation in the lateral or posterolateral coronary vein for biventricular pacing intended for CRT. Patients with haemodynamic instability, recent acute coronary syndrome (<3 months), poor echogenicity, atrial fibrillation, or requiring permanent pacing were excluded. Informed consent was obtained from all patients, and the protocol was approved by our institutional review board.

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Biventricular pacemaker implantation

Three transvenous leads were inserted. The right atrial and ventricular (apical site) leads were positioned conventionally. The LV lead was inserted through the coronary sinus into either the lateral or the posterolateral cardiac vein. The biventricular pacing devices used were Biotronik, Berlin, Germany ($n = 2$), Saint Jude, Sylmar, CA, USA ($n = 3$), Guidant, Boston, MA, USA ($n = 8$), and Medtronic, Minneapolis, MN, USA ($n = 6$). After implantation, the atrioventricular interval was adjusted for optimal diastolic filling using Doppler echocardiography,[32] and no adjustment was made to the VV interval.

Echocardiography

For echocardiography study, patients were allowed to take their prescribed medication with an exception for beta-blocker therapy, which was withdrawn 48 h before the investigation. Before the test was started, baseline characteristics were recorded, and a venous line was secured. Patients were positioned in the left lateral decubitus, and images were obtained using a commercially available system (Vingmed system Seven, General Electric, Horten, Norway) with a 3.5 MHz transducer at a 16 cm depth in the parasternal and apical views. Echocardiographic data were successively acquired with CRT device on, 5 min after CRT deactivation (device programmed in VVI HR 30/min) and finally during low-dose dobutamine infusion. Dobutamine was infused in 3 min dose increments from 5 to 10 γ/kg/min to patients with CRT device off under continuous ECG and non-invasive blood pressure monitoring. Echocardiographic recordings consisted of 2D apical views coupled to colour Doppler data and LV outflow tract (LVOT) flow velocities using pulse Doppler flow signal. Echocardiographic data acquisition was repeated for each step (CRT device on, CRT device off, and after dobutamine infusion with CRT device off) and stored on optical disk for further analysis. For each measurement, three consecutive cardiac cycles were acquired during apnoea. For SV measurement, LVOT flow velocity was recorded in the apical view as recommended. Special care was taken to maintain the sample volume location throughout the echocardiographic study. SV was calculated using standard formulae.[33] TDI parameters were analysed offline from colour images (EchoPac, GE Vingmed, Horten, Norway). Myocardial velocities were computed from the basal portions of the septum and the LV lateral and posterior wall. LV dyssynchrony was defined as the delay in the peak systolic velocity between septum and LV wall receiving CRT, i.e. posterior or lateral wall according to chest X-ray. Significant LV dyssynchrony was considered when this time interval was $\geq$65 ms.[17] For all time measurement, ECG signal was amplified and mean value of three consecutive measures was used for analysis.

Contractile reserve

The apical cine loop sequences were interpreted qualitatively in accordance with previous guidelines[34] by two experienced observers blinded to clinical and other echocardiographic data. CR was solely considered for analysis in the target site of the LV-pacing device defined as lateral or posterolateral wall if LV-pacing lead was inserted in the lateral or posterolateral cardiac vein, respectively. Moreover, LV lead position was confirmed on chest X-ray (posterior–anterior and lateral views) systematically performed in days after device implantation. In this setting, regional myocardial function of mid-ventricular lateral and posterolateral walls was analysed at rest and under low-dose dobutamine and defined as (i) normal, (ii) hypokinetic, or (iii) akinetic. CR was considered present (CR+) in dysfunctional myocardium if segmental wall motion improved by one grade under dobutamine.

Follow-up

All patients were clinically and echocardiographically evaluated 6 months after device implantation. Patients without clinical improvement (NYHA class decrease $\leq$1) or with an episode of acute heart failure or requiring heart transplantation during the follow-up period were considered as non-responders.

Statistical analysis

Normally distributed continuous variables were expressed as mean $\pm$ SD. Dichotomous data were expressed as percentages. To compare numerical data between two or several groups, paired and unpaired student test or analysis of variance was used as appropriate. Dichotomized comparison was assessed by χ^2 test or the Fisher's exact test. Two-tailed P-values <0.05 were considered statistically significant. Analysis was performed using StatView® software (Version 5.0 for Windows®, SAS institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the population before CRT device implantation are summarized in *Table 1*. All patients fulfilled the recommended criteria for CRT.[35]

Left ventricular dyssynchrony and Stroke volume changes during cardiac resynchronization therapy

With CRT device off, mean LV dyssynchrony was 140 $\pm$ 88 ms and was considered as significant in 15 (79%) patients. Heart rate and blood pressure were unchanged with CRT device on or off (*Table 2*). On the whole, despite the non-significant decrease of LV dyssynchrony, the SV increased +10% with CRT device on, +10 and 7.5% in patients with and without LV dyssynchrony, respectively.

Table 1 Patient's characteristics ($n = 19$)

	Total	Responders	Non-responders
n	19	13	6
Age (years)	64 $\pm$ 13	64 $\pm$ 11	62 $\pm$ 15
Gender	14 M, 5 F	9 M, 4 F	5 M, 1 F
Baseline NYHA class III	15 (79)	11 (85)	4 (66)
Baseline NYHA class IV	4 (21)	2 (15)	2 (33)
QRS duration, ms	154 $\pm$ 25	154 $\pm$ 25	155 $\pm$ 27
Baseline ejection fraction (%)	27 $\pm$ 8	28 $\pm$ 10	22 $\pm$ 10
Baseline end diastolic volume (mL)	255 $\pm$ 56	274 $\pm$ 27	247 $\pm$ 64
Baseline end-systolic volume (mL)	189 $\pm$ 57	210 $\pm$ 36	179 $\pm$ 63
End-systolic volume at 6 months (mL)	177 $\pm$ 74	157 $\pm$ 57	233 $\pm$ 90*
Ischaemic, *n* (%)	9 (47)	7 (54)	2 (33)
Beta-blockers, *n* (%)	17 (89)	11 (85)	6 (100)
ACE-I/ARB, *n* (%)	18 (95)	12 (92)	6 (100)
Spironolactone, *n* (%)	12 (63)	7 (54)	5 (83)
LV lead in lateral vein, *n* (%)	10 (53)	7 (54)	3 (50)
LV lead in posterolateral vein, *n* (%)	9 (47)	6 (46)	3 (50)

*For $P < 0.05$ vs. responders.

NYHA, New York Heart Association; LV, left ventricular; ARB, angiotensin-receptor blocker.

Table 2 Clinical and echocardiographic characteristics under cardiac resynchronization therapy

		CRT off	CRT on	*P*
Stroke volume	mL	66 ± 25	73 ± 25	0.02
LV dyssynchrony	ms	139 ± 89	118 ± 82	0.11
Heart rate	bpm	75 ± 11	76 ± 12	0.2
Systolic blood pressure	mmHg	112 ± 17	114 ± 18	0.4

CRT, cardiac resynchronization therapy; LV, left ventricular.

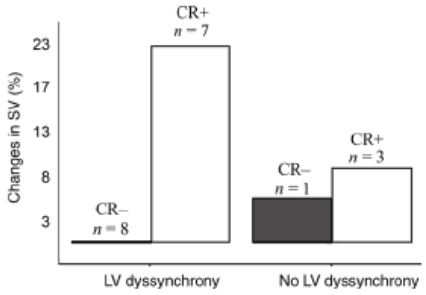

Figure 1 Changes of left ventricular dyssynchrony under cardiac resynchronization therapy in patients with and without contractile reserve.

Contractile reserve and response to cardiac resynchronization therapy

Acute haemodynamic response

According to chest X-ray, LV myocardial segment first stimulated was the lateral in 10 and the posterolateral wall in 9 patients. All these segments were graded as dysfunctional at baseline (10 hypokinetic and 9 akinetic). CR under low dose of dobutamine was observed in 10/19 of them, with no difference between ischaemic and idiopathic cardiomyopathy (5/9 and 5/10, respectively). In patients with CR in the LV target site for pacing, LV dyssynchrony (120 ± 76 vs. 78 ± 64 ms, $P = 0.02$, *Figure 1*) was significantly reduced with CRT device on, and likewise absence of CR (161 ± 100 vs. 163 ± 80 ms, ns) was associated with non-significant improvement of mechanical dyssynchrony. Mean increase of SV was 22% and 0% in desynchronized patients ($n = 15$) with and without CR, respectively (*Figure 2*).

After 6 months follow-up

One patient was heart transplanted, two admitted for acute heart failure, and three did not feel improved by CRT. End-systolic volume (ESV) reduction at 6 months was greater in responders than in non-responders (−12 ± 11 vs. +13 ± 27%, $P = 0.01$, *Table 1*). All non-responder patients ($n = 6$) had a LV lead placed in a segment without CR. In contrast, LV lead positioned in a segment with CR+ was observed in 10 of the 13 responders and was associated with greater ESV reduction ($P = 0.02$, *Figure 3*). ESV reduction was nearly unchanged (−0.04, 0, and −0.03%, respectively) for three patients with clinical improvement and LV lead in segment without CR.

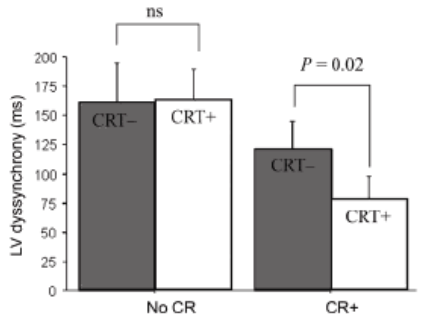

Figure 2 Changes in stroke volume according to contractile reserve and to the presence of left ventricular dyssynchrony. $P = 0.02$ between patients with and without contractile reserve.

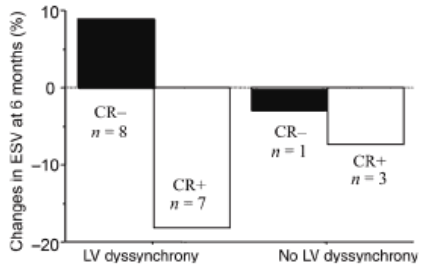

Figure 3 Changes in end-systolic volume at 6 months according to contractile reserve and to the presence of left ventricular dyssynchrony. $P = 0.02$ between patients with and without contractile reserve.

Discussion

The findings in the present study suggest that for efficient mechanical resynchronization in ischaemic and non-ischaemic cardiomyopathy, CRT requires the presence of myocardial viability in the LV lead target site. This underlines the importance of assessing viability before device implantation in order to guide LV lead position to ensure a pacing efficiency.

In patients with severe heart failure (NYHA III–IV), depressed LV function (ejection fraction < 35%), and wide QRS complex (QRS > 120 ms), the beneficial effects of CRT has been largely documented with improvement of symptoms and prognosis.[21] Reduced mechanical dyssynchrony under CRT decreases wall stress and mitral regurgitation volume and increases SV and LV dP/dt, and finally participates in reverse remodelling process.[36] However, most CRT studies demonstrated that up to 30% of patients were non-responders, because mechanical dyssynchrony could be absent despite wide QRS duration. This electro-mechanical dissociation has been confirmed by several studies,[20,37] and in this population, LV dyssynchrony was absent in nearly one-third of the patients with large QRS duration. This suggested that mechanical dyssynchrony

would be a more accurate predictor of CRT response. Several observational studies[10–19] and our data supported that LV dyssynchrony, and specifically the delay of posterolateral wall contraction, is a determining factor in the prediction of response to CRT. Besides the presence of LV dyssynchrony, some authors[21] hypothesized that viability of the stimulated LV area should be required in order to obtain efficient pacing substratum, and therefore successful CRT. In this situation, baseline echocardiography associated to dobutamine echocardiography provides the unique opportunity to assess accurately the CR matched to the desynchronized segment. Using this approach, we identified 8 of 15 desynchronized patients without CR. These patients exhibited a limited increase in SV under CRT (<5%) and reverse remodelling (ESV reduction at 6 months <10%). Unchanged mechanical dyssynchrony under CRT in patients with non-viable LV lead region suggests that lack of haemodynamic response could be partly due to an inefficient pacing. This supports the theory that in myocardium with advanced remodelling process, fibrosis and loss of contractile material may have severely altered myocardial conduction and contractile properties, which impeaches efficient biventricular pacing. Finally, lack of haemodynamic response and reverse remodelling under CRT in patients without CR, despite severe LV dyssynchrony, provide the strong evidence that LV dyssynchrony is necessary but not sufficient for CRT response. Finally, lack of haemodynamic response and reverse remodelling under CRT in patients without CR, despite severe LV dyssynchrony, provide the strong evidence that LV dyssynchrony is necessary but not sufficient for CRT response. Indeed, delayed wall motion is mainly a marker of myocardial dysfunction[38,39] and could be exhibited in viable and non-viable[40] segment according to load conditions.[40,41] Furthermore, extracellular matrix changes induced by remodelling were also found responsible for electrical conduction delay.[26,29] Thus, LV dyssynchrony is not a specific marker of response to CRT, and characterization of viability in desynchronized segments appears necessary to improve the selection of patients. This was recently supported by Bleeker *et al.*[23] who showed that in patients with severe ischaemic cardiomyopathy, 95% of responders to CRT have LV dyssynchrony (assessed by TDI) and no scar tissue (using late contrast MRI) in the posterolateral wall. In addition, Hummel *et al.*[24] using contrast ultrasound echocardiography for myocardial viability assessment reported similar findings in the ischaemic population. In our study, we extended these observations to patients with idiopathic-dilated cardiomyopathy, which represents nearly 50% of the population study.

In regards to these concordant results using different approaches, we suggest a routine assessment of myocardial viability together with dyssynchrony assessment before CRT to guide LV-pacing lead implantation. Indeed, the present study did not suggest that CRT should be avoided in the presence of scar, since three patients felt clinically improved despite a LV lead placed in the segment without CR. However, the results underline the importance to optimize the LV lead position, i.e. in a viable myocardial segment to ensure the chance of LV reverse remodelling. Finally, correlation between viability and CRT response raises the potential interest to perform CRT in less advanced stages of heart failure when reverse remodelling is still possible.

Limitations

These results should be regarded cautiously and some limitations should be underlined. First, lack of difference between ischaemic and non-ischaemic patients may be resulted from the small number of patients, and then results should be confirmed by a larger study. Second, response to CRT may be underestimated since RV lead was placed in the RV apex in all patients. Finally, one major difficulty of the study is the unclear correlation of the echocardiographically determined regions and the pacing site even after chest X-ray control. Others studies using NOGA system or CT should be performed to confirm these results.

Conclusions

In patients with severe, dilated cardiomyopathy, response to CRT required both the presence of LV dyssynchrony and preserved CR of the region where the LV-pacing lead was inserted in order to ensure efficient mechanical resynchronization. It is proposed that the detection of myocardial viability as well as the assessment of LV dyssynchrony should be routinely performed before CRT to guide LV-pacing lead implantation.

Conflict of interest: none declared.

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Les études en IRM cardiaque de l'équipe de Bax[97] montrent que la présence d'une nécrose transmurale dans la zone stimulée (latérale ou postéro-latérale, **Figure 40**) était associée à l'absence de réponse favorable à la resynchronisation cardiaque. Cependant, d'après l'équipe de White[98], il faut aussi prendre en compte la présence d'une nécrose septale qui serait un facteur de non-réponse à la resynchronisation cardiaque.

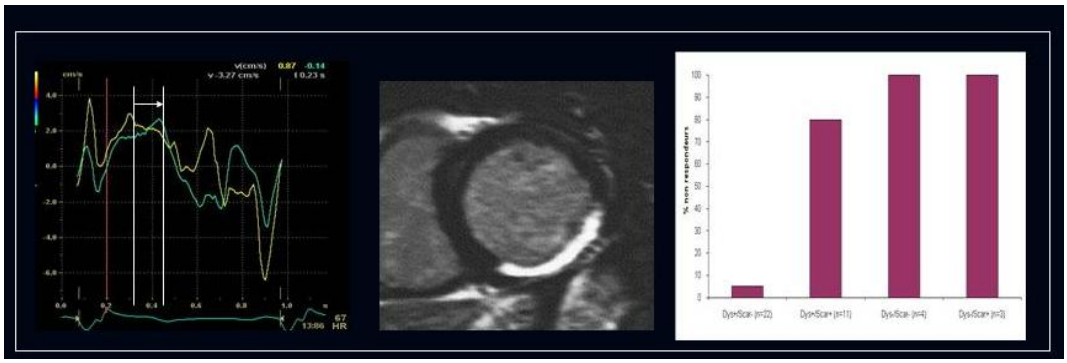

Figure 40: Réponse à la resynchronisation cardiaque en fonction de la présence d'une nécrose transmurale dans la paroi stimulée.

Enfin, cette même équipe de Bax[99] a finalement souligné qu'il existait une relation étroite entre le nombre de segments viables en **scintigraphie** et la variation de la fraction d'éjection ventriculaire gauche après CRT chez les patients ayant une cardiopathie ischémique (n=61). Les auteurs montrent qu'il faut plus de 44% (8/18 segments, **Figure 41**) de myocarde viable pour identifier les répondeurs avec une sensibilité de 74% et une spécificité de 87%.

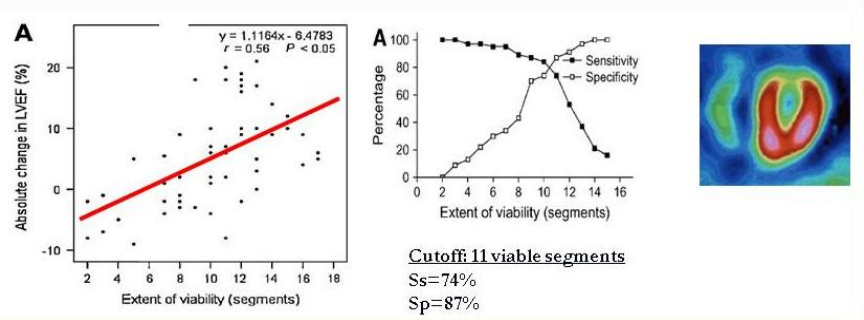

Figure 41 : Corrélation entre viabilité et augmentation de la FEVG après resynchronisation cardiaque

L'échographie d'effort peut également être utilisée pour identifier une réserve contractile et prédire la réponse à la CRT. L'équipe de Liège de Luc Pierard[100] a démontré qu'une augmentation de 6.5% de la fraction d'éjection à l'effort permettait d'identifier les répondeurs avec une sensibilité de 90% et une spécificité de 85%. Une étude récente de l'équipe de Guido Rocchi[101] a utilisé l'échographie d'effort pour caractériser la viabilité de la paroi latérale avant resynchronisation cardiaque. Le groupe montre 100% de réponse lorsque cette paroi est viable et que l'asynchronisme d'effort est supérieur aux données de repos pour prédire la réponse à la resynchronisation cardiaque.

IV- Combinaison de la contractilité et de l'asynchronisme

Ces études montrent les limites de l'asynchronisme dans la détermination de la réponse à la resynchronisation cardiaque. La nécessité de prendre en compte la contractilité résiduelle a été récemment soulignée par Patricia Réant[102] qui a clairement démontré que les super-répondeurs et les répondeurs à la resynchronisation cardiaque avaient une contractilité évaluée par le strain global supérieure aux non-répondeurs. Une étude intéressante de l'équipe de Carasso[103] a aussi montré qu'une altération sévère de la contractilité régionale évaluée sur le profil des courbes de déformation longitudinale en speckle tracking était fortement prédictive de l'absence de réponse à la CRT. L'investigation complémentaire par une imagerie de la viabilité apparaît donc comme un complément nécessaire. Mais cette approche multi-modalité est en pratique contraignante et coûteuse. La solution alternative serait de coupler l'information sur la contractilité et l'asynchronisme dans un seul et même indice.

4.1 Choix de l'outil de quantification de la déformation myocardique

La première étape avant le développement de cet indice a été de déterminer l'outil (entre le Doppler tissulaire et le speckle tracking) à utiliser pour apprécier la déformation myocardique et l'asynchronisme mécanique. Les résultats de l'étude PROSPECT ont jeté un doute sur la reproductibilité des paramètres dérivés du DTI. Il est donc licite de se demander si le Doppler tissulaire permet d'apprécier précisément la déformation myocardique chez les patients insuffisants cardiaques. La réduction de la contractilité et l'élargissement du ventricule gauche dans cette population peuvent en effet contribuer à réduire le rapport signal sur bruit et rendre l'analyse plus délicate. Ce problème est abordé dans l'étude suivante [104].

4.1.1-Impact de la dilatation ventriculaire sur la précision du DTI

Dans cette étude**,** nous avons évalué l'influence de la dilatation ventriculaire gauche sur les mesures de déformation myocardique et d'asynchronisme mécanique par la méthode du Doppler tissulaire et par la méthode du speckle tracking. Cette étude, menée chez 92 patients insuffisants cardiaques adressés pour une resynchronisation cardiaque, a comparé la précision du Doppler tissulaire et du speckle tracking pour la quantification de la contraction régionale et l'asynchronisme myocardique. Ces comparaisons ont été ajustées au volume ventriculaire gauche. Les résultats montrent que les indices de déformation myocardique dérivés du speckle tracking restaient corrélés au score de contraction visuelle indépendamment de la taille du ventricule gauche. En revanche, le pic de vélocité systolique (onde S) en DTI ne permettait pas de distinguer les segments à contraction normale et altérée lorsque le volume télé-diastolique était >250mL **(Figure 42)**. Par ailleurs, les indices d'asynchronisme mécanique dérivés du DTI n'étaient pas corrélés au bénéfice de la resynchronisation cardiaque. Ces résultats démontrent que la quantification de la déformation et l'asynchronisme myocardique sont limités en DTI par l'imprécision induite lorsque le ventricule gauche est dilaté.

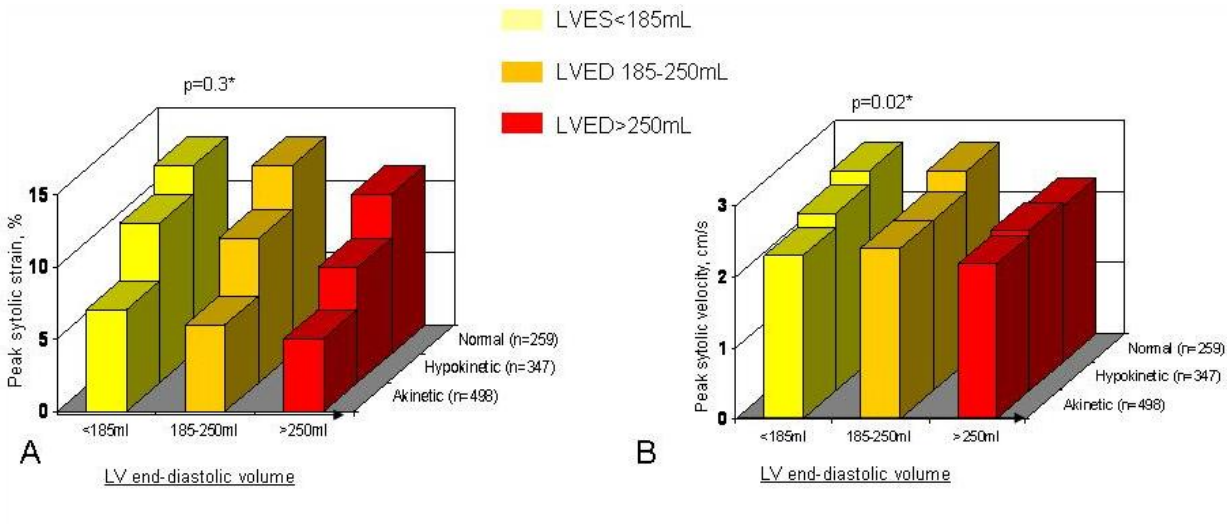

Figure 42: Corrélation entre le strain longitudinal en speckle tracking (A) et le pic de vélocité en DTI avec le score de contraction régionale selon la taille du ventricule gauche

Impact of Left Ventricular Size on Tissue Doppler and Longitudinal Strain by Speckle Tracking for Assessing Wall Motion and Mechanical Dyssynchrony in Candidates for Cardiac Resynchronization Therapy

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Background: Myocardial dysfunction and left ventricular (LV) geometry deformation may reduce the accuracy of tissue Doppler imaging (TDI) in assessing myocardial contractility.

Methods: In 92 patients with heart failure who underwent cardiac resynchronization therapy (CRT), we assessed the impact of LV end-diastolic volume on the accuracy of peak longitudinal velocity (TDI) and strain (ϵ_L by speckle tracking) to assess regional wall motion and LV dyssynchrony.

Results: Peak-ϵ correlated to normal (−13% ± 6%, n = 259), hypokinetic (−10% ± 5%, n = 347), and akinetic (−7% ± 5%, n = 498, $P < .0001$) wall motion independent of LV size. In contrast, velocity failed to distinguish normal from dysfunctional segments in patients with severe LV dilatation (end-diastolic volume > 250 mL). The 12 standard deviation of time to peak systolic velocity and the opposing septal-lateral wall delay by strain and TDI failed to predict response to CRT, whereas the 12 segment standard deviation of time to peak ϵ correlated to end-systolic volume reduction ($r = -0.39$, $P < .001$).

Conclusion: Accuracy of TDI in assessing LV wall regional motion is limited in severely dilated ventricles and probably affects LV dyssynchrony measurement. (J Am Soc Echocardiogr 2009;22:695-701.)

Keywords: Cardiac resynchronization therapy, Tissue Doppler, Speckle tracking

Several large clinical trials have confirmed the sustained benefit of cardiac resynchronization therapy (CRT) in patients with symptomatic severe left ventricular (LV) dysfunction and wide QRS duration.[1-8] The beneficial effects of CRT include improvement of symptoms,[1-8] ejection fraction,[2,4,8] mitral regurgitation,[1,4] LV remodeling,[1,2,4] and survival.[8] Despite these encouraging results, approximately 30% of patients selected according to QRS duration criteria do not respond to CRT.[8] Observational studies have consistently demonstrated that the main predictor of responsiveness to CRT is mechanical rather than electrical dyssynchrony.[9-14] Measurement of regional longitudinal myocardial electrical-mechanical events at the base of the heart using velocity data acquired with tissue Doppler imaging (TDI)[12,15] has been proposed to enhance the identification of mechanical dyssynchrony and thus patient selection for those likely to respond to CRT. In patients with heart failure (HF), TDI has had an ever increasing clinical utility because peak systolic longitudinal velocity is used for assessing ventricular function.[16] However, in patients with HF, spherical LV deformation affects the base of the heart predominantly and increases the misalignment of Doppler incidence angle along with myocardial motion. Together with reduction of tissue velocity caused by myocardial dysfunction, the reduction in signal/noise ratio could explain the lesser accuracy of TDI to reliably represent myocardial motion in patients with HF. In the present study, we evaluated the impact of LV size on the accuracy of peak velocity and time to systolic velocity by TDI to quantify LV regional wall motion and dyssynchrony in patients with HF before CRT compared with peak and time to peak strain (ϵ) by two-dimensional (2D) speckle tracking.

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Dr Pascal Lim was funded by a grant from the French Federation of Cardiology and the French Society of Cardiology. This work was also supported in part by the National Space Biomedical Research Institute through NASA NCC 9-58, the Department of Defense (Ft Dietrich, MD, USAMRMC Grant 02360007). This work is also supported in part by the National Institutes of Health, National Center for Research Resources, General Clinical Research Center Grant MO1 RR-018390.

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0894-7317/$36.00

doi:10.1016/j.echo.2009.04.015

MATERIALS AND METHODS

Study Population

The study included 92 patients with symptomatic HF and QRS duration > 120 ms who had conventional TDI and longitudinal ϵ analysis by 2D speckle tracking before implantation of a biventricular device. The study was conducted in a retrospective and prospective consecutive group of patients.

The retrospective group was selected from 589 consecutive patients with HF who underwent implantation of a biventricular device

at the Cleveland Clinic between January 2005 and December 2006. Patients were selected if they had a complete baseline echocardiographic study performed 3 months before device implantation on a Vivid 7 system (GE, Vingmed System 7, Horten, Norway) and an echocardiographic follow-up (>3 months) was available (120/589). Complete baseline echocardiography included standard grey scale and color TDI in the apical views (2, 3, and 4 chamber) with high frame rates (>35 frame/sec). Of these 120 selected patients, 50 were excluded (5 had implants < 3 months after an acute coronary syndrome or cardiac surgery, 41 had > 2 nonanalyzable segments by 2D speckle tracking [n = 30] or TDI [n = 17], and 4 had permanent atrial fibrillation). After device implantation, 5 additional patients were excluded (inadequate CRT delivery, ie, LV pacing rate was < 50%, 3 with paroxysmal atrial fibrillation, and 2 with an increased LV lead threshold). Ultimately, 65 patients were included in the retrospective group.

Prospective

The study was prospectively conducted in a cohort of patients with HF who were recruited consecutively before biventricular device implantation at the Cleveland Clinic from January 2007 to May 2007. Patients were included if they met all the following criteria: symptomatic HF, age between 18 and 75 years, left ventricular ejection fraction (LVEF) < 35%, and sinus rhythm with QRS duration > 120 ms. Exclusion criteria were recent cardiac event (<3 months after an acute coronary syndrome or cardiac surgery), inadequate CRT delivery after 3-month follow-up (LV pacing rate was < 50%), and > 2 nonanalyzable segments by speckle tracking or TDI. Patients in the study (n = 27) underwent 2D echocardiography before implantation on a Vivid 7 system with high frame rate and color TDI in the apical views. At 3 months, 2D echocardiography was repeated to quantify reverse remodeling after CRT. All patients had given informed consent, and the study protocol was approved by the Cleveland Clinic Review Board.

Biventricular Pacemaker Implantation

CRT was provided in the standard fashion with 3 transvenous leads. The right atrial and ventricular (apical site) leads were positioned conventionally. The LV lead was inserted through the coronary sinus and positioned into the lateral (n = 33), posterolateral (n = 41), anterolateral (n = 8), or middle cardiac vein (n = 4). Lead position was defined by coronary sinus angiogram data. Epicardial implantation was required in 6 patients. Biventricular pacing devices used included Medtronic (Minneapolis, MN, n = 54), Saint Jude Medical (Sylmar, CA, n = 25), and Guidant-Johnson and Johnson (Boston, MA; n = 13). After implantation, the atrioventricular interval was adjusted for optimal diastolic filling using Doppler echocardiographic assessment of mitral inflow, and V-V timing was programmed to be simultaneous in all cases. All devices were systematically interrogated within 3 months after the CRT procedure to ascertain their proper functioning.

Follow-up

Baseline and 3-month clinical characteristics were extracted from medical reports. Responders were defined by the presence of significant reverse remodeling (LV end-systolic [LVES] volume reduction > 15% by Simpson biplane method) at 3 months after CRT.

Quantification of Myocardial Function

Regional wall motion was graded semiquantitatively as normal, hypokinetic, and akinetic in the 12 apical segments (mid and base) of the ventricle by 2 independent experienced physicians blinded to strain values. A consensus grading was used for segments with discordant scoring. The apical segments were not analyzed because of the unfavorable angle of apical myocardial motion and geometry with respect to the transducer orientation. End-diastolic volume (EDV) and end-systolic volume were determined using biplane Simpson method to compute LVEF by an experimented physician blinded to strain and TDI data.

Peak Velocity (by Tissue Doppler Imaging) Analysis

Basal and midventricular velocity curves (n = 12) derived from color TDI sequences (EchoPac, GE Vingmed, Horten, Norway) were exported for off-line analysis. Peak and time to peak velocity were automatically computed on Excel (Microsoft Corp, Redmond, WA). The reference timing point was defined at the end diastole (at the peak of the R wave on the electrocardiogram tracing) with the timing of systole defined as aortic valve opening and closure determined by sampling LV outflow tract pulsed Doppler flow. When the velocity curve was exclusively negative during the systolic ejection period, time to peak velocity was defined at end systole and peak velocity was considered to be zero. Significant LV dyssynchrony was considered when the 12-segment standard deviation of time to peak systolic velocity (12SD-TDI) and the septal-lateral opposing wall delay were > 33 ms[15] and > 65 ms,[12] respectively.

Peak Longitudinal Strain by Speckle Tracking Analysis

To compute longitudinal ϵ curves by 2D speckle tracking (EchoPac), end diastole was chosen as the reference time point. Mid and basal ventricular segment strain curves were exported for an automatic analysis in Excel. Peak ϵ and time to peak ϵ in the 12 segments was defined as the minimum value of the ϵ curve within the cardiac cycle and the time to this minimum value, respectively. The 12 segment standard deviation of time to peak ϵ (12SD-ϵ)[17] and the opposing septal-lateral strain delay were used to define LV dyssynchrony.

Statistical Analysis

Normally distributed continuous variables were expressed as mean ± SD. Dichotomous data were expressed as percentages. We assessed the impact of segment location and LV size on the accuracy of peak systolic velocity and strain to evaluate wall motion by using 2-way analysis of variance. To compare numeric data between 2 groups, paired and unpaired Student *t* tests were used as appropriate. Dichotomized comparisons were assessed by the chi-square test or Fisher's exact test. Linear correlation was used to compare continuous variables. SD-TDI and SD-ϵ were adjusted to RR interval according to Bazett's formula[18] for comparison. Interobserver and intraobserver variability were assessed in 10 random patients and expressed as the SD of the difference between 2 paired measurements and as a percentage of variability (SD was divided by the average value of the variable). Two-tailed probability values less than .05 were considered statistically significant.

RESULTS

The study population had an average age of 63 ± 13 years, 66 were male, and 93% (n = 86/92) were severely symptomatic (New York Heart Association class III) with a mean LVEF of 25% ± 9%, a QRS duration of 154 ± 29 ms, and a mean EDV of 235 ± 90 mL (Table 1).

Accuracy of Speckle Tracking in Assessing Left Ventricular Wall Motion

Of the 1104 segments, 259 (23.5%) were graded as normal, 347 (31.5%) were graded as hypokinetic, and 498 (45%) were graded as akinetic before CRT. All segments were analyzable by speckle tracking and TDI. Longitudinal peak strain identified normal (−13% ± 6%), hypokinetic (−10% ± 5%), and akinetic (−7% ± 5%) wall motion. Longitudinal strain values correlated to regional wall motion without being affected by segment location (Figure 2A). Finally, the mean value of the 12 regional peak strain correlated well with LV ejection fraction ($r = -0.59$, $P < .0001$, Figure 3C).

Accuracy of Peak Systolic Velocity in Assessing Left Ventricular Wall Motion

For velocity by TDI, peak systolic velocity was higher in the basal portion than in the midportion of the ventricle (Figure 2B, $P = .0007$ for interaction between wall motion and segment location). Peak systolic velocity adjusted to segment location was greater in normal segments than in dysfunctional segments but did not differ between akinetic and hypokinetic segments. In addition, peak systolic velocity decreased with the severity of LV enlargement (Figure 3B, $P = .02$ for interaction between wall motion and LV size) and failed to correlate with wall motion score in patients with severe LV enlargement (EDV > 250 mL, Figure 3B).

Accuracy of Speckle Tracking in Assessing Response to Cardiac Resynchronization Therapy

After 3 months of follow-up, 49 patients (53%) were clinically improved by CRT, 33 patients (36%) were unchanged, and 10 patients (11%) had worsened outcomes (5 died, 2 underwent heart transplantation, and 3 had worsened New York Heart Association class). The mean LVES volume reduction was −16% ± 24% (range −59% to +54%). The end-systolic volume reduction was > 15% in 57 patients (62% of responders), between −15% and 0% in 14 patients (15%), and increased in 21 patients (23%). The baseline clinical and standard echocardiographic parameters of responders and nonresponders are addressed in Table 1. The 12 SD-ϵ was higher in responders than nonresponders (125 ± 34 ms vs 100 ± 34 ms, $P = .0005$) and correlated with QRS duration ($r = 0.25$, $P = .01$) and LVES volume reduction at 3 months ($r = -0.39$, $P < .001$, Figure 4A). In contrast, opposing wall delay by strain failed to predict response to CRT (Figure 4B).

Accuracy of Tissue Doppler Imaging in Assessing Response to Cardiac Resynchronization Therapy

Significant dyssynchrony was observed in 83 of 92 patients (90%) for 12SD-TDI > 33 ms and in 40 of 92 patients (43%) for opposing wall delay > 65 ms without difference between responders and nonresponders (34/35 vs 49/57, $P = .07$ for 12SD-TDI and 17/35 vs 23/57, $P = .4$ for opposing wall delay). Neither 12SD-TDI nor opposing wall delay correlated with LVES reduction regardless of HF cause (Figure 4C-D), QRS duration, and SD-ϵ even after adjustment to LV size.

Reproducibility

Intra- and interobserver reproducibility were 1.3% (8%) and 1.4% (9%) for peak strain (0.4 cm/s [17%]) and peak systolic velocity (0.5 cm/s [23%]), respectively. For dyssynchrony indexes, intra- and interobserver reproducibility were 19 ms (17%) and 27 ms (24%) for the 12SD-ϵ, respectively, and 7 ms (13%) and 9 ms (17%) for the 12SD-TDI, respectively.

Table 1 Population characteristics of responders and nonresponders

	All	Responders	Nonresponders
N	92	57	35
Age (y)	63 ± 13	65 ± 12	60 ± 14[a]
Gender, M, n (%)	66 (72)	41 (72)	25 (71)
Baseline NYHA class III, n (%)	86 (93)	53 (93)	33 (94)
QRS duration, ms	154 ± 29	157 ± 28	147 ± 30
Baseline EF (%)	25 ± 9	26 ± 9	24 ± 8
EDV, mL	235 ± 90	220 ± 82	258 ± 98
ESV, mL	178 ± 80	165 ± 72	200 ± 88[a]
Ischemic, n (%)	35 (38)	18 (32)	17 (49)
Beta-blockers, n (%)	78 (85)	48 (84)	30 (86)
ACEI/ARB, n (%)	57 (88)	35 (83)	22 (95)
Spironolactone, n (%)	31 (48)	17 (40)	14 (61)
Lead position, L or PL	74 (80)	47 (82)	27 (77)

NYHA, New York Heart Association; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]For P value < .05 between responders and nonresponders.

DISCUSSION

TDI of longitudinal myocardial velocities has been proposed as a method to quantify intraventricular mechanical dyssynchrony in patients with HF and to predict response to CRT. However, this study brings to light a significant limitation of TDI to represent accurately the velocity amplitude and timing of wall motion in patients with severe LV dilatation. Indeed, these results demonstrate that peak systolic velocity by TDI does not accurately represent myocardial contractility in patients with severe LV enlargement. This may explain why the time delay used to quantify intraventricular LV dyssynchrony does not correlate to CRT response as defined by reverse remodeling. This limitation may in part account for the somewhat disappointing results reported using TDI to assess dyssynchrony in some single-center studies[19] and in the recently reported multicenter PROSPECT trial.[20] Accordingly, the sum of these data should lead to caution before using the TDI time to peak velocity method as a tool to assist current practice and selection of candidates for CRT.

Limitation of Tissue Doppler for Wall Motion Quantification

TDI is commonly viewed as a quick and easy tool for wall motion quantification, generally available on current echocardiography systems. The Doppler signal assimilated as tissue velocity is a noised signal processed from active and passive myocardial contractility, the translational global heart motion, and a part of nonfiltered blood flow signal. The amplitude of Doppler signal for each component will depend on the alignment of the probe and its accuracy to represent the effective part of active myocardial contractility on the signal/noise ratio. In dysfunctional segments, the Doppler signal from the myocardial contractility is reduced and the noise is unchanged. As shown in the present study, the signal/noise ratio may be so critically reduced in some patients that velocity profiles fail to represent contractility and prevent an accurate discernment between akinetic and hypokinetic contraction. In addition, the malalignment of the probe with respect to the myocardial motion increases in patients with spherical LV deformation[21] and contributes to further reduce the signal noise in this population.

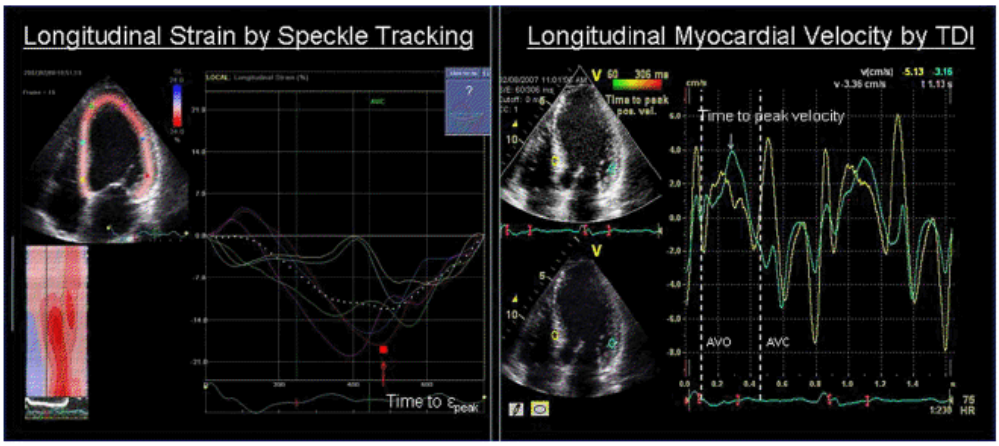

Figure 1 Peak longitudinal strain by speckle tracking was defined as the lower strain value during the cardiac cycle, and peak systolic velocity by TDI was defined as the maximum velocity value during the systolic period defined by aortic valve opening and closure. TDI, Tissue Doppler imaging.

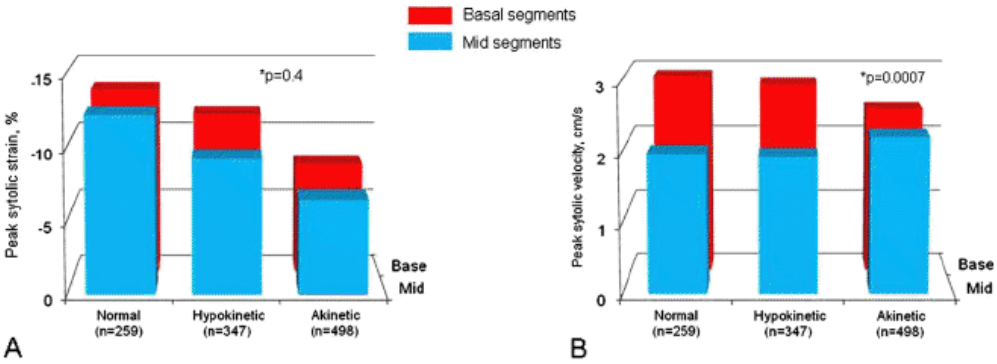

Figure 2 Peak longitudinal strain **(A)** and systolic velocities **(B)** according to wall motion score after adjustment to segment location. *For 2-way analysis of variance showing a significant impact of segment location for velocities and not for longitudinal strain.

Limitation of Tissue Doppler for Dyssynchrony Quantification

These limitations must be appreciated and incorporated into our daily practice because TDI measurement is being routinely used for clinical decision making.[22] Indeed, in patients with symptomatic HF who are candidates for CRT, the 12-segment SD > 33 ms of time to peak systolic velocity and the septal-lateral opposing wall delay > 65 ms are commonly considered the gold standard to define significant intraventricular dyssynchrony and to predict reverse remodeling after CRT.[11] However, in a prospective, multicenter setting, the PROSPECT study,[20] which sought to test the performance of these mechanical dyssynchrony markers, neither the SD-TDI nor the opposing wall delay was predictive of response to CRT. In addition, the TDI parameters were highly variable with an interobserver variability > 30%. In the present study, despite an objective automatic assessment of time to peak velocity and a careful review of TDI velocity curves, peak systolic velocity did not accurately reflect the regional wall motion, especially in dilated LV and dysfunctional segments. Thus, it seems potentially problematic to use the timing of wall motion to assess mechanical dyssynchrony if the amplitude fails to represent myocardial contractility. The limitations of time delay by TDI to assess LV dyssynchrony to predict response to CRT in patients with HF have also been reported by others (Soliman et al[19] and RETHINQ trials[23]). The suboptimal accuracy of TDI to predict response to CRT may be explained by a drawback of the Doppler technique in patients with HF in whom the signal-to-noise ratio of TDI is particularly affected by the myocardial dysfunction (minimal base to apex motion), translational and tethering effects,[24] and malalignment of the Doppler sample volume, which increases as LV geometry becomes globular. These issues may explain the difficulty in identifying peak contraction in the flat velocity contour of a failing heart.[25] This is particularly salient in this study because the patients had significantly larger LV volumes than those in the validation study by Yu et al[11] (231 ± 90 mL vs 193 ± 81 mL in Yu et al's study; $P < .05$).

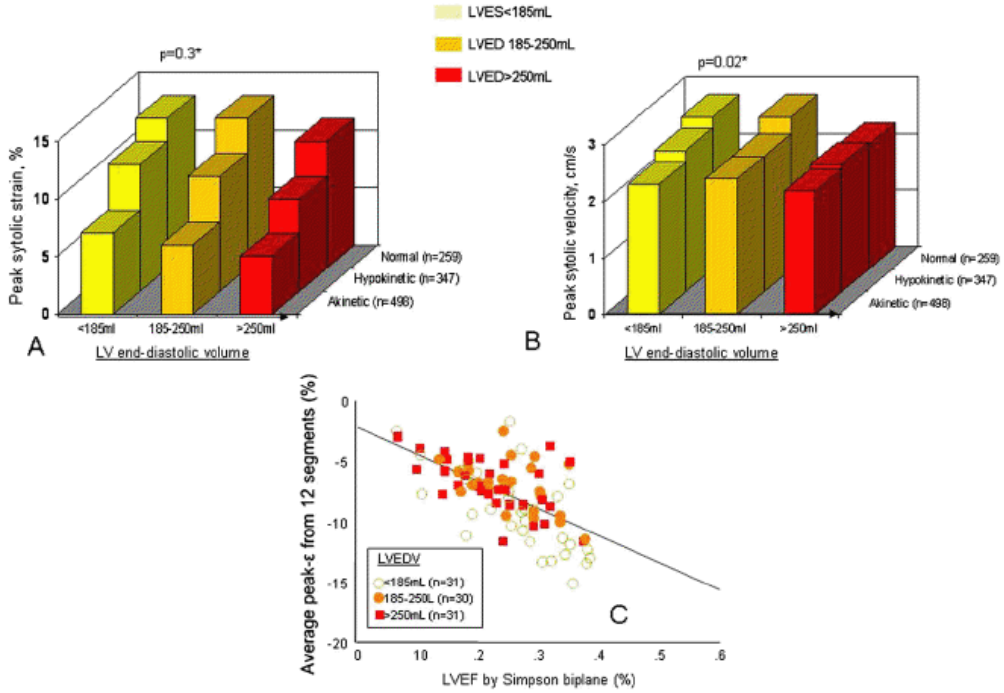

Figure 3 Peak longitudinal strain by speckle tracking **(A)** and peak systolic velocity **(B)** according to the wall motion score (z) and severity of LV enlargement (x). *For 2-way analysis of variance showing the significant interaction between LV enlargement and wall motion score for peak systolic velocity but not for longitudinal strain by speckle tracking. **C**, Correlation of the 12-segment mean peak longitudinal strain value and LVEF by Simpson biplane. LVES, Left ventricular end systolic; LVED, left ventricular end diastolic; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.

Longitudinal Strain by Speckle Tracking for Dyssynchrony Quantification

Time delay from speckle tracking appears better correlated to QRS duration and reverse remodeling after CRT. The superiority of strain dyssynchrony index over TDI index to predict response to CRT is debated.[24,26-28] Discrepancies may be related to the technical aspects of strain imaging. Strain as compared with velocity imaging is free from the passive effect of tethering and translational motion and appears more robust in assessing wall motion and probably timing. In addition, strain by speckle tracking has the advantage over strain by TDI through angle independence and is less affected by the ventricular geometric deformation compared to the Doppler signal, which is confounded by the nonfiltered blood flow and the global translational motion. However, despite the relative superiority of longitudinal strain by speckle tracking, the SD of time to peak strain has a moderate accuracy in assessing response to CRT. This limitation may be partly explained by the fact that dyssynchrony index based on time measurement does not take into account the residual contractility of the underlying myocardium to predict response to CRT. In ischemic and dilated cardiomyopathy, delayed contraction is a nonspecific marker of myocardial dysfunction.[29-31] Indeed, postsystolic shortening may be observed in scar,[32,33] fibrosis,[34,35] and viable myocardium depending on the load condition. This limitation has been underlined recently, and some authors have suggested investigating myocardial viability[36-38] and contractile reserve[39,40] as complementary to LV dyssynchrony to better identify responders. Notably, the superiority of SD-ε over strain septal lateral wall delay to predict response suggests that dyssynchrony assessment should not be limited to only 2 segments.

STUDY LIMITATIONS

The study was performed in patients with a good image quality. We did not attempt to evaluate speckle tracking dyssynchrony index in patients with a poor acoustic window because the quality of echocardiographic imaging is important for all strain-based analysis. Optimal image quality is a limitation preventing the extensive use of speckle tracking analysis in all patients. Peak and time to peak of regional contractility by TDI and longitudinal strain by speckle tracking were quantified automatically and reviewed carefully. This approach may limit the accuracy of these measurements because the experience of the investigator was not required. However, we think that this analysis is the best way to avoid a bias of measurement. In view of these limitations, we believe that LV dyssynchrony parameters from TDI and speckle tracking should both be used carefully for clinical decision making.

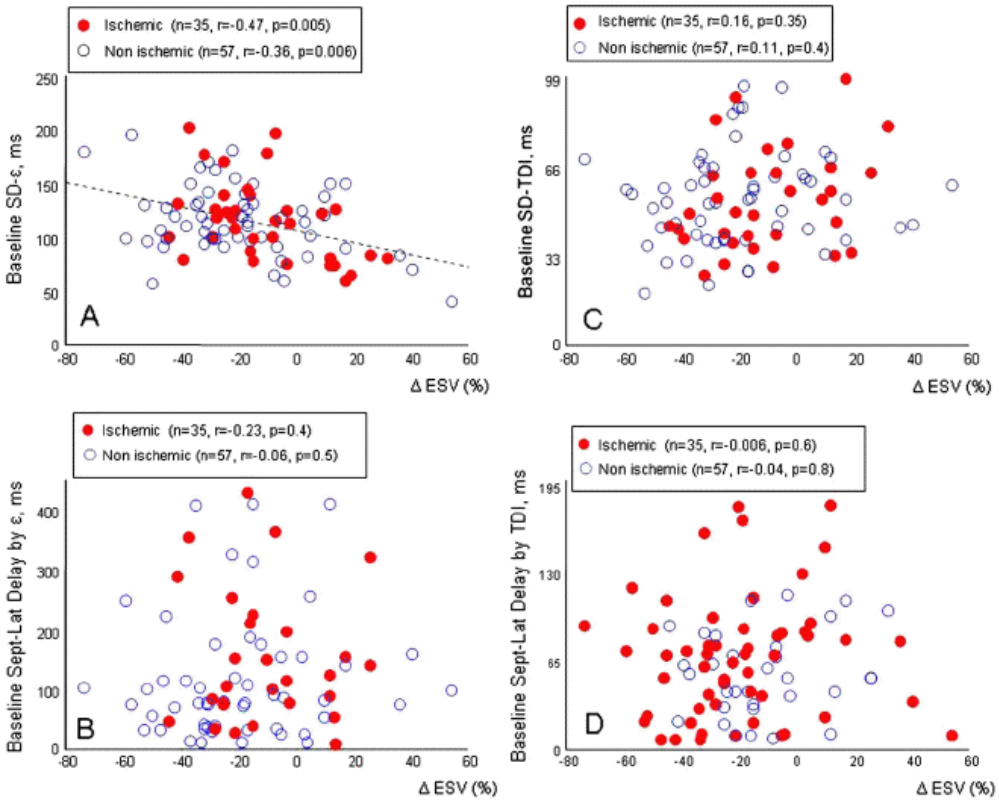

Figure 4 Correlation between the 12SD by strain **(A)** and TDI **(C)** and the opposing wall delay by strain **(B)**, TDI **(D)**, and reverse remodeling after CRT. SD, Standard deviation; TDI, tissue Doppler imaging; ESV, end-systolic volume.

CONCLUSIONS

In patients with severely dilated LV dysfunction, peak systolic velocity by TDI was not accurate enough to assess regional LV wall motion and dyssynchrony. In contrast, longitudinal strain by speckle tracking is not affected by LV size and correlates better to myocardial contractility. This may explain the superiority of SD of time to peak strain compared with 12SD-TDI for the identification of CRT responders.

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4.1.2- La supériorité du speckle tracking

par rapport au Doppler tissulaire a été renforcée dans ce second travail (Nahum et al. Circulation Imaging, 2010) comparant la valeur pronostique du strain longitudinal global en speckle tracking et de l'onde S à l'anneau mitral chez les patients insuffisants cardiaques. Cette étude incluait 125 patients insuffisants cardiaques symptomatiques (63±16 ans, 61% NYHA >II) présentant une dysfonction ventriculaire gauche systolique (FEVG=31±10%). L'onde de vélocité systolique à l'anneau mitral et le strain global longitudinal en speckle tracking ont été comparés à la survenue d'un évènement cardiaque majeur (n=47, 38%) incluant le décès (n=15), une nouvelle hospitalisation pour insuffisance cardiaque (n=29) et la transplantation ou assistance cardiaque (n=4). En analyse univariée selon un model de Cox, le strain global mais pas l'onde S en DTI était prédictif de la survenue d'un évènement majeur. En analyse multi-variée ajustée au taux de BNP et à la fraction d'éjection , le strain longitudinal global restait associé à la survenue d'un évènement majeur chez les patients insuffisants cardiaques (**Figure 43**). La supériorité du speckle tracking pour l'évaluation de la fonction systolique a été confirmée par d'autres équipes dans l'insuffisance cardiaque systolique et diastolique[105, 106]. Par ailleurs, la robustesse du strain longitudinal global en speckle tracking est certainement liée à son excellente reproductibilité qui ne nécessite pas de courbe d'apprentissage particulière[107].

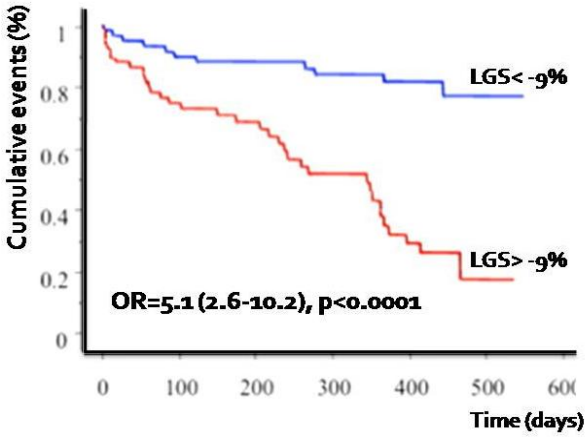

Figure 43: Courbes de survie des patients insuffisants cardiaques selon la valeur du strain global en speckle tracking

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Impact of Longitudinal Myocardial Deformation on the Prognosis of Chronic Heart Failure Patients

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Circ Cardiovasc Imaging 2010;3;249-256; originally published online Mar 16, 2010;
DOI: 10.1161/CIRCIMAGING.109.910893
Circulation: Cardiovascular Imaging is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 1941-9651. Online ISSN: 1942-0080

Impact of Longitudinal Myocardial Deformation on the Prognosis of Chronic Heart Failure Patients

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***Background*—**Longitudinal myocardial deformation indexes appear superior to left ventricular ejection fraction (LVEF) in assessing myocardial contractility. However, few studies have addressed the prognostic value of longitudinal motion markers (velocity, strain, and strain rate) in predicting outcome in heart failure patients.

***Methods and Results*—**The study included 125 consecutive symptomatic heart failure patients (63±16 years, 77% male, LVEF=31±10%). All patients underwent a complete echocardiographic and clinical examination, and brain natriuretic peptide level was assessed in 93 patients. Longitudinal myocardial velocity by tissue Doppler imaging, global-ε, and strain rate by speckle tracking were computed from apical views (4-, 3-, and 2-chambers views) and compared with the occurrence of major adverse cardiac events. On the whole, peak longitudinal velocity, global-ε, and strain rate averaged 5±2 cm/s (range, 1 to 9), −8±3% (range, −3 to −18), and −0.33±0.16 s^{-1} (range, −0.83 to −0.05), respectively. During the follow-up period (266±177 days), major adverse cardiac events occurred in 47 (38%) patients (15 deaths, 29 recurrent heart failure, and 4 heart transplantations). By univariable analysis using Cox model global-ε, strain rate, and LVEF were associated with the occurrence of major adverse cardiac events, whereas only global-ε remained independently predictive of outcome by multivariate analysis.

***Conclusions*—**In the heart failure population, longitudinal global strain by speckle tracking is superior to LVEF and other longitudinal markers in identifying patients with poor outcome. **(*Circ Cardiovasc Imaging*. 2010;3:249-256.)**

Key Words: heart failure ■ prognosis ■ longitudinal function ■ global strain

Heart failure (HF) prevalence ranges between 2% and 3% in the general population,[1] with increasing trend because of the population ageing and a survival improvement.[2] Overall 4-year mortality rate averages 50%, with a large individual variability.[3] Myocardial contractility is a strong outcome predictor, with a major impact on the medical decision.[4,5] Consequently, myocardial contractility should be quantified by a sensitive and accurate method. In daily practice, systolic left ventricular (LV) contractility assessment is based on the LV ejection fraction (LVEF) measurement computed from apical views using echocardiographic imaging.[6] However, several studies suggested that LVEF is poorly sensitive in detecting early myocardial dysfunction, whereas longitudinal myocardial velocity, strain, and strain rate (SR) appear to be more sensitive and specific.[7–9] On the whole, SR values are less dependent of load conditions and may be superior to strain and velocity.[10] Tissue Doppler imaging (TDI) is conventionally used to assess longitudinal myocardial velocity,[11] whereas, for longitudinal strain and SR, speckle tracking appears to be less noised than TDI-derived data and provides accurate measurements correlated with sonomicrometry and cardiac MRI.[12,13] TDI and, more recently, speckle tracking modality, are available on current echocardiography systems and can be used in daily practice to improve myocardial contractility assessment. However, assessment of all these contractile markers is time-consuming and cannot be routinely performed. The purpose of the present study is to define which longitudinal contractile marker is relevant for clinical decision by comparing their prognostic value in HF population.

Clinical Perspective on p 256

Methods

Population Study

We prospectively enrolled 125 consecutive patients (age, 63±16 years; 77% men; Table 1) admitted for optimization of medical HF treatment. After discharge, 76%, 80%, and 60% of patients were receiving β-blocker, ACE inhibitor, and aldosterone antagonist therapy, respectively. Patients in atrial fibrillation were not excluded from the study. Clinical data and medical history were collected using a standard questionnaire. Before discharge, all patients underwent a complete echocardiographic examination.

Received September 21, 2009; accepted February 4, 2010.

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Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org DOI: 10.1161/CIRCIMAGING.109.910893

Table 1. Baseline Characteristics

Clinical data	
Age, y	63±16 [23 to 90]
Sex, male (%)	96 (77%)
CAD (%)	65 (52%)
NYHA class ≥III	74 (61%)
SBP, mm Hg	126±23 [80 to 180]
HR, beats · min^{-1}	76±15 [53 to 118]
Creat clear, mL · min^{-1}	57±26 [9 to 142]
BNP	1031±1182 [10 to 6554]
Echocardiographic data	
LEVF, %	31±10 [10 to 49]
LVED volume, mL	191±71 [62 to 415]
LVESV volume, mL	134±62 [39 to 349]
TAPSE, mm	17±4 [7 to 28]
$S_{tricuspide}$, cm · s^{-1}	9±3 [3 to 16]
SPP, mm Hg	45±11 [30 to 72]
E/e′	16±9 [4 to 49]
Longitudinal myocardial shortening index	
S_{mitral}, cm · s^{-1}	5±2 [1 to 9]
Global-ε, %	−8±3 [−2 to −18]
Peak strain rate, s^{-1}	−0.42±0.15 [−0.83 to −0.17]

SBP indicates systolic blood pressure; CAD, coronary artery disease; HR, heart rate; Creat clear, creatinine clearance; LVED, left ventricular end-diastolic volume; $S_{tricuspid}$, peak tricuspid annular velocity; SPP, systolic pulmonary blood pressure; and S_{mitral}, peak mitral annular velocity.

Outcome

A composite outcome that affects heart failure patient survival and quality of life was used to ensure a sufficient statistical power. The primary end point combined cardiovascular death (sudden death, death from HF, or unexplained death), recurrent hospitalization for HF, and cardiac transplantation or mechanical circulatory support. Follow-up information was obtained either from medical report or direct patient interview or from the referring physician. The time to follow-up was considered as the time to first defined cardiovascular events.

Echocardiography Analysis

A standardized complete echocardiographic examination was performed before discharge using a commercially available Vivid 7 system (GE Vingmed, Horton, Norway). All data were stored digitally for off-line analysis on Echo-Pac PC software (V8.1 GE, Horton, Norway). LV volume and LVEF were computed from standard apical views according to the Simpson biplane method.[9] Peak tricuspid annular systolic velocity (by TDI) and tricuspid annular plane systolic excursion (TAPSE) were used to assess right ventricular (RV) systolic function.[14] The ratio of early transmitral velocity (E wave by conventional pulsed Doppler) to tissue Doppler mitral annular early diastolic velocity (e′ by TDI) was used to assess pulmonary capillary wedge pressure.

Longitudinal Myocardial Function

Peak systolic mitral annular velocity (S) using pulsed TDI was determined from the lateral wall. Global systolic longitudinal strain (global-ε) and SR were computed using speckle tracking analysis. For strain processing, the peak of the R wave on the ECG was used as the reference time point for end-diastole. Global-ε was obtained by averaging the 16 regional longitudinal strain curves computed from high-frame-rate (>50; mean, 74±17) apical views (4-chamber, 2-chamber, 3-chamber). On the whole, 132 of 2000 (6.5%) segments were excluded from global strain calculation because of inadequate tracking. Peak global SR was computed from the first derivative global strain curve during isovolumic contraction period (Figure 1).

B-Type Natriuretic Peptide Measurements

Venous blood samples for B-type natriuretic peptide (BNP) assessment were drawn the day of echocardiography in 93 patients (76%). Chilled EDTA tubes were centrifuged immediately at 4000*g* (4°C) for 15 minutes. Separated plasma samples were processed by immunofluorescence assay (Beckman-Coulter, Biosite, Paris, France). The assay detection limit was 1 pg/mL. The interassay and intra-assay variations were 5% and 4%, respectively.

Statistical Analysis

To assess the predictive value of global longitudinal myocardial indexes (peak S by TDI, global-ε, and SR) in identifying primary outcome in HF patients, we used a Cox model analysis adjusted to other covariables. Continuous variables with normal distribution were expressed as mean±SD and skewed variables as median and quartiles. Dichotomous data were expressed as percentages. To compare numeric data between 2 groups, an unpaired Student *t* test was used with skewed variables (as BNP level) log-transformed for all statistical comparison. Nominal variables were compared using χ^2 test or Fisher test. Pearson correlation was used to compare longitudinal myocardial shortening indexes to LVEF and BNP levels. Univariate analysis of primary outcome was performed using a Cox model analysis. Proportional hazards assumption was checked graphically by plotting scaled Schoenfeld residuals against time with LOWESS smoothing function[15] used to test for nonproportionality. Variables from univariate analysis with $P<0.2$ were included in multivariate Cox analysis to identify independent predictor of outcome. For multivariate analysis, 2 models were used, the first (n=93) including and the second (n=123) without including BNP level. To determine the optimal global-ε cutoff value, the Youden test[16] was performed from data computed from receiver-operating characteristic curves. Survival curves were established by the Kaplan-Meier estimation method, and the event rates were compared using the log-rank test. Two-tailed probability values <0.05 were considered statistically significant.

Results

Of the 125 patients enrolled (age, 63±16 years; 77% men; Table 1), LVEF averaged 31±10% (range, 10 to 49) and HF etiology was ischemic in 52% (n=65), with 61% (n=74) of patients severely symptomatic (New York Heart Association functional class ≥III) at inclusion. Blood pressure and heart rate averaged 126±23 mm Hg and 76±15 bpm, respectively. Mean BNP level at discharge was 1031±1182 pg/mL (median, 697; range, 10 to 6554).

Baseline Echocardiography

End-diastolic and systolic volumes averaged 191±71 mL (range, 62 to 415) and 134±62 mL (range, 39 to 349), respectively. E/e′ ratio and systolic pulmonary blood pressure averaged 16±9 (range, 4 to 39) and 45±11 mm Hg (range, 30 to 72), respectively. RV dysfunction was observed in 33% (n=41) when defined by TAPSE <15 mm (17±4 mm, range, 7 to 28) and 53% (n=65) using tricuspid annular systolic velocity <10 cm/s (mean, 9±3 cm/s; range, 3 to 16).

Longitudinal Shortening Indexes

Peak systolic mitral velocity by TDI (S_{mitral}), global-ε, and peak SR by speckle tracking averaged 5±2 cm/s (range, 1 to 9), −8±3% (range, −18 to −2), and −0.42±0.15 s^{-1} (range, −0.83 to −0.17), respectively. Correlation between

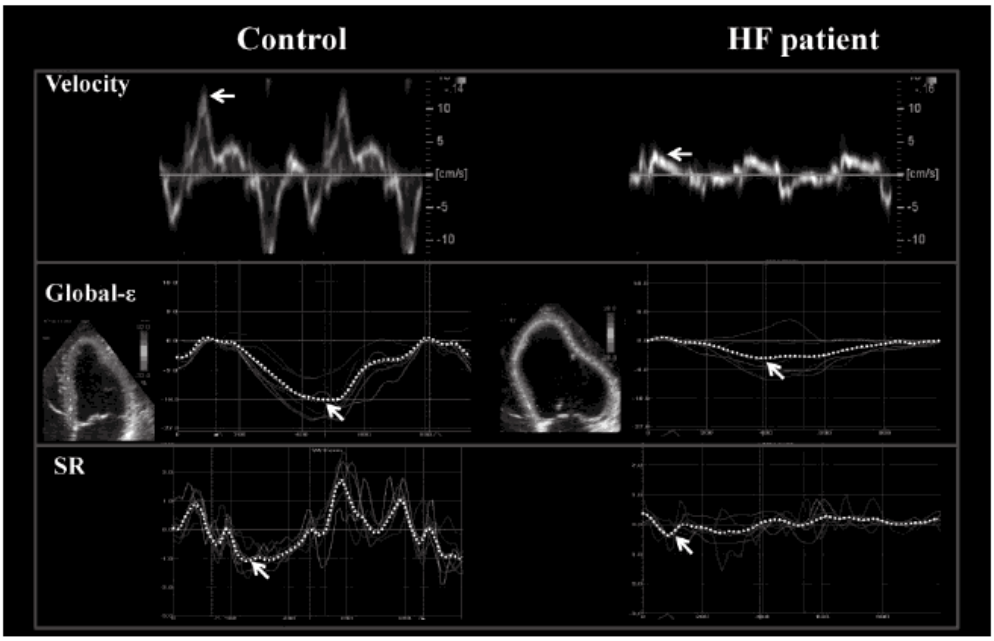

Figure 1. Peak systolic velocity, longitudinal global strain, and SR in control and HF patients.

LVEF and longitudinal myocardial contractile markers was good with global-ε ($r=-0.72$ $P<0.0001$, Figure 2), moderate with SR ($r=-0.58$, $P>0.0001$), and poor with S_{mitral} by TDI ($r=0.26$, $P=0.01$). Similarly, correlation with BNP level was better for global-ε ($r=-0.45$ $P<0.0001$, Figure 1) and peak SR ($r=-0.46$ $P<0.0001$) than for S_{mitral} ($r=-0.16$, $P=0.16$). Importantly, pulmonary capillary wedge pressure (by E/e′ ratio) correlated with global strain ($r=0.46$, $P<0.0001$), S_{mitral} ($r=-0.39$, $P<0.0001$), and global SR ($r=0.38$, $P<0.001$) as well.

Patient Follow-Up

During a median follow-up period of 283 days (25% to 75% IQ; 90 to 429 days; range, 2 to 550 days), 47 (37.6%) patients reached the primary outcome end point: 29 (23.2%) hospitalized for recurrent HF, 4 (3.2%) referred for cardiac assistance (n=3) or heart transplant (n=1), and 15 (11.2%) deaths including 14 from cardiovascular reasons and 1 patient from pancreatic cancer. After the first episode of recurrent HF (160±87 days), 3 of the 29 patients died of cardiovascular reasons and 1 was referred to heart assistance. Only 2 (1.6%) patients were lost to follow-up, excluded from prognosis analysis.

Univariable analysis using the Cox model (Figure 3 and Table 2) showed that LV contractile markers associated with adverse cardiac events included LVEF (odds ratio [OR]=0.50, $P<0.0001$), global-ε, (OR=1.2, $P<0.0001$), and SR by speckle tracking (OR=1.41, $P=0.002$), whereas no significant correlation was found with S_{mitral} by TDI. The other significant variables were NYHA functional class (OR=1.73, $P=0.001$), systolic blood pressure (OR=0.86, $P=0.003$), heart rate (OR=1.23, $P=0.03$), BNP level (OR=1.62, $P<0.0001$), TAPSE (0.92, $P=0.03$), and LV end-diastolic volume (OR=1.05, $P=0.03$).

By multivariate analysis model including (n=93) and not including (n=123) BNP level, only NYHA functional class and global-ε remained predictive of cardiovascular events (Figure 4). A global-ε cutoff >−9% identified patients with poor outcome with a sensitivity and specificity of 83% and 54%, respectively (Figure 5). Negative and positive predictive values associated were 84% and 53%, respectively. Kaplan-Meier analysis showed that the risk of major cardiac events was 5.1-fold greater (2.6 to 10.2, $P<0.0001$, Figure 5) in patients with than without global-ε <−9%.

Reproducibility

Intraobserver reproducibility was 7% for longitudinal global strain, 9% for SR, 14% for systolic peak mitral annular velocity by TDI, and 8% for LVEF. The interobserver reproducibility was 8% for longitudinal strain, 12% for SR, 20% for systolic peak mitral annular velocity, and 10% for LVEF by Simpson biplane.

Discussion

Myocardial function assessment plays an important role in the prognosis and affects the medical decision in HF and valvular diseases.[4,5,17] In daily practice, myocardial contractility is based on LVEF by echocardiography using the Simpson biplane model. However, LVEF lacks sensitivity to

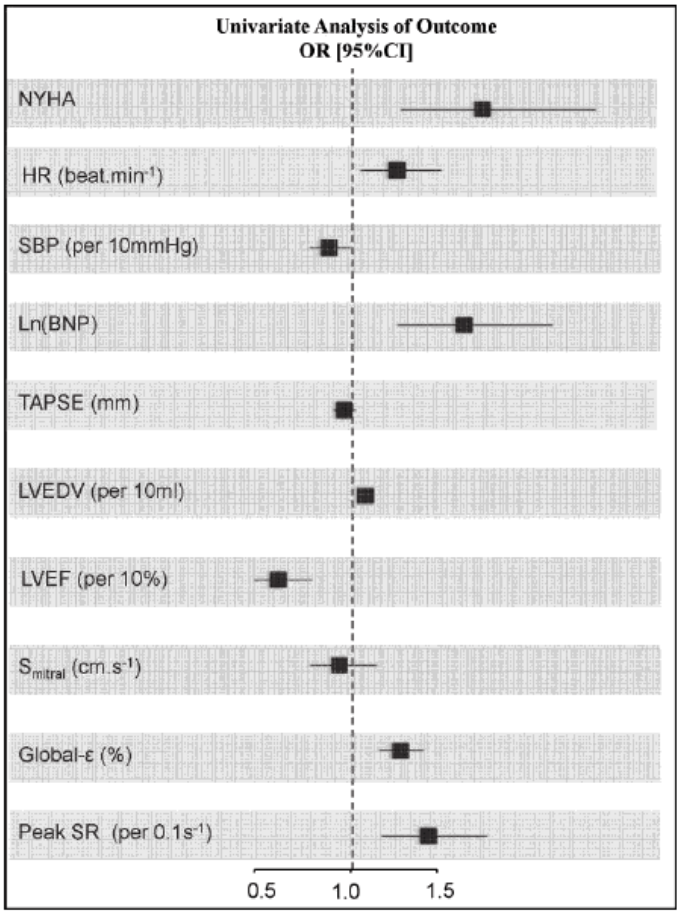

Figure 3. Outcome (death, cardiac assistance or transplant, and recurrent HF) predictors by univariable analysis using the Cox model. SBP indicates systolic blood pressure; HR, heart rate; Ln (BNP), natural logarithm of BNP; and LVEDV, LV end-diastolic volume.

global-ε and SR by speckle tracking is easy and fast to compute and especially does not require a specific training to ensure a good reproducibility.[24]

However, an exact linear correlation of longitudinal global strain and SR with LVEF should not be expected because longitudinal motion partly contributes to LVEF value. Indeed, impaired myocardial contractility appears to first affect the endocardial layers, explaining that longitudinal motion markers may be more sensitive than LVEF in identifying early changes of myocardial contractility.[9,20] Longitudinal motion may be quantified either by strain or SR, which is supposed to be load independent[10] and superior to strain in assessing myocardial contractility and prognosis. However, our data demonstrate that both strain and SR values correlate with pulmonary wedge pressure estimated using E/e′ ratio. In addition, SR does not appear to be superior to strain in predicting outcome in HF patients. Superiority of strain over SR may also be related to less noised data, allowing an easier assessment of peak value. The use of longitudinal global strain by speckle tracking in assessing LV contractility should be encouraged in clinical practice for its good reproducibility and ability to stratify the outcome of HF patients. The negative predictive value (84%) of global strain ($<-9\%$) is particularly interesting in identifying patients at low risk of cardiac events. Despite its limited specificity (54%) and positive predictive value (53%), a severe reduced global strain $>-9\%$ indicates an increase of the risk of cardiac events by 5.1. This suggests that these patients may require a more aggressive medical treatments and monitoring.

Limitations

Myocardial contractility was assessed by 2D imaging, although 3D echocardiography or cardiac cine-MRI may provide better LVEF[25] and volume measurements. However, comparison with 2D LVEF, largely available, better reflects

Table 2. Univariate Predictors of Outcome

	All (n=123)		Cox Model	
	Event-Free (n=77)	Event (n=46)	OR	*P* Value
Clinical data				
Age, y	61±14	65±17	1.01 [0.94–1.41]	0.2
Sex, male (%)	76.1	76.9	1.08 [0.91–1.25]	0.8
NYHA class ≥III (%)	36 (49%)	37 (79%)	1.73 [1.25–2.38]	0.001
SBP, per 10 mm Hg	129±22	122±24	0.86 [0.75–0.98]	0.03
CAD (%)	38 (49%)	27 (59%)	1.03 [0.58–1.80]	1.03
HR, beats · min^{-1}	73±14	79±15	1.23 [1.02–1.48]	0.03
Creat clear, mL · min^{-1}	59±26	55±29	0.99 [0.97–1.00]	0.9
Ln (BNP)	6.0±1.4	7.0±1.1	1.62 [1.23–2.13]	<0.0001
Echocardiographic data				
LVEF, per 10%	33±11	28±7	0.54 [0.40–0.74]	<0.0001
LVEDV, per 10 mL	182±73	201±66	1.05 [1.01–1.09]	0.03
TAPSE, mm	18±4	16±4	0.92 [0.86–0.99]	0.03
$S_{tricuspid}$, cm · s^{-1}	9±2	9±3	0.95 [0.83–1.08]	0.43
SPP, mm Hg	44±10	45±13	1.01 [0.98–1.05]	0.5
E/e'	15±8	17±10	1.00 [0.99–1.01]	0.7
Strain data				
S_{mitral}, cm · s^{-1}	5.0±1.5	4.7±1.7	0.89 [0.72–1.1]	0.32
Global-ε, %	−9±3	−7±2	1.25 [1.13–1.38]	<0.0001
SR, per 0.1 s^{-1}	−0.46±0.16	−0.36±0.12	1.41 [1.14–1.75]	0.002

SBP indicates systolic blood pressure; CAD, coronary artery disease; HR, heart rate; Creat clear, creatinine clearance; LVED, left ventricular end-diastolic volume; $S_{tricuspid}$, peak tricuspid annular velocity; SPP, systolic pulmonary blood pressure; and S_{mitral}, peak mitral annular velocity.

current clinically practices. In addition, the study was focused on longitudinal strain data, which are known to be a sensitive marker of early LV dysfunction. Available short-axis data have not been included in the analysis because the strain data from the whole myocardium (16-segment model) cannot be obtained in all patients. The primary end point of the study was a composite outcome that included recurrent HF, cardiac assistance, and death. However, most of events (n=47) reported were recurrent HF (29/47, 62%). Future study including a larger number of patients should address the individual impact of longitudinal global on HF mortality and also on the occurrence of ventricular arrhythmia and recurrent myocardial ischemia.

Conclusion

Impaired longitudinal global strain >−9% is associated with an increase of cardiovascular events in HF patients. Importantly, longitudinal global strain by speckle tracking appears to be superior to SR and LVEF in predicting outcome in chronic HF. This highlights the need of future

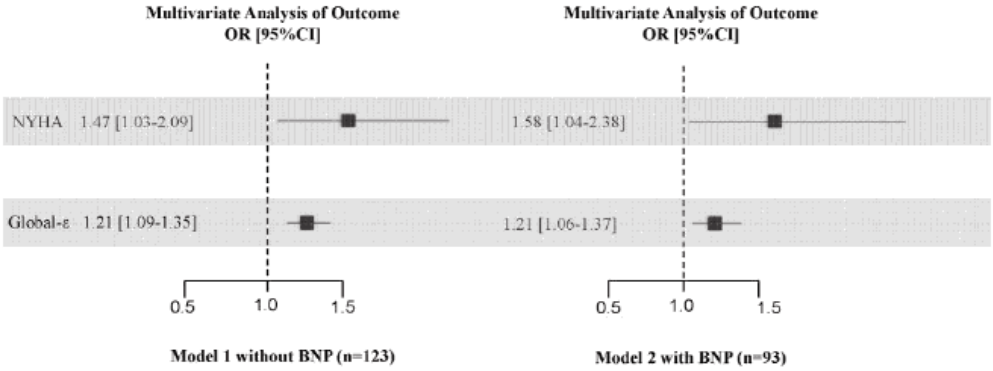

Figure 4. Independent predictors of outcome (death, cardiac assistance or transplant, and recurrent HF) by multivariate Cox analysis with and without including BNP levels.

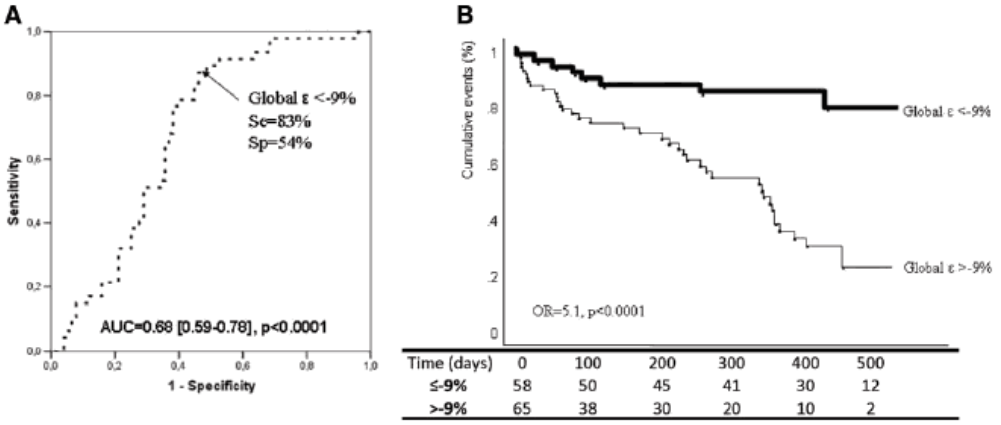

Figure 5. Optimal cutoff value of global-ε to identify patients with adverse outcome (death, cardiac assistance or transplant, and recurrent HF) using receiver-operating characteristic curve analysis (A) and Kaplan-Meier survival curves (B).

studies assessing the impact of medical decision based on strain measurement rather than LVEF.

Disclosures

None.

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4.2- Indice de perte d'énergie, le strain delay index

Dans la théorie de l'asynchronisme mécanique, un segment retardé ne va pas pleinement contribuer à l'éjection systolique. Il existe donc une perte de contractilité ou d'énergie contractile appelée « le strain delay index ». Cet indice peut aussi être interprété comme le degré de contractilité récupérable après une resynchronisation optimale. La perte d'énergie s'exprime mathématiquement comme la différence entre la force contractile maximale développée au cours du cycle cardiaque et celle au moment de la systole. L'avantage de la perte d'énergie est sa capacité à prendre en compte à la fois l'importance du retard de contraction et la contractilité résiduelle **(Figure 44)**. Dans un segment nécrosé ou siège d'une fibrose évoluée, la déformation myocardique retardée est de faible amplitude. La perte d'énergie dans ces segments est plus faible que dans un segment présentant le même retard. Cette perte d'énergie est calculée pour l'ensemble des 16 segments du myocarde et s'exprime en pourcentage de raccourcissement moyen perdu.

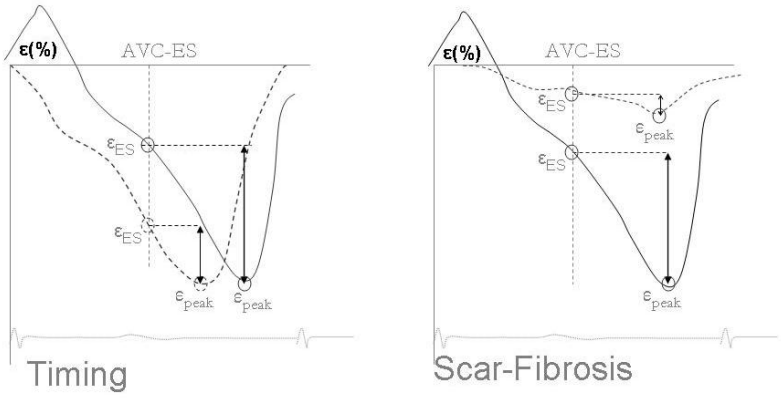

Figure 44: Perte d'énergie ($\varepsilon\text{-}_{peak} - \varepsilon\text{-}_{ES}$) augmentant avec la sévérité de l'asynchronisme mais pour un même retard de contraction, la perte d'énergie est plus importante lorsque la contractilité est conservée.

Dans un travail publié en 2008[108], nous avons évalué la perte d'énergie chez 100 patients adressés pour une resynchronisation cardiaque. Ces patients avaient des QRS larges, une fraction d'éjection <35% et restaient symptomatiques malgré un traitement médical

optimal. Nous avons démontré que cette perte d'énergie était bien corrélée au remodelage inverse après resynchronisation cardiaque. Un strain delay index >25% permettait d'identifier 82% des répondeurs et 92% des non répondeurs. Le strain delay index était bien corrélé au remodelage inverse dans les cardiopathies ischémiques et non ischémiques **(Figure 45)**.

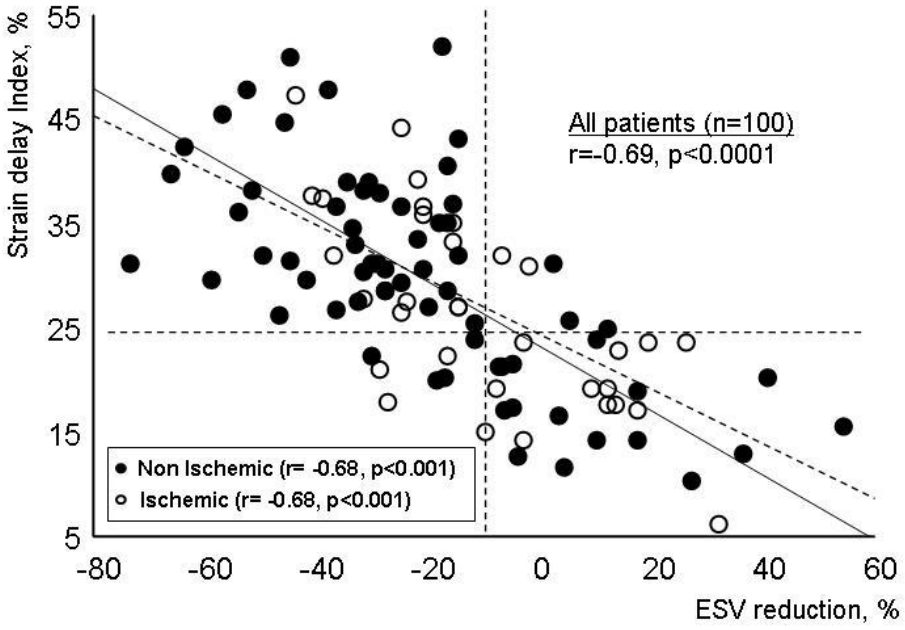

Figure 45 : Corrélation entre perte d'énergie totale et remodelage après resynchronisation cardiaque.

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Longitudinal Strain Delay Index by Speckle Tracking Imaging: A New Marker of Response to Cardiac Resynchronization Therapy

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Circulation 2008;118;1130-1137; originally published online Aug 25, 2008;
DOI: 10.1161/CIRCULATIONAHA.107.750190
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Longitudinal Strain Delay Index by Speckle Tracking Imaging

A New Marker of Response to Cardiac Resynchronization Therapy

Pascal Lim, MD; Adisai Buakhamsri, MD; Zoran B. Popovic, MD, PhD; Neil L. Greenberg, PhD; Dimpi Patel, MD; James D. Thomas, MD; Richard A. Grimm, DO

Background—In heart failure patients with left ventricular dyssynchrony, contractility in delayed segments does not fully contribute to end-systolic function. We quantified this reserve of contraction related to mechanical dyssynchrony to predict response to cardiac resynchronization therapy by the strain delay index, which was defined as the sum of the difference between peak and end-systolic strain across 16 segments.

Methods and Results—In 100 heart failure patients (ejection fraction=26±9%, QRS=154±29 ms, 94% in New York Heart Association class III), we studied left ventricular dyssynchrony before cardiac resynchronization therapy by the strain delay index using longitudinal strain by 2D speckle tracking and by the SD of time to peak myocardial velocity in 12 segments. The optimal cutoff value of the strain delay index to predict response to cardiac resynchronization therapy was determined in a retrospective group (n=65) and then confirmed in a validation group (n=35). Left ventricular end-systolic volume reduction at 3 months >15% (responder) occurred in 64 of 100 patients. In the retrospective group, the strain delay index but not the SD of time to peak myocardial velocity was greater in responders (n=42/65) than nonresponders (35±8% versus 19±7%, $P<0.0001$), and the optimal cutoff value to identify response to cardiac resynchronization therapy was 25%. In the validation group, strain delay index ≥25% identified 82% (18/22) of responders and 92% (12/13) of nonresponders. Among the entire population (n=100), strain delay index correlated with reverse remodeling in both the ischemic ($r=-0.68$, $P<0.0001$) and nonischemic ($r=-0.68$, $P<0.0001$) population.

Conclusions—Use of the strain delay index with longitudinal strain by speckle tracking has a strong predictive value for predicting response to cardiac resynchronization therapy in both ischemic and nonischemic patients. **(*Circulation*. 2008; 118:1130-1137.)**

Key Words: heart failure ■ pacemakers ■ echocardiography ■ prognosis ■ mechanics ■ remodeling

Several large clinical trials have established the long-term benefits (such as improvement of symptoms,[1–8] ejection fraction,[2,4,8] mitral regurgitation,[1,4] left ventricular [LV] remodeling,[1,2,4] and survival[8]) with cardiac resynchronization therapy (CRT) in symptomatic patients who have severe LV dysfunction and a wide QRS complex.[1–8] Despite these promising results, ≈30% of patients selected on the basis of QRS duration do not respond to CRT.[8] Observational studies have consistently shown that the main predictor of responsiveness to CRT is mechanical rather than electrical dyssynchrony.[9] Measurement of regional myocardial electrical-mechanical events with velocity data acquired with tissue Doppler imaging (TDI)[10,11] has been shown to enhance identification of mechanical dyssynchrony and can be used to select patients who may better respond to CRT; however, limitations of this technique still exist, in particular the lack of specificity associated with delayed contraction in patients with ischemic cardiomyopathy.[12,13] Patients with significant mechanical dyssynchrony may be nonresponsive because myocardial segments may be scarred and therefore lack residual contractility. This phenomenon is particularly evident in ischemic patients who have myocardial segments with delayed contraction, which is often caused by scar.[14–16] Current identification of responders by time-delay indexes alone is inherently limited, because residual myocardial contraction is not taken into account. To overcome these limitations, we propose a new method, the strain delay index. The strain delay index can predict response to CRT by directly assessing the potential for incremental contractility gain after resynchronization rather than by simply quantify-

Received August 24, 2007; accepted July 7, 2008.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.750190/DC1.

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Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.107.750190

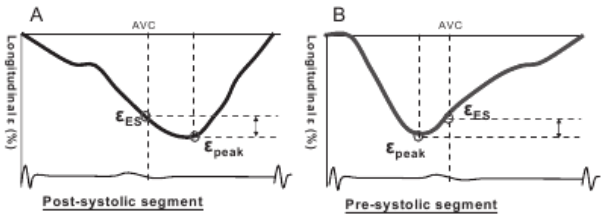

Figure 1. In dyssynchronized myocardium, ε-peak of delayed segment does not fully contribute to ES function. The wasted energy due to dyssynchrony is mathematically expressed as the difference ($\varepsilon_{peak} - \varepsilon_{ES}$) in postsystolic (A) and presystolic (B) segments. AVC indicates aortic valve closure.

ing LV dyssynchrony by regional timing. In the present study, the strain delay index was calculated by use of longitudinal strain (ε) assessed by 2D speckle tracking, which was then compared to the SD of time to peak velocity and time to peak longitudinal strain to predict future reverse remodeling after CRT.

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Methods

Population

The study included 100 patients with symptomatic heart failure (HF), an ejection fraction <35%, and QRS duration >120 ms who had conventional TDI and longitudinal ε analysis by 2D speckle tracking before undergoing implantation of a biventricular device. The study was conducted in 2 consecutive groups of patients, with hypothesis testing to determine the optimal cutoff value for the strain delay index to predict response to CRT, which was first assessed in a retrospective cohort (derivation group, n=65) followed by validation in a prospective cohort (validation group, n=35).

Derivation Group

The derivation group was selected from 589 consecutive HF patients who underwent implantation of a biventricular device at the Cleveland Clinic (Cleveland, Ohio) between January 2005 and December 2006. Patients were selected if they had a complete baseline echocardiographic study performed 3 months before device implantation on a Vivid 7 system (GE, Vingmed System 7, Horten, Norway) and if an echocardiographic follow up (>3 months) was available (120 of 589 patients). Complete baseline echocardiography included standard gray-scale and color TDI in the apical views (2-, 3-, and 4-chamber views) with high frame rates (>35 frames/s). Of these 120 selected patients 50 were excluded (5 with implantation <3 months after an acute coronary syndrome or cardiac surgery, 41 with >2 nonanalyzable segments by 2D speckle tracking or TDI, and 4 with permanent atrial fibrillation). After device implantation, another 5 patients were excluded (inadequate CRT delivery, ie, LV pacing rate was <50%; 3 with paroxysmal atrial fibrillation and 2 owing to an increased LV lead threshold). Ultimately, 65 patients were entered into the derivation group.

Validation Group

This phase of the study was conducted prospectively in a cohort of HF patients recruited consecutively before biventricular device implantation at Cleveland Clinic from January 2007 to May 2007. Patients were included if they met all of the following criteria: symptomatic HF, age between 18 and 75 years, LV ejection fraction <35%, and sinus rhythm with QRS duration >120 ms. Exclusion criteria were recent cardiac event (<3 months after an acute coronary syndrome or cardiac surgery), inadequate CRT delivery after 3-month follow-up (LV pacing rate <50%), and >2 nonanalyzable segments by either speckle tracking or TDI. Patients in the study (n=40) underwent 2D echocardiographs before device implantation on a Vivid 7 system with a high frame rate and color TDI in the apical views. At 3 months, 2D echocardiography was repeated to quantify reverse remodeling after CRT. Five patients were excluded because of limited echocardiographic images and inadequate CRT delivery during the 3-month follow up. Overall, 35 patients were selected as the validation group. All patients had given informed consent, and the study protocol was approved by the Cleveland Clinic Institutional Review Board.

Biventricular Pacemaker Implantation

CRT was provided in the standard fashion with 3 transvenous leads inserted. The right atrial and ventricular (apical site) leads were positioned conventionally. The LV lead was inserted through the coronary sinus and positioned into the lateral (n=38), posterolateral (n=43), anterolateral (n=8), or middle (n=4) cardiac vein. Epicardial implantation was required in 7 patients. Biventricular pacing devices used included those manufactured by Medtronic (Minneapolis, Minn; n=59), St Jude Medical (Sylmar, Calif; n=27), and Guidant–Johnson & Johnson (Boston, Mass; n=14). After implantation, the atrioventricular interval was adjusted for optimal diastolic filling by Doppler echocardiographic assessment of mitral inflow, and V-V timing was programmed to be simultaneous in all cases. All devices were interrogated systematically within 3 months after the CRT procedure to ascertain their proper functioning.

Follow-Up

Baseline and 3-month clinical characteristics were extracted from medical reports. Responders were defined by the presence of significant reverse remodeling (LV end-systolic volume [ESV] reduction >15% by Simpson biplane method) at 3 months after CRT.

Strain Delay Index

In dyssynchronous ventricles, delayed segments do not contribute fully to end-systolic (ES) function. The wasted energy per segment caused by dyssynchrony can be expressed mathematically as the difference between peak (ε_{peak}) and ES strain (ε_{ES}). Theoretically, this difference ($\varepsilon_{ES} - \varepsilon_{peak}$) increases with the severity of dyssynchrony (Figures 1 and 2A). The wasted energy is expected to be greater in the segment with preserved contractility than in the segment with no or minimal residual contractility at a similar degree of delayed contraction. This can be well appreciated in scar or fibrotic myocardium (Figure 2B). The strain delay index (Figure 3) represents the sum of the wasted energy due to LV dyssynchrony across all (n) myocardial segments:

$$\text{strain delay index} = \sum_{i}^{n} (\varepsilon_{peak} - \varepsilon_{ES})$$

The strain delay index can be computed from any quantitative regional wall-motion method, because it expresses a difference of contractility amplitude; however, its accuracy depends on the precision of the method for quantifying regional wall motion. Prior to this investigation, we compared longitudinal, transversal, circumferential, and radial ε by 2D speckle tracking, TDI-derived myocardial velocity, and TDI-derived longitudinal ε in 29 HF patients (Supplemental Table I). We observed that regional peak longitudinal ε by speckle tracking provided an accurate measure of regional myocardial wall motion, with global peak strain closely correlated to LV ejection fraction ($r = -0.84$, $P < 0.0001$; Supplemental Table II). The strain delay index was then computed from longitudinal ε by 2D

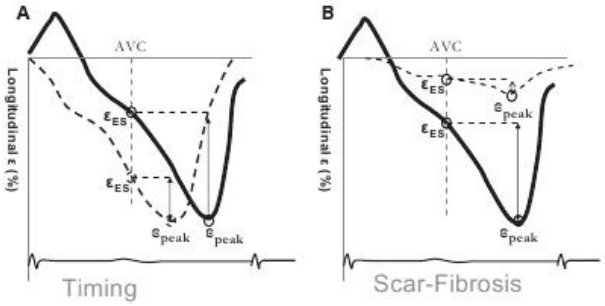

Figure 2. Effects of time to peak strain and status of myocardium on wasted contractile energy. Theoretically, the wasted energy due to dyssynchrony ($\varepsilon_{peak}-\varepsilon_{ES}$) in each segment increases with the severity of the delayed contraction (A). For segments with a similar degree of dyssynchrony (B), the difference ($\varepsilon_{peak}-\varepsilon_{ES}$) would be greater in a myocardial segment with preserved contractility than in those with no or minimal residual contractility, as in scar or fibrotic myocardial tissue. AVC indicates aortic valve closure.

speckle tracking (EchoPac version 7.0.0, GE Vingmed). The peak of the R wave on the ECG was used as the reference time point for end diastole. Strain curves derived from a single cardiac cycle were exported for an automatic analysis in Excel. The different steps of strain delay index processing can be summarized as follows: First, we computed a global ε curve representing LV function by averaging 16 regional LV ε curves. To average strain curves with different RR intervals and frame rates, we normalized the time as a percent of the RR interval, and strain value at every 2.5% of the RR interval was calculated with linear interpolation for missing values. Second, we used the time to the peak of this global ε curve to determine the timing of ES and to compute the ε_{ES} in the 16 segments. Third, we also defined peak and time to peak ε in the 16 segments as the ε curve reached its minimum value during the cardiac cycle. Finally, the difference ($\varepsilon_{peak}-\varepsilon_{ES}$) in each segment (all 16 segments) was summed to generate the strain delay index. For a segment that exhibited positive strain or biphasic strain with a peak positive ε greater than the maximal absolute negative strain, the term

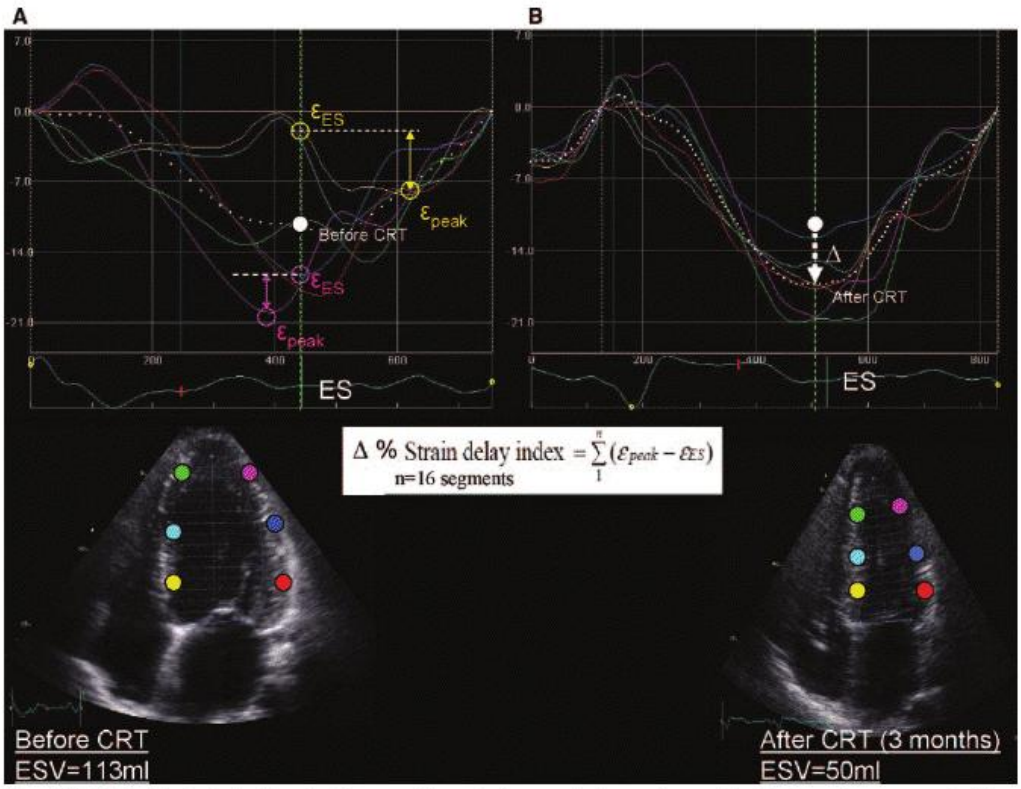

Figure 3. A, Strain delay index is defined as the sum of the wasted energy, ie, ($\varepsilon_{ES}-\varepsilon_{peak}$) caused by LV dyssynchrony across the 16 myocardial segments (colored curves) of the LV. B, After CRT, the increase (Δ) of global strain curve (white dashed curve) is supposed to be proportional to strain delay index.

Table. Comparison Between Responders and Nonresponders

	Retrospective Group (n=65)		Prospective Group (n=35)	
	Responders, n=42 (64%)	Nonresponders, n=23 (36%)	Responders, n=22 (63%)	Nonresponders, n=13 (37%)
Age, y	65±10	63±13	62±13	62±12
Male sex, n (%)	33 (79)	18 (78)	12 (54)	7 (54)
Baseline NYHA class III, n (%)	39 (93)	23 (100)	21 (95)	11 (85)
QRS duration, ms	157±28	144±26	156±26	159±37
Baseline ejection fraction, %	26±10	23±6	27±10	27±9
End-diastolic volume, mL	225±85	260±87	205±72	243±122
ESV, mL	169±75	200±72	152±63	187±120
Ischemic, n (%)	14 (33)	11 (48)	5 (23)	5 (38)
Baseline medications, n (%)				
β-Blockers	36 (86)	20 (87)	18 (82)	11 (85)
ACEI/ARB	35 (83)	22 (95)	21 (95)	12 (92)
Spironolactone	17 (40)	14 (61)	10 (45)	6 (46)

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

($\varepsilon_{peak} - \varepsilon_{ES}$) was entered as zero for the calculation of strain delay index. This methodology is based on the assumption that dyskinetic segments with predominant stretch are unlikely to be improved immediately by CRT. Time to peak longitudinal ε by speckle tracking was used to calculate the 12-segment (base and mid) SD of time to peak-ε (SD-ε). In segments with positive or biphasic strain curve, time to absolute maximal ε was chosen to compute SD-ε.

TDI Analysis

We also defined LV dyssynchrony using the SD in 12 segments of time to peak velocity by TDI (SD-TDI) and the septal-lateral delay of time to peak velocity (T_{SL}). These indexes were computed automatically with modified software developed in our laboratory. Automatic and manual measurements were compared in 20 random patients and results reported with Bland-Altman analysis (Data Supplement, Figure I). The process can be summarized as follows: (1) Basal and midventricular velocity curves (n=12) derived from color TDI sequences (EchoPac version 7.0.0) were exported for analysis in Excel. (2) Time to peak velocity was defined when peak velocity reached its maximum positive value during the systolic ejection period. (3) The reference timing point was defined at end diastole (at the peak of the R wave on the ECG tracing), and the systolic period was defined by aortic valve opening and closure with LV outflow tract pulse-wave Doppler flow. (4) Segments with only negative velocity during the systolic ejection period were excluded from the calculation of SD-TDI and T_{SL}. Significant LV dyssynchrony was considered when SD-TDI was >33 ms[10] and T_{SL} was ≥65 ms.[11]

Statistical Analysis

Continuous variables with normal distribution are expressed as mean±SD. Dichotomous data are expressed as percentages. To compare numerical data between 2 groups, paired and unpaired Student tests were used when appropriate. Dichotomized comparisons were assessed by χ^2 test or the Fisher exact test. Receiver operating characteristic curves were determined to evaluate the diagnostic performance of LV dyssynchrony indexes to detect responders to CRT. An optimal cutoff value for the diagnosis of responders was chosen to maximize the Youden index (sensitivity+specificity−1). The optimal cutoff value of strain delay index was assessed in the derivation group, and then the accuracy was confirmed in the validation group. Linear correlation was used to compare LV ESV reduction and strain delay index. Reproducibility was performed in 10 randomly selected patients. Interobserver and intraobserver variability were expressed as the SD of the difference between 2 paired measurements and as a percentage of variability (SD was divided by the average value of the variable). Two-tailed probability values <0.05 were considered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

The entire study population averaged 63±12 years of age; 94% were in New York Heart Association class III, with ejection fraction of 26±9% (35% with ischemic origin of HF) and QRS duration of 154±29 ms. Baseline characteristics of the derivation and validation populations are summarized in Supplemental Table III. After 3 months of CRT, 53 of 100 patients were clinically improved by CRT, 35 (54%) of 65 in the derivation group and 18 (51%) of 35 in the validation group. Eleven patients experienced worsening symptoms, 7 (11%) in the derivation group (4 died and 2 underwent heart transplantation) and 4 (11%) in the validation group (1 died). The overall population had a mean LV ESV reduction of 17.6±24% (range −54% to 66%); 64 patients had ESV reduction >15%, 14 had reductions between 0% and 15%, and 22 had increased ESV. Baseline clinical and echocardiographic parameters were similar between responders and nonresponders in the 2 populations (Table 1).

Derivation Group

TDI and Strain for Reverse Remodeling

In the initial 65 patients, ESV reduction at 3 months was 16±24% (range −54% to 59%). In 42 (65%) of 65 patients, ESV reduction was >15%; in 6 (9%), it was between 0% and 15%; and in 17 (26%), the ESV increased. Neither SD-TDI (52±17 ms, range 19 to 93 ms) nor the opposing-wall T_{SL} (100±51 ms, range 0 to 250 ms) correlated with QRS duration or reverse remodeling ($r=0.2$, $P=0.1$ for SD-TDI; $r=0.2$ $P=0.1$ for T_{SL}). Significant dyssynchrony by TDI (SD-TDI >33ms) was observed in 59 (91%) of 65 patients and did not differ between responders and nonresponders (37/42 versus 22/23, $P=0.3$; mean 51±16 versus 56±14 ms, $P=0.2$). Similarly, T_{SL} ≥65 ms was observed in 51 (78%) of 65 patients and did not

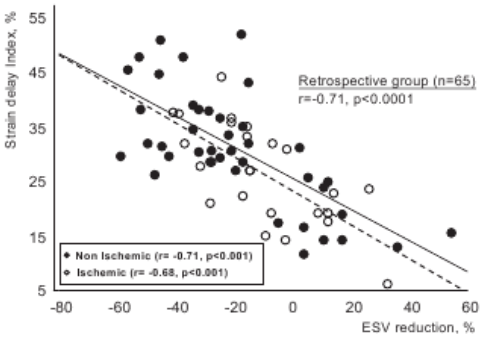

Figure 4. Correlation between strain delay index and ESV reduction after CRT in ischemic and nonischemic patients in the derivation group (n=65).

provide significant predictive value for CRT response. In contrast, SD-ε did correlate with baseline QRS duration ($r=0.42$, $P<0.001$) and ESV reduction ($r=-0.38$, $P=0.002$). Finally, the correlation between reverse remodeling and SD-ε was significant in nonischemic patients ($r=-0.4$, $P=0.01$) but not in ischemic patients ($r=-0.35$, $P=0.08$).

Strain Delay Index for Reverse Remodeling

The strain delay index (29±10%, range 6% to 52%) was found to be higher in responders than nonresponders (35±7% versus 19±6%, $P<0.0001$). Furthermore, the strain delay index increased with QRS duration ($r=0.32$, $P=0.01$) and was closely correlated with reverse remodeling ($r=-0.71$ for all, $P<0.0001$; Figure 4) in both the ischemic ($r=-0.68$, $P<0.001$) and nonischemic ($r=-0.71$, $P<0.0001$) patients. All patients with a strain delay index ≥75th percentile (≥35%) exhibited a significant LV ESV reduction (33±13%, range 15% to 57%), whereas all patients with a strain delay index below the 25th percentile (<20%) showed ESV reduction ≤10% (mean −12±18%, range −54% to 10%). The optimal cutoff value to predict response to CRT determined from the receiver operating characteristic curve of the derivation group was a strain delay index ≥25% (Figure 5). The sensitivity, specificity, negative predictive value, and positive predictive value were 95% (95% CI 87% to 99%), 83% (95% CI 72% to 91%), 90% (95% CI 81% to 96%), and 90% (95% CI 81% to 96%), respectively.

Validation Group

Validation of Strain Delay Index

The mean ESV reduction at 3 months was 20±25% (range −40% to 70%). ESV reduction was >15% in 22 (63%) of 35 patients and between 0% and 15% in 8 (23%), and ESV increased in 5 (14%). Strain delay index (28±9%, range 10 to 47%) was significantly greater in responders than nonresponders (32±8% versus 20±5%, $P<0.0001$). A strain delay index cutoff ≥25% was observed in 18 of 22 patients (82%; 95% CI 66% to 93%) among responders and was <25% in 12 (92%; 95% CI 77% to 98%) of 13 nonresponders. The positive predictive value was 75% (95% CI 57% to 87%) with a cutoff ≥25% and increased to 83% (95% CI 66% to

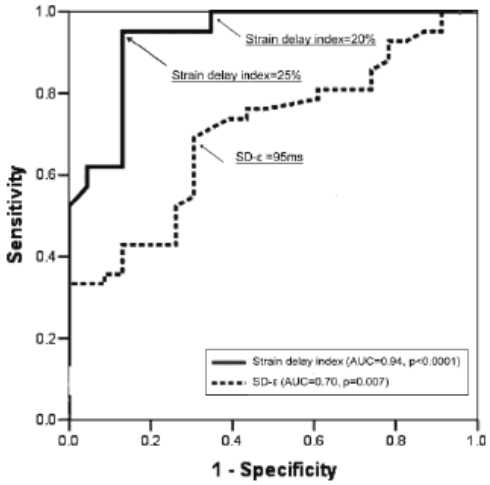

Figure 5. Receiver operating characteristic curves for diagnosis of response to CRT from the derivation group (n=65). *P* value for area under the curve (AUC) vs the null hypothesis of a true area=0.5.

93%) with a strain delay index >20%. Conversely, the negative predictive value was 95% (95% CI 81% to 99%) with a cutoff ≥25% and decreased to 73% (95% CI 54% to 85%) with a strain delay index >20%. Similar to the derivation group, the strain delay index correlated to reverse remodeling after CRT ($r=-0.68$, $P<0.0001$ for all) in the ischemic ($r=-0.68$, $P=0.04$) and nonischemic ($r=-0.68$, $P<0.001$) population. The correlation between strain delay index and ESV reduction for the entire population (n=100) is displayed in Figure 6. In the validation group, SD-ε tended to correlate with reverse remodeling ($r=-0.37$, $P=0.05$), whereas no significant association was observed for either SD-TDI ($r=0.15$, $P=0.5$; Supplemental Figure II) or the opposing-wall T_{SL} ($r=0.1$, $P=0.6$).

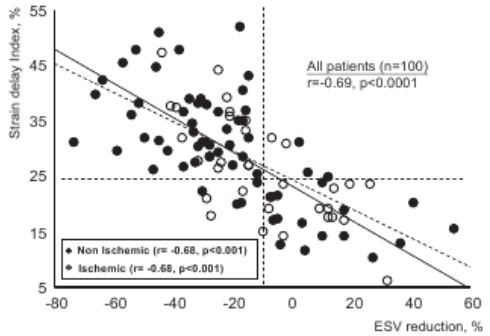

Figure 6. Correlation between strain delay index and ESV reduction after CRT in ischemic and nonischemic patients among the entire population of patients (n=100).

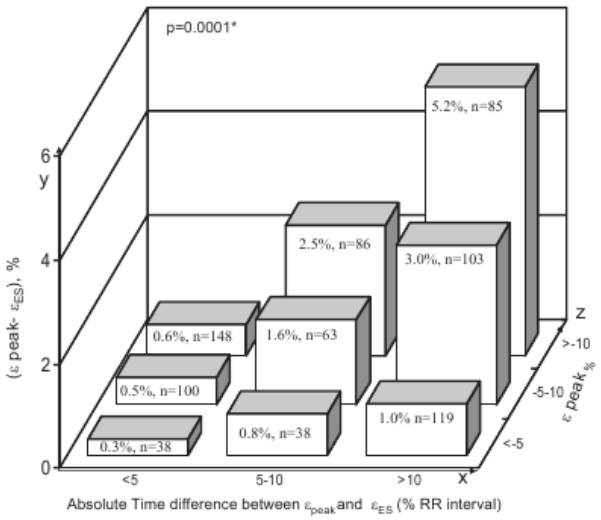

Figure 7. Data from the 780 mid and basal segments of the derivation group demonstrating that the wasted energy ($\varepsilon_{peak}-\varepsilon_{ES}$) is related to the severity of dyssynchrony (x-axis) and to the residual contractility (z-axis).

Study Limitations

The results of the present study are limited to patients with wide QRS duration and should not be extended to patients with QRS <120 ms until a specific validation study can be conducted in this population. In addition, the quality of echocardiographic images is important for all strain-based analysis; therefore, our index may not reach its full capability if the image quality is suboptimal. However, the strain delay index can be applied to other imaging modalities. Next, LV ESV is critical for defining responders to CRT. Other accurate measures, such as 3D echocardiography, should be used in the future to reduce observer-related variability. In the present study, the SD-TDI was computed automatically with modified software rather than manually as reported by Yu et al.[10,17] We reported that SD-TDI computed automatically was not accurate for identification of responders to CRT, and according to recently published studies,[18–21] this appears to be related to TDI limitations. However, we cannot exclude the possibility that the automated approach may be less accurate than the manual approach, which may be effective in predicting response to CRT if performed in a laboratory with special expert knowledge, skill, and experience.

Conclusions

The strain delay index from a longitudinal strain amplitude measurement by 2D speckle tracking appears to be an accurate predictor of CRT response both in ischemic and nonischemic patients alike.

Sources of Funding

Dr Pascal has been funded by the French Federation of Cardiology and the French Society of Cardiology. This work was also supported in part by the National Space Biomedical Research Institute through NASA NCC 9-58, the Department of Defense (Ft. Dietrich, Md, USAMRMC grant No. 02360007), and the National Institutes of Health, National Center for Research Resources, General Clinical Research Center grant MO1 RR-018390.

Disclosures

Dr Grimm receives consulting fees and honoraria from GE; consulting fees, honoraria, and grant support from Medtronic; and consulting fees from St Jude Medical. Dr Thomas receives consulting fees and research support from GE. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

Recent results from the PROSPECT and RETHINQ trials might suggest that a relatively limited and simple quantification of left ventricular dyssynchrony has suboptimal accuracy for the identification of responders to cardiac resynchronization therapy. In the present study, we introduce a new method, the strain delay index, to quantify response to cardiac resynchronization therapy. Rather than simply measuring left ventricular dyssynchrony, we propose to quantify the potential gain of contractility expected after the best possible cardiac resynchronization. The potential gain, in turn, should predict reverse remodeling after resynchronization therapy. The strain delay index combines the importance of left ventricular dyssynchrony and residual contractility and provides a better understanding of the physiological response to cardiac resynchronization therapy. This index should improve the ability to identify potential responders to cardiac resynchronization therapy in the future. The sophistication of the strain delay index relative to Doppler-derived parameters might be of particular importance in the narrow-QRS population, in whom the degree of dyssynchrony may be less and thus more challenging to quantify. Future efforts should focus on validation of the method in current clinical practice along with implementation of software modifications to facilitate ease of use. Additionally, because the strain delay index is computed from regional strain curves, its accuracy is dependent on the precision of the method used to quantify myocardial contractility. Importantly, therefore, the strain delay index can be computed from imaging modalities other than ultrasound (ie, cardiac magnetic resonance and CT) and should be tested in patients with poor acoustic windows.

Dans un second travail soumis à l'European Heart Journal, nous avons mené une étude multicentrique sur 189 patients et avons montré que l'asynchronisme et le strain delay index diminuaient après la resynchronisation cardiaque chez les patients répondeurs. Chez les non répondeurs, l'asynchronisme persiste et le strain delay index qui était faible avant resynchronisation cardiaque ne change pas. Ces données démontrent qu'un myocarde ne peut être resynchronisé efficacement que s'il existe un certain degré de contractilité résiduelle, donc une valeur assez élevée de perte d'énergie. L'avantage de combiner la contractilité et le retard de contraction a également été rapporté par d'autres auteurs[109]. Cette approche apparaît plus physiologique et pourrait enfin offrir un outil clinique permettant de mieux identifier les répondeurs à la resynchronisation biventriculaire.

Title: Multicenter Study **U**sing **S**train Delay **I**ndex for Predicting Response to **C**ardiac Resynchronization Therapy **(MUSIC study).**

Short title: Strain Delay Index and Response to CRT

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Journal Subject Codes

Aims: Strain delay index (SDI) allows quantification of the wasted contraction or gain of myocardial contractility expected after Cardiac Resynchronization Therapy (CRT). The present multicenter prospective study aims to assess the accuracy of the SDI in predicting responses to CRT in real life patients that include wide and narrow (<130ms) QRS complexes. **Methods and Results**: CRT was performed in 189 heart failure patients (65±12 years, LVEF=26±8%, 63 ischemic) with narrow (n=51) and wide QRS complexes. Mechanical dyssynchrony before CRT was quantified by the 12-segment standard deviation of peak longitudinal strain by speckle tracking (12SD-ε), and SDI, defined as the sum of difference between end-systolic and peak-ε across the 16 segments. Response to CRT was defined by end-systolic volume reduction (ESVR) at 6 months >15%. After CRT, ESVR>15% observed in 60% (n=114/189) of patients was greater in non-ischemic (68% vs. 44%, p=0.003) and wide QRS patients (65% vs. 49%, p=0.04). Correlation between 12SD-ε and ESVR was poor (r=0.18, p=0.01). In contrast, SDI correlated with reverse remodeling (r=0.61, p<0.0001 for all) in both wide and narrow QRS patients and ischemic and non ischemic patients. Decrease in strain delay index after CRT was greater in responders and correlated with ESVR. Finally, SDI>25% identified responders to CRT (positive and negative predictive value of 80% and 84%, respectively) with 6% of inter-observer variability. **Conclusion:** The present multicenter study demonstrates the robustness of SDI in identifying responders to CRT in narrow and wide QRS patients, and ischemic and non-ischemic patients.

Key words: Cardiac resynchronization therapy, strain, speckle tracking, dyssynchrony

INTRODUCTION

Randomized studies demonstrated that cardiac resynchronization therapy (CRT) has a beneficial impact on reverse remodeling and survival in heart failure (HF) patients with large QRS interval(1-4). However, up to 40% of patients failed to respond to CRT despite enlarged QRS duration(2, 5). Observational studies have consistently shown that the main predictor of responsiveness to CRT is mechanical rather than electrical dyssynchrony. Accuracy of mechanical dyssynchrony measurement of regional myocardial electrical-mechanical events with velocity data acquired with tissue Doppler imaging (TDI) has been proposed to enhance identification of mechanical dyssynchrony, and to select patients with wide and narrow QRS duration who may better respond to CRT(6, 7). However, myocardial dyssynchrony markers are usually based on time-delay measurements which are inherently limited, as residual myocardial contraction is not taken into account(8-10). Two recent studies demonstrated the limited accuracy of time delay markers to identify responders to CRT in wide (PROSPECT study(5)) and narrow (RETHINQ study(11)) QRS populations. To overcome these limitations, we recently proposed a new method, the strain delay index(12) (SDI) to predict response to CRT by directly assessing the potential for incremental contractility gain after resynchronization rather than by simply quantifying LV dyssynchrony by regional timing. In the present multicenter study, the SDI was assessed in a large cohort of HF patients referred for CRT (that includes wide and narrow QRS duration) and used to predict future reverse remodeling after CRT.

METHODS

This study was designed as a multicenter observational clinical trial, and aims to assess the accuracy of the strain delay index in identifying response to CRT. Four French university centers equipped with GE ultrasound echocardiography system participated in the study. To test our hypothesis, we enrolled optimally treated heart failure patients who received CRT. Before CRT, all patients underwent a comprehensive echocardiography examination using a GE ultrasound system. Patients with chronic atrial fibrillation were not included. Before enrollment, all patients received informed consent and our local ethics committee approved the study. Overall, 235 heart failure patients who received CRT were enrolled from November 2008 to November 2009, and 20% of patients were excluded because of a limited acoustic windows preventing 2D strain analysis (>2 non analyzable segments). Of the 189 analyzable patients (120 from Henri Mondor University, Table I), 51 (27%) had QRS<130ms (narrow) and 138 wide QRS complex. In wide QRS patients, a CRT device was implanted in patients with severe LV dysfunction (LVEF≤35% by 2D echocardiography, mean=25±8%) that had remained symptomatic despite optimal medical treatment (New York Heart Association, NHYA class>II). Medical treatment included beta-blocker (79%), angiotensin inhibitors (87%) and aldosterone inhibitors (40%). In the narrow QRS population, the decision to add biventricular pacing to standard implantable cardioverter defibrillator was taken by referring cardiologist that identified significant mechanical dyssynchrony. For all patients, medical decision was independent of the strain delay value.

2D echocardiography: A comprehensive echocardiographic study was performed before (GE, Vingmed System 7, Horten, Norway) and six months after CRT. During the echocardiography study, apical views (2- 3-, and 4-chamber) with high frame rates (≥50 frames/s) were acquired during breath hold and stored in cine-loop format. All echocardiography data were collected and analyzed in a centralized core lab (Henri Mondor Hospital). From the apical 2- and 4-chamber views, the LV volumes and ejection fraction were

calculated using the Simpson's rule. Speckle tracking analysis was performed by an independent operator unaware of clinical and echocardiography data (Caroline Dussault).

Strain delay index and LV dyssynchrony: The method to compute SDI has been described in detail previously(12). In dyssynchronous ventricles, delayed segments do not contribute fully to end-systolic function. The wasted energy per segment caused by dyssynchrony can be expressed mathematically as the difference between peak (ε_{peak}) and ES strain (ε_{ES}). Theoretically, this difference (ε_{ES}-ε_{peak}) increases with the severity of dyssynchrony (Figure 1). The wasted energy is expected to be greater in the segment with preserved contractility than in the segment with minimal or no residual contractility at a similar degree of delayed contraction. The different steps of SDI processing can be summarized as follows: first, a global strain (ε) curve representing LV function was obtained by averaging 16 regional LV strain curves. Next, the time to the peak of this global-ε curve was used to determine the timing of end-systole (ES) and to compute the strain in ES in the 16 segments. Then, peak and time to peak-ε in the 16 segments was defined as the minimum strain value during the cardiac cycle. Finally, the difference (ε_{peak}– ε_{ES}) in each segment (all 16 segments) was summed to generate the SDI (Figure 2). For a segment that exhibited positive strain or biphasic strain with a peak positive strain greater than the maximum absolute negative strain, the term (ε_{peak}– ε_{ES}) was entered as zero for the calculation of SDI. This methodology is based on previous data demonstrating that dyskinetic segments with a predominant stretching motion are unlikely to be contributive to CRT response(13). Time to peak longitudinal strain by speckle tracking was used to calculate the 12-segment (base and mid) SD of time to peak-ε (12SD–ε). In segments with positive or biphasic strain curves, time to minimum ε was chosen to compute 12SD-ε. The entire process was computed automatically on Excel file (free download on http://www.cardiologie-henri-mondor.fr/ for research purpose).

Device implantation: CRT was performed in the standard fashion with 3 trans-venous leads inserted. The right atrial and ventricular (apical site) leads were positioned conventionally. The LV lead was inserted through the coronary sinus and positioned into the lateral or posterolateral cardiac vein. Epicardial implantation (n=3) was required when coronary sinus catheterization failed. Biventricular pacing devices used included those manufactured by Medtronic (Minneapolis, Minn), St Jude Medical (Sylmar, Calif), and Guidant–Johnson & Johnson (Boston, Mass). After implantation, the atrioventricular interval was adjusted for optimal diastolic filling (by pulsed mitral Doppler): no VV delay setting was performed. In all patients, a device control was performed at 6 months to confirm the appropriate biventricular pacing (pacing time >80% in all patients included).

Follow-Up: Baseline and 6-month follow-up clinical characteristics were obtained from medical reports. Echocardiography examination was repeated 6 months after CRT. Response to CRT was defined by a significant LV reverse remodeling (LVES volume reduction [ESVR] >15%) 6 months after CRT. Changes in strain delay index and mechanical dyssynchrony after CRT were available in 82 patients that underwent the 6-month follow-up echocardiography with the GE system.

Statistical analysis: All continuous variables were presented as mean±SD and dichotomous data as percentage. To compare numerical data between two groups paired and unpaired Student t-tests were used when appropriate. Correlations between variables were assessed using a Pearson's linear correlation. Inter and intra-observer reproducibility was expressed as the difference between 2 measurements divided by the mean of these measurements. Sensitivity, specificity and positive and negative predictive value of strain delay index was computed using previous validated cutoff value (SDI>25%). Receiver operating characteristic curves (ROC) were determined to evaluate the diagnostic performance of LV dyssynchrony indexes to detect responses to CRT in narrow QRS patients. An optimal cutoff value for the diagnosis of responders was chosen to maximize the Youden index (sensitivity+specificity-1). To identify predictors of

a CRT response, multivariate analysis using the logistic regression model was performed with the inclusion of a variable with p value <0.1 by univariate analysis. Significant statistical analysis was considered when the p value was <0.05.

RESULTS

Characteristics of the whole population are summarized in the Table 1. During the 6 month follow up, 65% of patients had clinically improved (changes in NYHA score ≥I). The increase in LVEF averaged 11±20% and mean ESVR was 18±25%. Response to CRT (ESVR>15%) was observed in 114 (60%) patients, less in ischemic (44% vs. 68%, p=0.001, Table 2) and narrow QRS patients (49% vs. 65%, p=0.04, Table 3). Responders to CRT had more preserved global strain (-8±3% vs. -7±3%, p=0.01), more dyssynchrony (12SD-ε=112±37ms vs. 97±30ms, p=0.005) and had greater SDI (39±10% vs. 24±9%, p<0.0001, Table 1). A poor correlation with reverse remodeling after CRT was observed for baseline QRS duration (r=0.17 p=0.02), 12SD-ε (r=0.18, p=0.01) and global strain (r=0.20, p=0.005). In contrast, SDI correlated with LVEF improvement (r=0.45, p<0.0001) and ESVR (r=0.61, p<0.0001, Figure 3). Multivariate analysis adjusted to QRS duration, LV dyssynchrony, global strain, and cardiac etiology showed that only SDI (OR=1.8, p<0.001) was predictive for response to CRT. Using the cutoff value previously reported, SDI>25% identified 92% of responders with a positive predictive value of 80% and a negative predictive value of 84% (Figure 4).

Strain delay index in ischemic patients (Table 2): Compared to the non-ischemic group, ischemic patients responded less to CRT despite similar level of dyssynchrony and QRS duration. However, compared to the non-ischemic group, strain delay index was lower in ischemic patients (30±11% vs. 35±12%, p=0.01) and differed between responders and non-responders (Figure 5), while LV dyssynchrony failed to predict response to CRT. Importantly, strain delay index similarly correlated with ESVR in both the ischemic (r=0.55, p<0.001) and non-ischemic group (r=0.61, p<0.0001, Figure 3).

Strain delay index in narrow QRS patients (Table 3): Despite a similar level of LVEF impairment, narrow QRS patients in comparison to wide QRS patients had a less dilated ventricle, severe myocardial dyssynchrony (97±30ms vs. 110±37, p=0.02) and lower strain delay index value (30±10% vs. 34±13%, p=0.01). Response to CRT in the narrow QRS group was observed in 49% vs. 65% in the wide QRS group (p=0.04). Response to CRT was not associated with LV dyssynchrony (Figure 5) and baseline follow-up QRS duration. In contrast, strain delay index was greater in responders and correlated with ESVR similarly in narrow and wide QRS population (Figure 3). In narrow QRS patients, a strain delay index >25% identified responders with a sensitivity and specificity of 88% and 50% (Figure 4), respectively and a positive and negative predictive value of 63% and 81%, respectively. Accuracy was markedly increased with a strain delay index >30% in this population with a sensitivity and specificity of 84% and 85%, respectively and a positive and negative predictive value of 84% and 85%, respectively.

Changes in dyssynchrony and strain delay index: In responders, decrease in LV dyssynchrony (-13±48ms vs. +9±49ms, p=0.05) and in strain delay index (-7±18% vs. 4±11%, p=0.002) was more marked than in non responders. Changes in strain delay index correlated with ESVR (r=0.35, p=0.001) and LVEF improvement after CRT (r=0.27, p=0.01). In non responders, LV dyssynchrony (+9±49ms) and strain delay index (4±11%) remained unchanged despite efficient pacing.

Reproducibility: Intra and inter-observer variability performed in 10 random subjects was 8% and 12%, respectively for automatic 12SD-ε and 5% and 6%, respectively for automatic strain delay index.

DISCUSSION

Reverse remodeling of LV after CRT provides an objective measurement of CRT response, which correlated to improved survival and LV function. In this multicenter non randomized study including a

large number of patients (n=189), CRT response (ESVR>15%) was observed in 65% of patients with prolonged QRS duration, and in 49% of patients with narrow QRS duration ($p<0.05$). LV mechanical dyssynchrony (12SD-ε) derived from time-delay measurement with speckle tracking analysis was lower in non-responder patients but its accuracy is limited to identify responders to CRT. In contrast, SDI, which quantifies the amount of wasted energy due to LV dyssynchrony, was found to correlate closely with LVEF improvement and reverse remodeling after CRT in both narrow ($r=0.59$, $p<0.001$) and wide QRS patients ($r=0.66$, $p<0.0001$, Figure 3).

Most CRT studies have demonstrated that up to 40% of patients are non-responders, presumably because mechanical dyssynchrony was absent despite a wide QRS duration(1, 5). Several methods based on the time-delay measurement of regional wall motion have been proposed to quantify LV dyssynchrony. Single-center studies have demonstrated that the 12SD of peak velocity by TDI(14) (SD-TDI) and opposing-wall delay(15) by radial strain or longitudinal velocity correlated to the clinical response to CRT. However, in the PROSPECT(5) study, neither the SD-TDI nor the opposing-wall delay by TDI was predictive of response to CRT. The suboptimal accuracy of echocardiography markers to predict response to CRT was attributed to the limited accuracy and reproducibility of Doppler technique in HF patients (16, 17) and/or the use of a single marker approach. To overcome these limitations, Lafitte et al(18) has proposed a multi-parametric approach using conventional echocardiography markers to improve identification of responders. In the same way, several authors(19) have suggested to better predict response to CRT by quantifying myocardial dyssynchrony with the use of speckle tracking that provides a more accurate assessment of myocardial deformation. However, neither the predictive value of mechanical dyssynchrony derived from speckle tracking(20) for responsiveness to CRT nor the multi-parametric(21) approach have been confirmed. The controversial accuracy of time delay measurement using either TDI or speckle tracking may be explained by the fact that delayed contraction is a nonspecific marker of myocardial dysfunction that can be seen in scar(8, 10), fibrosis(22, 23), and viable(24) myocardium and

may be further impacted by loading conditions(25, 26). This limitation particularly affects ischemic patients but may be overcome by investigating myocardial viability and contractile reserve(9, 27-29) as a complement to LV dyssynchrony to better identify responders.

In a recent study(12), we proposed a new method, the SDI that combines within a single marker mechanical dyssynchrony measurement and myocardial contractility to predict response to CRT. SDI is not a simple measurement of contractility or time delay but a combination (and relative weighting) of both of these parameters (Figure 1). The importance of considering contractility and dyssynchrony to predict responsiveness to CRT is particularly crucial in ischemic patients(13), (30). Indeed, ischemic patients respond less to CRT despite similar dyssynchrony level and QRS duration than non-ischemic patients. This may be explained by the presence of extensive scar in delayed segments that prevents efficient biventricular pacing. In non ischemic patients, severe myocardial dysfunction related to myocardial fibrosis and remodeling may also limit the beneficial effect of CRT. Reant et al(30) has recently demonstrated that responders and super responders to CRT had greater longitudinal global strain than non responders. Scar and fibrosis in delayed segments may be investigated by stress echocardiography or magnetic resonance and nuclear imaging. However, the physiological approach of strain delay index may simply overcome these complex and costly investigations. The strain delay index incorporates the degree of impaired contractility related to myocardial dyssynchrony rather than dyssynchrony alone. This explains the close correlation between strain delay index and reverse remodeling after CRT in ischemic and non- ischemic patients. In the present study, we demonstrated that strain delay index and decrease in strain delay index after CRT was greater in responders. In addition, decrease in strain delay index after CRT correlates with reverse remodeling and LVEF improvement. These results strongly support the concept that the strain delay index can be inferred as the gain of contractility expected after optimal resynchronization therapy.

In narrow QRS patients, the robustness of the SDI has never been reported. Mechanical dyssynchrony in narrow QRS patients is less severe than in wide QRS patients. In the present study, we found that narrow QRS patients whose response to CRT has a similar SDI to wide QRS patients despite lower mechanical dyssynchrony. This can be explained by the fact that narrow QRS patients had less advanced heart disease and more preserved contractility in delayed segments. Indeed, the wasted energy in segments with limited dyssynchrony (5-10% of RR interval) and preserved contractility can reach a similar level than severely dyssynchronized segments (>10% delay from ES, Figure 6). Finally, these results highlight the concept of mechanical dyssynchrony by demonstrating that limitation of time delay markers is not simply related to the accuracy of the method used to quantify timing but rather to the need to consider contractility. The strain delay index overcomes this limitation by quantifying the wasted energy related to dyssynchrony that can be recruited by biventricular pacing. This unique index includes contractility and timing measurements and can be applied in both wide and narrow QRS population to predict response to CRT. The optimal cutoff to identify responders to CRT should be lower (SDI>25%) in wide QRS patients to ensure optimal negative predictive value (85%). In contrast, for narrow QRS population, optimal cutoff value should instead be >30% to ensure a high positive predictive value (84%). Importantly, compared to conventional dyssynchrony markers published in PROSPECT study, all data were automatically computed (excepted for the tracking). This explains the good reproducibility of strain delay index.

Study Limitations: Despite the large number of patients included in the study, only a limited number of patients with narrow QRS duration underwent CRT. The size of the study is a limitation to firmly conclude that the SDI in narrow QRS population is an accurate method to identify responders to CRT. Randomized study should be performed in this setting to confirm our results. Radial and circumferential strain were not used to quantify strain delay index because their values cannot be computed from the whole myocardium

and reproducibility remains limited. Finally, the study had excluded 20% of patients with limited acoustic windows to provide the real accuracy of strain delay index.

Conclusions: The present multicenter prospective study that includes non-selected patients referred for CRT demonstrates that SDI, which considers LV dyssynchrony and residual contractility, provides a satisfactory accuracy to identify responders to CRT in wide and narrow QRS population.

Sources of Funding: This work has been funded by the French Federation of Cardiology and the French Society of Cardiology.

Conflict of Interest Disclosures: none

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Figure legends

Figure 1: Changes of wasted energy (ε_{peak} -ε_{ES}) according to myocardial dyssynchrony and contractility: the panel A shows the increase of the wasted energy relative to dyssynchrony in two segments with preserved contractility; the panel (B) shows how the wasted energy considers the residual contractility. Scar segment with depressed contractility (dotted line) has lower wasted energy than segment with preserved contractility; the panel (C) shows that moderate delayed segments with preserved contractility has greater wasted energy than delayed segments with impaired contractility.

Figure 2: Strain delay index is defined as the sum of the wasted energy (ε_{ES}¬ε_{peak}) caused by LV dyssynchrony across the 16 myocardial segments of the LV (colored curves). B, After CRT, the increase (Δ) of global strain curve (white dashed curve) is supposed to be proportional to strain delay index.

Figure 3: Correlation between strain delay index and ESVR according to QRS complex (A) and to cardiac etiology (B). DCM for dilated cardiomyopathy and CAD for coronary artery diseases

Figure 4: ROC curves showing the accuracy of strain delay index in predicting response to CRT in the whole population (A), in wide (B) and narrow (C) QRS patients. SDI for strain delay index, 12SD-ε for the 12 standard deviation of time to peak strain by speckle tracking.

Figure 5: Greater LV dyssynchrony (A) was only observed in patients with wide QRS duration and non ischemic cardiac diseases. In contrast, strain delay index (B) was greater in responders independently of QRS duration and cardiac etiology.

Figure 6: Data from wide (A) and narrow (B) QRS patients demonstrating that the wasted energy per segment (ε_{peak}¬ε_{ES}) is related to the severity of dyssynchrony (x-axis) and to the residual contractility (z-axis).

Table 1: Population characteristics of responders and non-responders

	All	Responders	Non responders	p
n	189	114	75	
Age, y	65±12	63±11	63±11	0.5
Male, n(%)	132 (70)	77 (68)	55(73)	0.4
NYHA class	3±0.3	3.0±0.3	2.9±0.4	0.4
QRS duration, ms	151±34	157±32	143±37	0.009
CAD, n (%)	63 (33)	28 (25)	35 (47)	0.002
Baseline				
LVEF, %	26±8	26±9	25±8	0.5
EDV, ml	227±81	221±77	236±87	0.2
ESV, ml	172±71	166±68	180±76	0.2
global strain, %	-7±3	-8±3	-7±3	0.01
12SD-ε, ms	106±35	112±37	97±30	0.005
SDI, %	33±12	39±10	24±9	<0.0001
Follow up				
Δ QRS duration, ms	-11±50	-18±44	-1±55	0.1
Δ LVEF, %	11±20	12±11	0±9	<0.0001
Δ EDV, %	-10±20	-21±16	6±14	<0.0001
Δ ESV, %	-18±25	-35±16	6±14	<0.0001
Δ 12SD-ε, ms	-3.4±49	-13±48	9±49	0.05
Δ SDI, %	-2.4±16	-7±18	4±11	0.002

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Δ LVEF, %	11±20	12±11	0±9	<0.0001
Δ EDV, %	-10±20	-21±16	6±14	<0.0001
Δ ESV, %	-18±25	-35±16	6±14	<0.0001
Δ 12SD-ε, ms	-3.4±49	-13±48	9±49	0.05
Δ SDI, %	-2.4±16	-7±18	4±11	0.002

Table 3: Clinical characteristics of narrow and wide QRS patients

	Narrow QRS	Wide QRS	p
n	51	137	
Age, y	62±13	65±11	0.07
Male, %	76	68	0.25
NYHA class	3.0±0.3	3.0±0.3	0.6
QRS, ms	109±18	167±24	<0.0001
CAD, %	37	32	0.5
Baseline			
LVEF, %	26±8	25±8	0.3
EDV, ml	184±63	210±94	0.002
ESV, ml	128±57	147±86	0.002
Global-ε, %	-8±3	-7±3	0.4
12SD-ε, ms	97±30	110±37	0.02
SDI, %	30±10	34±13	0.01
SDI>25%, %	63	71	0.2
SDI>30%, %	49	61	0.1
Follow up			
Δ QRS, ms	37±36	-32±39	<0.0001
Δ LVEF, %	6±12	8±12	0.3
Δ EDV, %	-14±38	-29±51	0.1
Δ ESV, %	-17±39	-35±48	0.05
Δ ESV >15%, %	49	65	0.04

Figure 1
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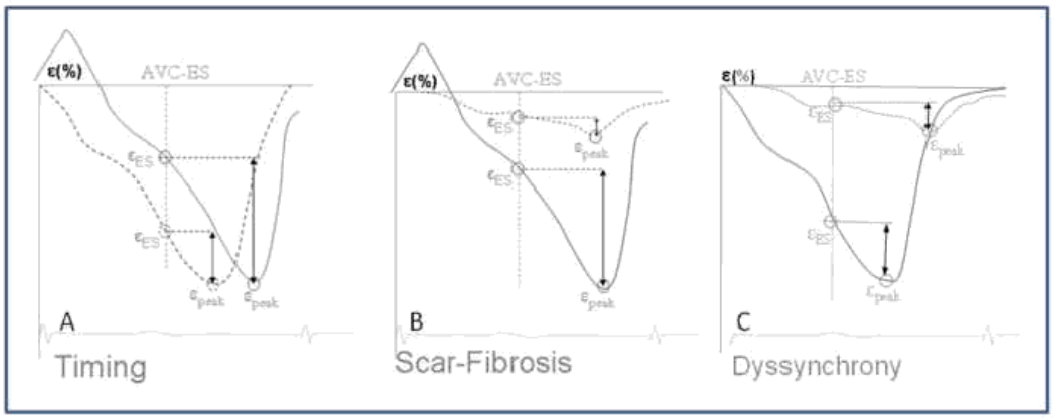

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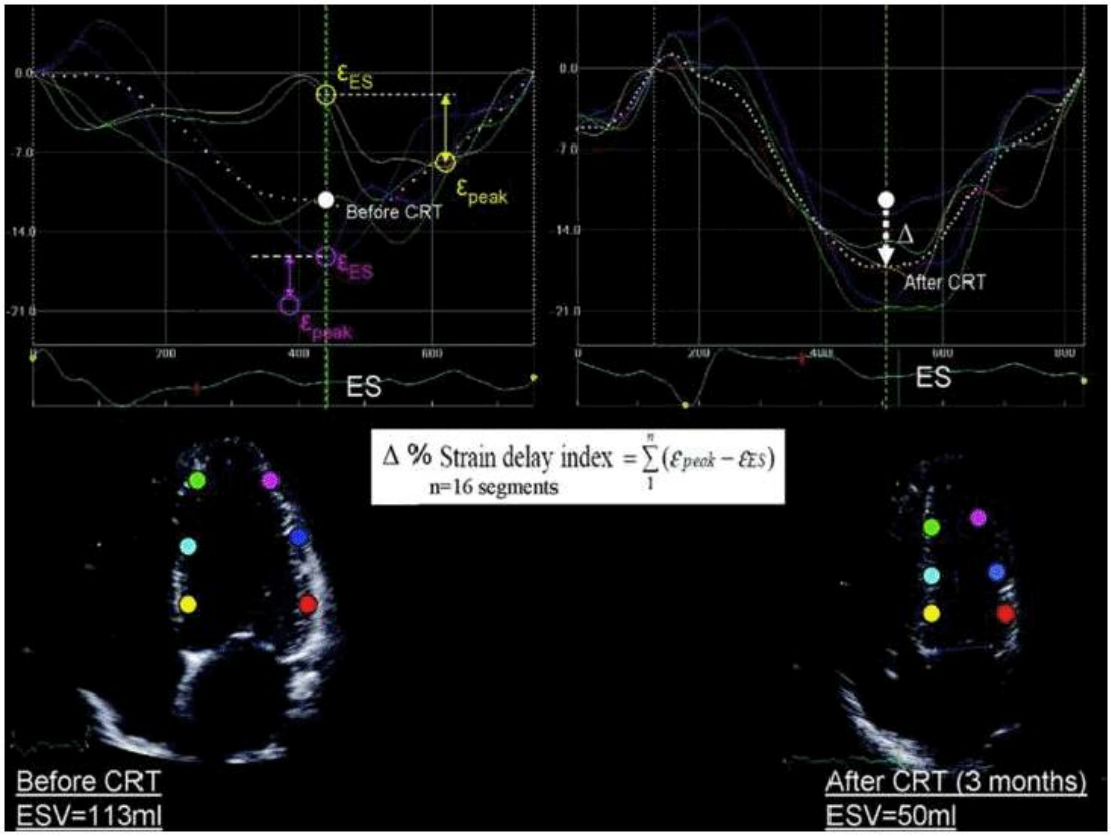

Figure 3

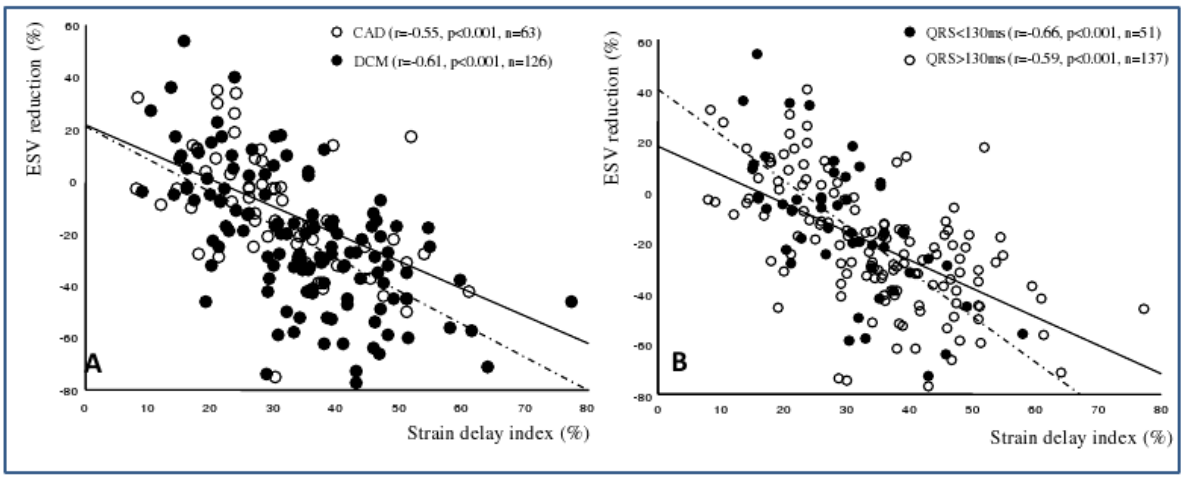
ESV reduction (%)
CAD (r=-0.55, p<0.001, n=63)
DCM (r=-0.61, p<0.001, n=126)
A
Strain delay index (%)
ESV reduction (%)
QRS<130ms (r=-0.66, p<0.001, n=51)
QRS>130ms (r=-0.59, p<0.001, n=137)
B
Strain delay index (%)

Figure 4
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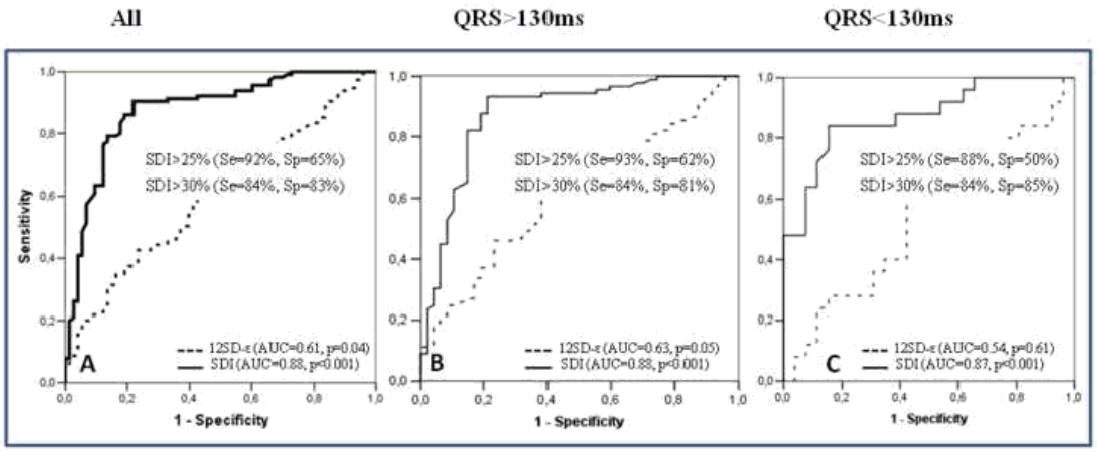

Figure 5
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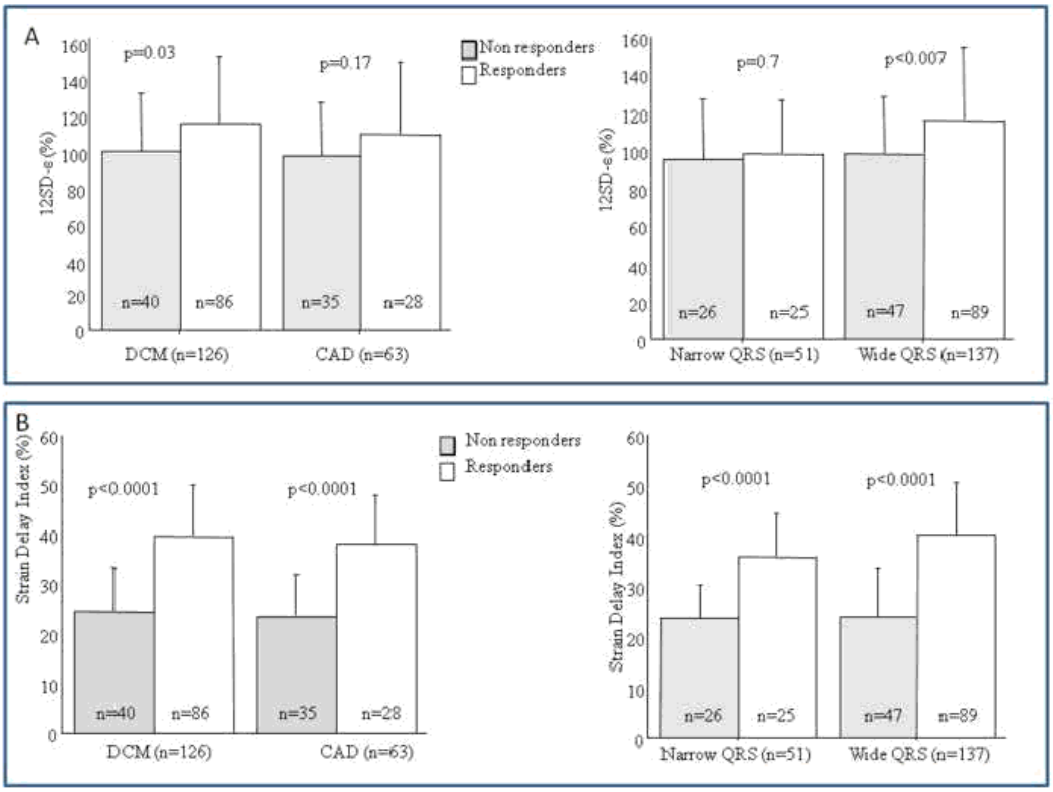

Figure 6
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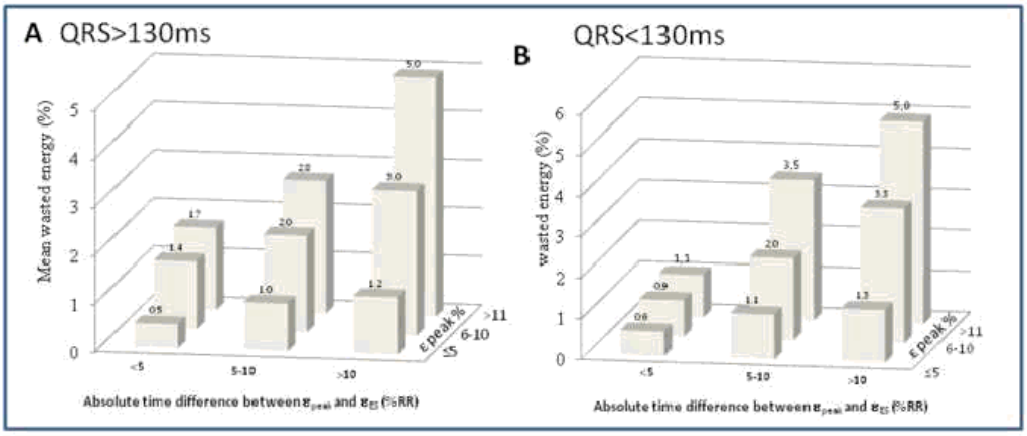

Conclusion et perspectives

La resynchronisation cardiaque permet d'améliorer les symptômes des insuffisants cardiaques mais, malgré la présence de QRS larges, seulement 50% à 60% des patients vont présenter une réponse objective avec remodelage inverse du ventricule gauche. A l'inverse, une faible proportion de patients ayant des QRS fins peut répondre à la resynchronisation cardiaque. Ces observations avaient amené à suggérer que la réponse à la resynchronisation cardiaque était conditionnée par la présence d'un asynchronisme mécanique. Les excellents résultats des premières études portant sur des populations sélectionnées n'ont cependant pas été confirmés par les études multicentriques (PROSPECT, RETHINQ). Les résultats de cette thèse ont montré qu'un retard de déformation myocardique était fréquemment retrouvé dans les zones cicatricielles d'infarctus et donc non spécifique d'un bloc de conduction électrique. La correction de l'asynchronisme mécanique et le bénéfice de la resynchronisation cardiaque nécessitent un myocarde retardé mais ayant une réserve contractile préservée. Ces résultats soulignent l'importance d'intégrer la contractilité résiduelle à l'asynchronisme pour prédire la réponse à la resynchronisation cardiaque. La combinaison des deux paramètres a été obtenue par un indice que nous avons appelé le « strain delay index » qui calcule la perte d'énergie contractile liée à l'asynchronisme. Nous avons montré que la perte d'énergie est plus importante chez les patients répondeurs et qu'elle diminue lorsque la resynchronisation cardiaque est efficace. Ces résultats ont permis de mieux comprendre les déterminants de la réponse à la resynchronisation cardiaque et ouvrent la perspective à des études comparatives permettant de valider le concept de perte d'énergie.

Annexes

Le mode Doppler tissulaire **:** La vélocimétrie Doppler s'appuie sur le fait que la fréquence des ultrasons réfléchis (Fr) par une particule en mouvement diffère de la fréquence des ultrasons émis (Fe). Si l'on considère une particule en mouvement à la vitesse *v* et une onde ultrasonore de fréquence Fe, dont la vitesse de propagation est *c* et l'angle de tir défini par la direction de propagation de l'onde incidente et la direction du vecteur de vitesse de la cible est *i*, alors le décalage en fréquence ou fréquence Doppler s'écrit : F = Fr-Fe et vaut : F = 2 Fe *v*/*c* cos *i*

L'ensemble des systèmes Doppler (pulsé ou continu) permet de déduire de la mesure de la fréquence Doppler, la vitesse des particules étudiées *v* ; et si l'angle de tir est de 90°, cos *i* est alors égal à 0 et la méthode n'est donc plus applicable. Il a été montré que les vélocités (et donc également les déformations) sont sous-estimées de 6% avec un angle de 20° entre le faisceau incident et la direction du déplacement de la paroi investiguée, de 13% à 30° et de 29% à 45° (88,89). La méthode Doppler nécessite donc un angle d'incidence le plus proche possible de 0° (classiquement inférieur à 60°) afin de limiter les erreurs de mesures. Le DTI a pour but d'étudier non plus les mouvements des hématies, comme le font les systèmes Doppler traditionnels, mais le mouvement des parois myocardiques. Or, les propriétés physiques et acoustiques des flux sanguins et du tissu myocardique sont différentes : d'une part, les vitesses de déplacement des parois myocardiques sont plus basses (<30cm/s) que celles des flux sanguins et, d'autre part, la réflectivité acoustique des interfaces myocardiques est supérieure à celle des interfaces sanguins d'où un signal de plus grande amplitude et de plus grande puissance que celui du sang. On a donc pu passer du Doppler spectral

au Doppler tissulaire en modifiant les filtres passe-haut et en ajustant l'échelle des vélocités. Il existe 3 modalités d'acquisition en DTI : le mode pulsé, le mode TM couleur et le mode bidimensionnel. En mode pulsé à l'anneau mitral, les mesures réalisées en pratiques sont le pic S' de vitesse myocardique systolique longitudinal, le pic E' protodiastolique (cm/s) et le pic A' télédiastolique (cm/s). Les améliorations suivantes ont permis de cartographier les vélocités et d'apprécier la déformation myocardique à partir des profils de vélocité (strain et strain rate). Il existe ainsi différents paramètres dérivés du Doppler tissulaire myocardique : des paramètres de mouvement (vélocité et déplacement) et des paramètres de déformation (vitesse de déformation ou strain rate et déformation ou strain).

Analyse des déformations en « speckle tracking » **:** Cette technique permet d'analyser, grâce à un logiciel dédié et de manière semi-automatique, les déformations par le suivi des marqueurs acoustiques de la paroi myocardique : on l'appelle « speckle tracking echocardiography » (STE) ou « strain bidimensionnel » (2D strain). Elle a pour autre avantage d'appréhender et de quantifier simultanément au niveau segmentaire ou global, toutes les composantes de la déformation myocardique : circonférentielle, radiale (ou transverse) et longitudinale. Le degré de torsion entre la base et l'apex peut également être quantifié. Le 2D strain ou STE consiste en un procédé de traitement d'images par un logiciel, configuré afin d'effectuer un suivi des marqueurs acoustiques contenus dans une région d'intérêt de la paroi myocardique (d'où le nom de « speckle tracking ») à partir de l'enregistrement d'une boucle échocardiographique bidimensionnelle noir et blanc (en échelle de gris). L'incidence

parasternale petit-axe permet d'évaluer la déformation radiale et la déformation circonférentielle alors que les incidences apicales appréhendent la déformation longitudinale et transverse du ventricule.

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