Left ventricular mechanics in advanced heart failure patients

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Left ventricular mechanics in advanced heart failure patients

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CHAPTER 1

General introduction and outline thesis

INTRODUCTION

Heart failure (HF) remains one of the major public health problems in developed countries. In United States, nearly 6 million patients have HF symptoms and 500,000 new patients are diagnosed yearly.[1] Recently, important advances in HF therapy, such as cardiac resynchronization therapy (CRT), have improved the outcome of these patients.[2] However, the prognosis remains poor with a 5-year mortality of 42.3% after hospitalization for HF.[1]

Selection of HF patients who are candidates for device therapies (such as CRT) is crucial to optimize the therapy results while minimizing the risk of potential complications (including lack of response to the device therapy). Advanced imaging techniques have helped to better understand the pathologic substrate of heart failure patients and have provided novel insight into the determinants of response to therapy.

The study of cardiac mechanics and in particular, left ventricular (LV) strain and twist are important aspects of cardiac mechanics.[3, 4] LV strain refers to the deformation of the LV, which occurs in the longitudinal, circumferential and radial directions. Furthermore, the spiral architecture of LV myofibers lead to a characteristic motion of rotation of the LV apex and base in opposite directions, counterclockwise and clockwise as viewed from the LV apex, respectively. The opposite rotation of LV apex and base leads to a LV systolic wringing motion during systole referred to as twist or torsion. In particular, LV twist is the net difference at isochronal time points between apex and base in the rotation angle along LV longitudinal axis, whereas LV torsion is LV twist indexed to the distance between LV apex and LV base.[5] This characteristic motion of the LV contributes significantly to LV systolic and diastolic function. In the last decade, assessment of myocardial strain and twist has emerged as novel LV functional parameters for risk stratification of patients with structural heart disease.

Nowadays, echocardiography and magnetic resonance imaging allow the study of LV mechanics. However, echocardiography remains as the imaging technique of first choice due to its wide availability and less time-consuming analysis compared with magnetic resonance imaging. Two-dimensional (2D) speckle tracking, tissue Doppler imaging and, less frequently, calibrated integrated backscatter imaging, are the echocardiographic techniques to assess several aspects of LV mechanics. From 2D speckle tracking echocardiography, the assessment of active myocardial deformation in multiple directions (radial, circumferential and longitudinal) and LV twist can be obtained. From tissue Doppler imaging, velocities and indirect information on deformation may be derived. Integrated backscatter, finally, through the analysis of assessment of myocardial ultrasound reflectivity, may quantify the percentage of myocardial fibrosis.

2D speckle tracking echocardiography

Based on 2D gray scale echocardiographic images, the myocardium exhibit natural acoustic markers or speckles that can be tracked frame-to-frame using speckle tracking software. Speckles are randomly distributed within the myocardium and the specific distribution of the speckles provides a distinguished pattern to each myocardial region, such as a fingerprint. The movement of the speckles along the cardiac cycle is tracked frame-to-frame independently from the ultrasound beam insonation angle permitting the evaluation of myocardial contraction/relaxation along the circumferential, longitudinal and radial direction.[6, 7] The LV contraction in these 3 directions leads to rotation movement of the left ventricle. The speckle tracking software calculates LV rotation from the apical and basal short-axis images as the average angular displacement of the 6 standard segments referring to the ventricular centroid, frame by frame. Counterclockwise rotation is marked as positive value and clockwise rotation as negative value when viewed from the LV apex. LV twist is defined as the net difference (in degrees) of apical and basal rotation at isochronal time points.[8]

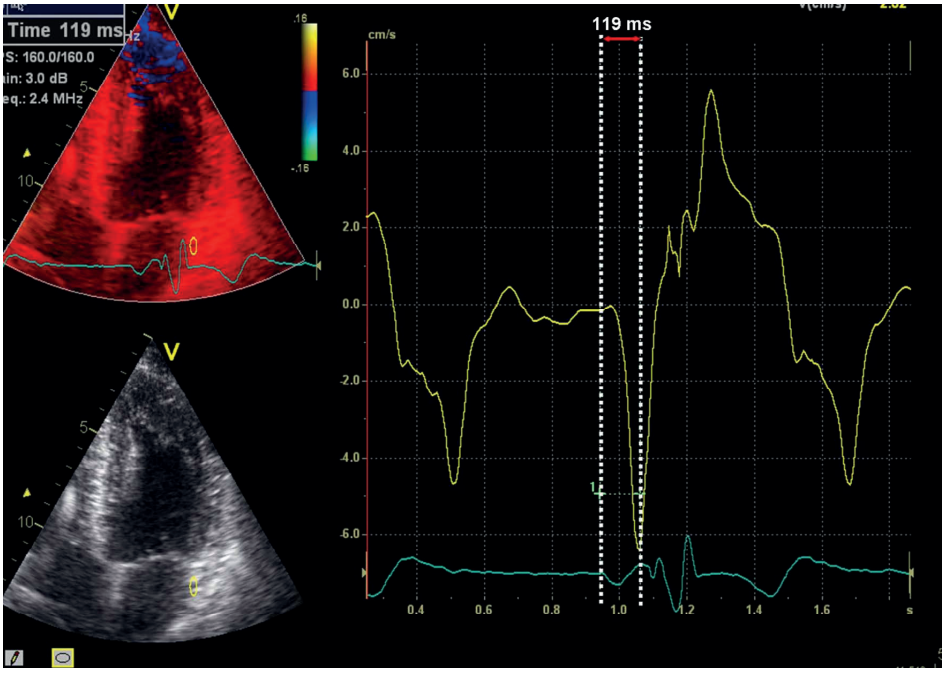

Figure 1. Examples of left ventricular (LV) twist in normal control (panel A) and in heart failure patient (panel B). In both panels, the upper parts represent apical and basal rotations and the lower parts represent LV twist calculation after exporting the data to a spreadsheet program (Excel 2003; Microsoft Corporation, Redmond, Washington). AVC: aortic valve closure. AVO: aortic valve opening.

1

Tissue Doppler imaging

Tissue Doppler imaging (TDI) permits the assessment of low velocities of the myocardium along the cardiac cycle. TDI can be applied with pulsed-wave Doppler or with color-coded TDI. While pulsed-wave TDI permits assessment of one myocardial region on-line, color-coded TDI permits assessment of several regions simultaneously off-line. In contrast to 2D speckle tracking echocardiography, the measurement of myocardial velocities with TDI is insonation angle dependent and therefore, the analysis is frequently limited to the basal and midventricular regions. From spatial derivation of myocardial velocities, regional strain rate can be obtained and from further temporal integration of strain rate, myocardial strain can be obtained.

The assessment of myocardial velocities and the time elapsed between electrical and mechanical (velocities) phenomena provide an estimate of the electromechanical delay within the myocardium. It has been hypothesized that the time delay between the P-wave on the surface ECG and the A' wave on TDI (total atrial conduction time) may reflect the amount of myocardial fibrosis. Total atrial conduction time may be estimated with color-coded tissue Doppler images by first placing the sample

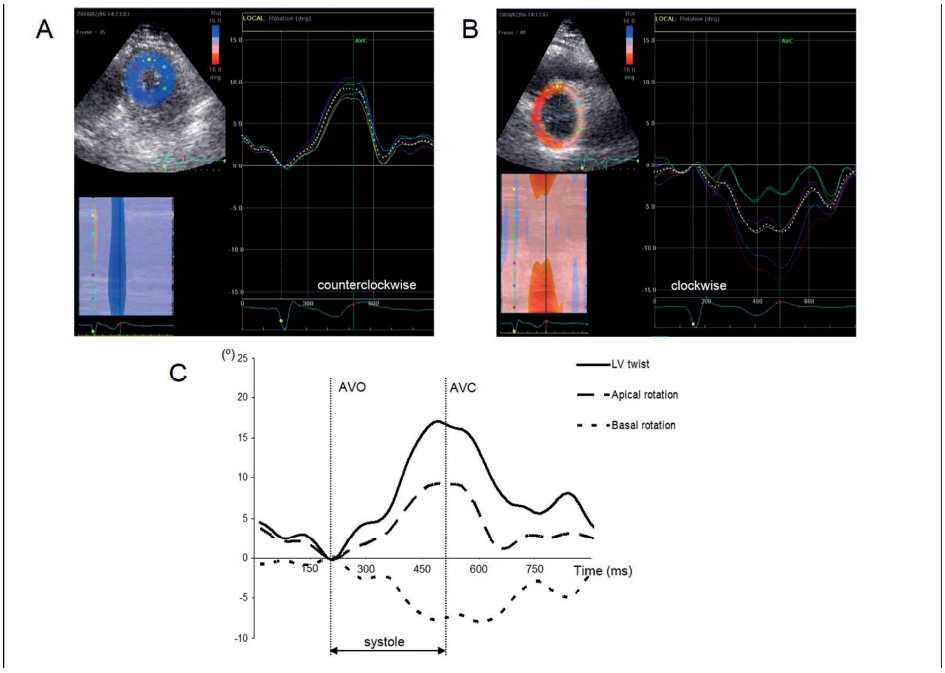

Figure 2. The time-interval from the beginning of the electrocardiogram P wave and the peak of A'$_{LATERAL}$ wave (PA-TDI duration) was obtained with tissue Doppler images by placing the sample size on the LA lateral wall just above the mitral annulus; next the PA-TDI duration was measured.

size on the LA lateral wall just above the mitral annulus. Next, the time-interval from the onset of the P-wave on lead II of the electrocardiogram (on echocardiographic images) to the peak of $A'_{LATERAL}$ wave (PA-TDI duration) is measured and an estima-

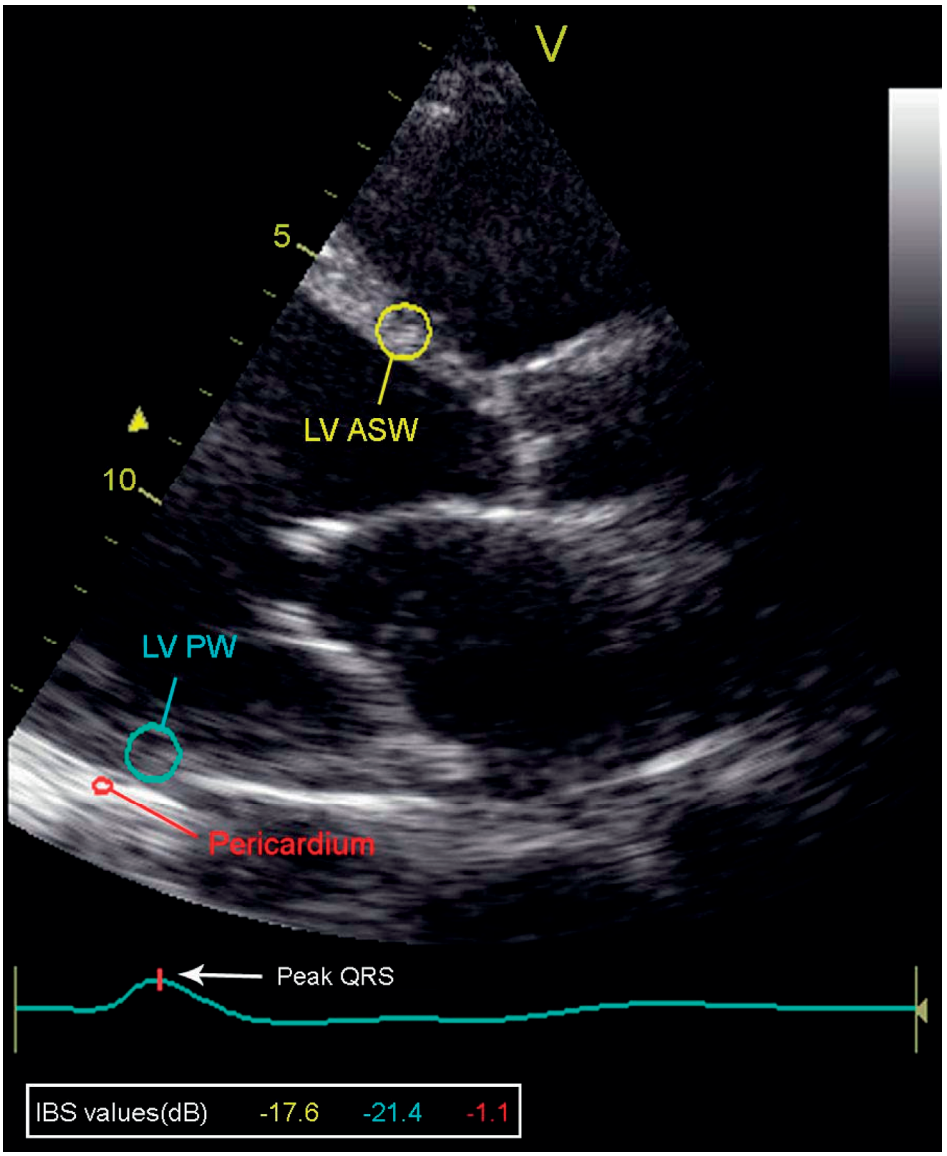

Figure 3: Example of assessment of LV fibrosis in the antero-septal and posterior walls with calibrated IB. A fixed 9x9-pixel region of interest was positioned in the mid-myocardium of the antero-septal (ASW) and posterior wall (PW) and a fixed 2x3-pixel region of interest was positioned in the pericardium. Calibrated IB for the ASW is calculated by subtracting the pericardial IB intensity from the ASW IB intensity, and the calibrated IB for the PW is calculated by subtracting the pericardial IB intensity from the PW IB intensity.

tion of atrial conduction time is obtained.[9] In HF patients, this TA-TDI duration has been associated with increased risk of atrial fibrillation at follow-up.[10]

Integrated backscatter

Calibrated integrated backscatter (IB) is a parameter based on gray-scale 2D images which evaluates myocardial ultrasound reflectivity. In the heart, the pericardium is the anatomic structure with the highest content of fibrosis and with the highest ultrasound reflectivity; whereas blood pool has the lowest ultrasound reflectivity since no fibrous tissue exists. The myocardium shows an intermediate ultrasound reflectivity and this reflectivity may increase together with the amount of fibrosis.[11, 12] Gray-scale 2D images may be obtained at parasternal long-axis view, with frame rates between 80 and 120 frames/s. A fixed region of interest is then positioned in the mid-myocardium of the antero-septal and posterior walls of the LV and a fixed region of interest is positioned in the pericardium. A measure of myocardial ultrasound reflectivity or tissue density is obtained with calibrated IB by subtracting pericardial IB intensity from myocardial IB intensity of the LV antero-septal and LV posterior walls.

Objectives and Outline of the Thesis

The objectives of this thesis were to investigate the role of LV mechanics in the assessment of HF patients who are candidates to CRT and to evaluate the prognostic value of parameters derived from the several imaging techniques to assess LV mechanics.

In **Part I**, the study of cardiac mechanics is applied to HF patients in order to: 1. distinguish LV mechanics between the different aetiologies of HF (**Chapter 3**); 2. to investigate the beneficial effects of CRT on long-term outcome of HF patients (**Chapters 4-6**); 3. how to optimize the response to CRT (**Chapter 7**).

Finally, **Part II** provides an overview of the several parameters, clinical and echocardiographic, that influence the outcome of HF patients. Specifically, **Chapter 8** demonstrates that echocardiographic response to CRT is an independent predictor of long-term outcome over other well-established prognostic indices of HF. **Chapter 9** focuses on the assessment of risk of ventricular tachyarrhythmias in HF patients based on LV cardiac mechanics. **Chapter 10** shows that LV global longitudinal strain is strong prognostic determinant of patients with ischemic HF. Finally, **Chapter 11** underscores the relevance of electromechanical delay within the atrial myocardium as a risk factor for atrial fibrillation in HF patients with an implantable cardioverter-defibrillator.

REFERENCES

(1) Lloyd-Jones D, Adams R, Carnethon M et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009 January 27;119(3):e21-181.

(2) Jeevanantham V, Daubert JP, Zareba W. Cardiac resynchronization therapy in heart failure patients: an update. *Cardiol J* 2009;16(3):197-209.

(3) Sengupta PP, Krishnamoorthy VK, Korinek J et al. Left ventricular form and function revisited: applied translational science to cardiovascular ultrasound imaging. *J Am Soc Echocardiogr* 2007 May;20(5):539-51.

(4) Sengupta PP, Narula J. Reclassifying heart failure: predominantly subendocardial, subepicardial, and transmural. *Heart Fail Clin* 2008 July;4(3):379-82.

(5) Takeuchi M, Otsuji Y, Lang RM. Evaluation of left ventricular function using left ventricular twist and torsion parameters. *Curr Cardiol Rep* 2009 May;11(3):225-30.

(6) Leitman M, Lysyansky P, Sidenko S et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004 October;17(10):1021-9.

(7) Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004 June;17(6):630-3.

(8) Bertini M, Sengupta PP, Nucifora G et al. Role of left ventricular twist mechanics in the assessment of cardiac dyssynchrony in heart failure. *JACC Cardiovasc Imaging* 2009 December;2(12):1425-35.

(9) De Vos CB, Weijs B, Crijns HJ et al. Atrial tissue Doppler imaging for prediction of new-onset atrial fibrillation. *Heart* 2009 May;95(10):835-40.

(10) Bertini M, Borleffs CJ, Delgado V et al. Prediction of atrial fibrillation in patients with an implantable cardioverter-defibrillator and heart failure. *Eur J Heart Fail* 2010 October;12(10):1101-10.

(11) Picano E, Pelosi G, Marzilli M et al. In vivo quantitative ultrasonic evaluation of myocardial fibrosis in humans. *Circulation* 1990 January;81(1):58-64.

(12) Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004 November 9;110(19):3081-7.

PART I

Heart failure

CHAPTER 2

Role of left ventricular twist mechanics in the assessment of cardiac dyssynchrony in heart failure.

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JACC Cardiovasc Imaging. 2009 Dec;2(12):1425-35.

ABSTRACT

Technologic innovations in cardiac imaging have provided new tools and algorithms for accurate assessment of left ventricular (LV) twist mechanics. This review provides a focused update on the incremental value of assessing LV twist mechanics in patients with heart failure (HF) and its potential role in characterizing response to cardiac resynchronization therapy (CRT). First, the findings are summarized from recent experimental and clinical studies that have specifically characterized the patterns of abnormal LV twist mechanics in HF. Next, the evolving application of LV twist is discussed in understanding response to CRT, elucidating the independent relationship between LV twist mechanics and reversal of LV remodeling at 6 months follow-up. Finally, the studies are addressed that underscore a critical relationship between LV lead position and changes in LV twist after CRT. These data suggests that the reversal of LV remodeling seen in HF patients following CRT primarily results from restoration of the global sequence of LV twist mechanics.

INTRODUCTION

Heart failure (HF) remains one of the major public health problems in developed countries. In United States, nearly 6 million patients have HF symptoms and 500,000 new patients are diagnosed yearly ([1]). Recently, important advances in HF therapy, such as cardiac resynchronization therapy (CRT), have improved the outcome of these patients ([2]). However, the prognosis still remains poor with a 5-year mortality of 42.3% after hospitalization for HF ([1]).

LV rotation, twist and torsion are important aspects of the cardiac mechanics. The term rotation is referred to the rotation of LV short-axis sections. Due to the spiral architecture of LV myofibers, the rotation of LV apex and base are counterclockwise and clockwise, respectively, as viewed from the LV apex. The opposite rotation of LV apex and base leads to a LV systolic wringing motion during systole referred to as twist or torsion. In particular, LV twist is the net difference at isochronal time points between apex and base in the rotation angle along LV longitudinal axis, whereas LV torsion is LV twist indexed to the distance between LV apex and LV base ([3]). This peculiar characteristic of the LV contributes significantly to LV systolic function, in addition to myocardial shortening and thickening.

Following a brief overview of physiology of LV rotational mechanics, an in-depth discussion is provided on different LV twist patterns in systolic HF and the evolving role of LV twist as a marker of LV-dyssynchrony for understanding response to CRT.

NORMAL LV TWIST MECHANICS

In the normal heart, the myofiber geometry of the LV changes gradually from a right-handed helix in the subendocardium to a left handed helix in the subepicardium. Taber et al. ([4]) explored the impact of this changing transmural myofiber orientation on LV rotational mechanics in a one-layer cylindrical model that consisted of obliquely aligned muscle fibers embedded in an isotropic matrix. The contraction of the epicardial fibers rotated the apical end of the model in the counterclockwise direction and the base in the clockwise direction. Conversely, shortening of the subendocardial fibers rotated the apex and base in clockwise and counterclockwise directions respectively. When both layers are coupled to contract simultaneously, a larger radius of rotation for the outer epicardial layer resulted in the epicardial fibers having a mechanical advantage in dominating the overall direction of rotation. The endocardial layer does provide some opposition to epicardial motion. This opposing action ensures that epicardial and endocardial sarcomere shortening in all directions are equilibrated during ejec-

tion, resulting in an optimal distribution of LV stress and strain ([5]). Elimination of twist decreases epicardial shortening at the expense of an increase in endocardial shortening. This in turn increases endocardial stress and strain, which increases oxygen demand and reduces the efficiency of LV systolic performance.

Taber's model also provides explanation for the temporal changes in the sequence of LV twist during a cardiac cycle. The initial shortening of subendocardium causes a brief clockwise rotation of LV apex during the isovolumic contraction ([3, 6]). Subsequent transmural spread of electrical activation, results in simultaneous shortening of subendocardial and subepicardial fibers. Due to the subepicardial fibers having a larger moment arm, the direction of rotation is shifted towards a counterclockwise rotation for the LV apex and a clockwise rotation for the LV base (Figure 1).

In the subepicardium, this twist supports contraction in the principal fiber direction. In the midwall, the twist enhances shortening in the circumferential direction.

Twist deformation of the LV wall causes fiber rearrangement that maximizes the LV wall thickening. In particular, twisting and shearing of the subendocardial fibers also deforms the matrix and results in storage of potential energy by compression of cardiac proteins such as titin ([6]). The potential energy stored in the titin is subsequently unleashed during diastole, aiding myocardial relaxation and diastolic filling.

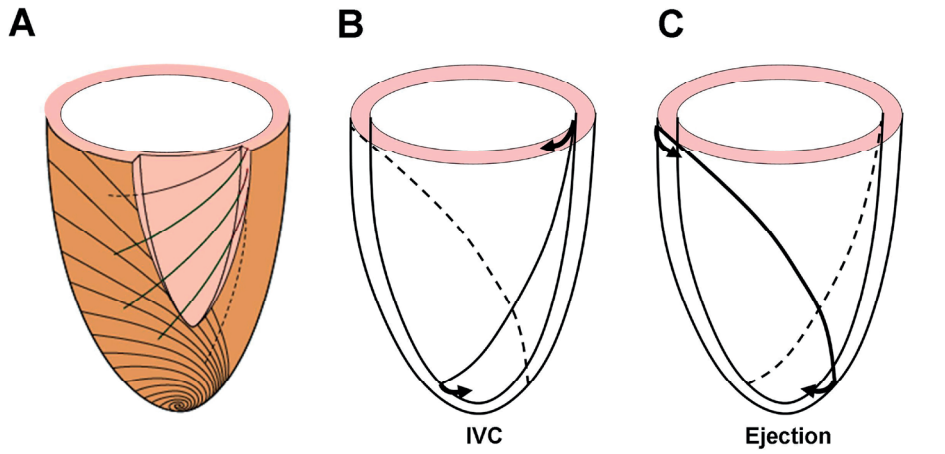

Figure 1. Mechanism of left ventricular twist

Left ventricular (LV) fiber orientation changes from a right handed helix in the subendocardium to a left handed helix in the subepicardium (**A**). During isovolumic contraction (IVC), circumferential components of force (arrows) are generated by endocardial fiber shortening, which rotates the LV about the long axis clockwise as viewed from the apex (**B**). During ejection, shortening of subepicardial fibers wrapped in an opposite, left-handed helix, rotates the LV counterclockwise (**C**). Twisting force by epicardial shortening overcomes the forces of subendocardial shortening because the torque of the epicardial force is larger due to a greater radius of the epicardial fibers from the central LV long axis.

Factors Affecting LV Twist

Alterations in preload, afterload and contractility have been shown to alter cardiac rotation ([5]). Loading mechanics influences twist through changes in LV end-diastolic and end-systolic volumes. The directly proportional relationship between torsion and LV end-diastolic volume and the inversely proportional relationship between torsion and end-systolic volume illustrate the volume dependency of LV torsion. Like changes in loading conditions, increasing contractility increases LV twist; for example, positive inotropic interventions such as dobutamine infusion and paired pacing, greatly increase LV twist, whereas negative inotropic interventions markedly reduce twist ([5]).

Moreover, the LV twist increases gradually from infancy to adulthood. Notomi et al. ([7]) assessed LV torsion and twisting velocities in individuals from 9 months to 49 years and found that with advancing age there was an increase in LV torsion and untwisting velocity. Several other investigations examining older individuals have shown LV torsion to be maintained or increased compared with younger adults. It has been proposed that endocardial function is more likely to reduce with age due to the subendocardium's greater susceptibility to fibrosis and/or subclinical reductions in perfusion. As per Taber's model, the reduced endocardial function would result in less opposition to the dominant epicardial action causing increase in rotation. The finding of reduced subendocardial function and increased torsion in older individuals results in preservation of global LVEF, suggesting a compensatory mechanism that helps to preserve global LVEF despite the presence of subendocardial dysfunction.

LV TWIST IN THE DYSSYNCHRONOUS, FAILING VENTRICLE

LV twist is emerging as an important parameter of LV systolic function. Several authors previously reported a significant correlation between LV twist and LVEF, the most commonly used index of LV systolic function in clinical practice ([8]). However, there is increasing evidence that LV twist is superior to LVEF in characterizing hemodynamic aberrations in patients with HF. For example, Kim et al. ([9]), in a recent experimental study, reported a strong correlation between dP/dt_{max} (an invasive, relatively load-independent, measure of LV contractility) and LV twist ($R^2 = 0.747$, $p < 0.001$); however, the correlation between dP/dt_{max} and LVEF, despite significant, was weaker ($R^2 = 0.408$, $p < 0.001$). This observation is related to specific differences in LV twist and LVEF: LV twist is an index of systolic myocardial deformation, while LVEF simply reflects LV volume reduction during systole.

In particular, the LV torsional deformation, related to the spiral architecture of LV myofibers, permits the generation of LVEF ≥60% from myofibers that can shorten by only 15%; otherwise, simple longitudinal or circumferential shortening would not allow LVEF higher than 30% ([10, 11]). Besides being a sensitive indicator of myocardial performance, the LV rotational mechanics appear strongly related to the sequence of LV depolarization as well; the propagation of the electrical cardiac activity is indeed significantly related to the spiral architecture and the anisotropic properties of cardiac myofibers ([12]). The assessment of LV twist, therefore, may provide more in-depth understanding of the pathophysiology of HF, as compared to the traditional parameters of LV systolic function.

The Ischemic versus the Non-ischemic Failing Ventricle

Significant alterations of LV rotational mechanics have been observed in patients with previous myocardial infarction (MI) and chronic ischemic and non-ischemic HF.

Myocardial infarction. Several studies showed an impairment of LV twist after MI ([5, 8]). The observed reduction of LV twist correlates with the reduction of LVEF (being more pronounced when LVEF is <45%) and the number of dysfunctional myocardial segments. In addition, Gjesdal et al. ([13]) recently observed a significant correlation between LV twist and the infarct mass ($r = -0.59$, $p < 0.001$). The injury caused by the infarction to the LV myofiber architecture, may explain these findings. Indeed, Wu et al. ([14]), using diffusion tensor magnetic resonance imaging, observed an increase of left-handed myofibers and a decrease of right-handed myofibers in the infarct area; the extent of these changes was associated to the infarct size. Interestingly, opposite changes were observed in the remote zone, likely representing an adaptive response to increased wall stress.

Ischemic versus non-ischemic HF. As compared to MI patients, HF patients present an even more pronounced impairment of LV rotational mechanics, irrespective of HF etiology as result of reduction of both LV basal and apical rotation (Figure 2) ([8, 15-17]). In particular, the typical counterclockwise rotation of the LV apex may be completely abolished, or even reversed in a clockwise rotation. Recently, in a population of advanced HF patients with prolonged QRS duration, Bertini et al.([18]) showed a modest but significant correlation between LV twist and LVEF ($r = 0.53$, $p < 0.001$). This finding supports the hypothesis that LVEF and LV twist are not identical parameters, and LV twist may provide incremental information on LV systolic performance.

According to previous experimental studies, several mechanisms may explain the impairment of LV twist in HF patients. First, as demonstrated by Taber et al. ([4]), LV

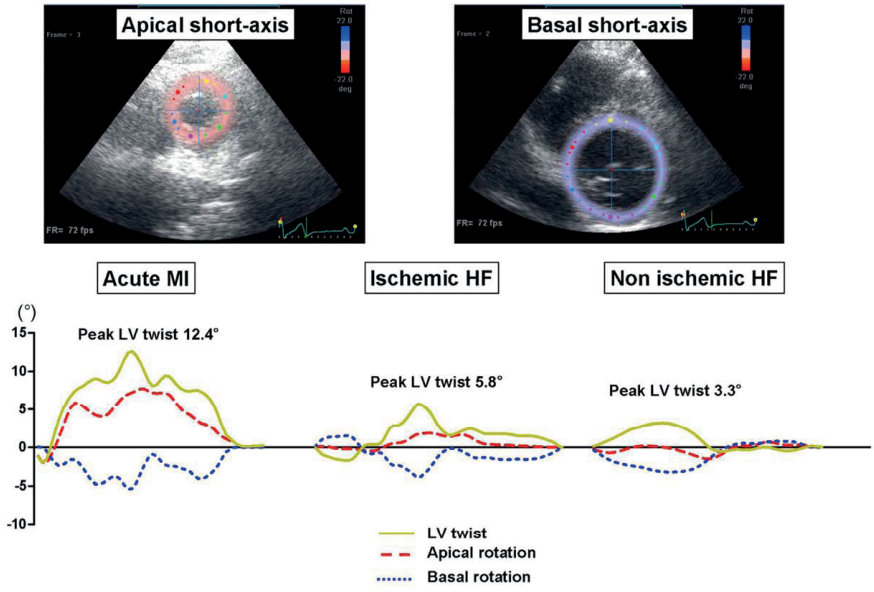

Figure 2. Left ventricular twist in acute myocardial infarction and ischemic versus non-ischemic heart failure.

Examples of left ventricular (LV) twist assessed with speckle tracking echocardiography in acute myocardial infarction (MI), and chronic ischemic versus non ischemic heart failure (HF). Of note, LV twist is markedly reduced in HF patients as compared to acute MI patient.

dilatation and thinning, present in dilated cardiomyopathy, equalize the radii of the subepicardial and subendocardial layers; as a result, the mechanical advantage of the subepicardial myofibers (the major determinants of LV twist under physiologic conditions) is reduced. Consequently, LV twist decreases with increasing cavity volume. Second, the long lasting processes determining dilated cardiomyopathy and eccentric hypertrophy, cause myofibers disarray and alterations in myofibers angle ([16]). These phenomena eventually lead to the loss of the physiological spiral architecture of the LV and to the impairment of LV twist ([19]). Last but not least, slowed transmural fiber activation, related to fibrosis and remodeling of gap junctions, may delay the activation of the epicardial myofibers, determining an initial clockwise twist (because of the unopposed rotation of the endocardial myofibers) and finally an impaired peak LV twist ([20, 21]).

According to these observations, it has been postulated that surgical techniques able to restore a more physiological shape of the LV would improve the LV torsional deformation ([17]). Indeed, in a preliminary study of 26 patients with ischemic dilated cardiomyopathy, LV reconstruction surgery improved LV twist in the patients with more severely impaired LV twist at baseline ([17]); these patients showed also significantly greater improvement of LVEF after surgery as compared to the patients with

relatively more preserved LV twist at baseline (ΔLVEF 15 ± 8% vs. 6 ± 8%, p = 0.005) ([17]).

Relation LV Twist-LV Dyssynchrony

An effective LV pumping function requires the combination of preserved LV architecture and a preserved electrical conduction system. The presence of an abnormal activation sequence of the ventricles (e.g. right ventricular apical pacing, right or left bundle branch block) results in a slower spread of the electrical breakthrough across the myocardium and in a dyssynchronous mechanical activation of the ventricles ([22]). In addition, the anisotropy of the LV myocardium determines the propagation of the electrical wavefront. As previously described, ([12, 23]) activation of the LV includes the development of a potential over the lateral-apical region which reflects endocardial-to-epicardial propagation of the LV free-wall activation front. Subsequently this epicardial potential is seen to migrate from the lateral LV apex toward the posterolateral base. The propagation is faster in the longitudinal direction of the myofibers rather than across in the circumferential cross-fiber direction due to the higher density of gap junctions concentrated in the intercalated disks along the longitudinal axis, as compared to the cross-fiber densities ([12]). In the remodeled, failing LV this particular architectural pattern may be distorted, with loss of anisotropy and gap junctions, resulting in a slower conduction of the electrical excitation.

Several experimental studies have demonstrated the deleterious effects of asynchronous ventricular activation on LV performance and the relation between the LV activation pattern and LV twist ([24-28]). Prinzen et al. ([26]) showed that ectopic activation induced asynchronous electrical activation and, subsequently, asynchronous cardiac motion (mechanical asynchrony). Interestingly, mechanical asynchrony was larger than electrical asynchrony because the time interval between the electrical activation and the onset of fiber shortening was more prolonged at the most delayed mechanical activated segments. Afterwards, changes in myofibers work within the LV wall were evaluated during right ventricular and LV pacing in normal hearts of dogs. Thus, both pacing modes determined a pronounced redistribution of midwall fiber shortening and work, with 50% decrease in myofiber work at the paced regions (hypofunctioning regions) and 150% increase at the remote areas (hyperfunctioning regions). These regional changes resulted in significant reductions in LV pump function, particularly when pacing from the right ventricle ([27]). Recently, Delgado et al. ([29]) compared the effects of right ventricular apical pacing on LV twist in 25 patients without structural heart disease. With the use of 2-dimensional speckle tracking imaging, the authors demonstrated that right ventricular apical pacing induced a

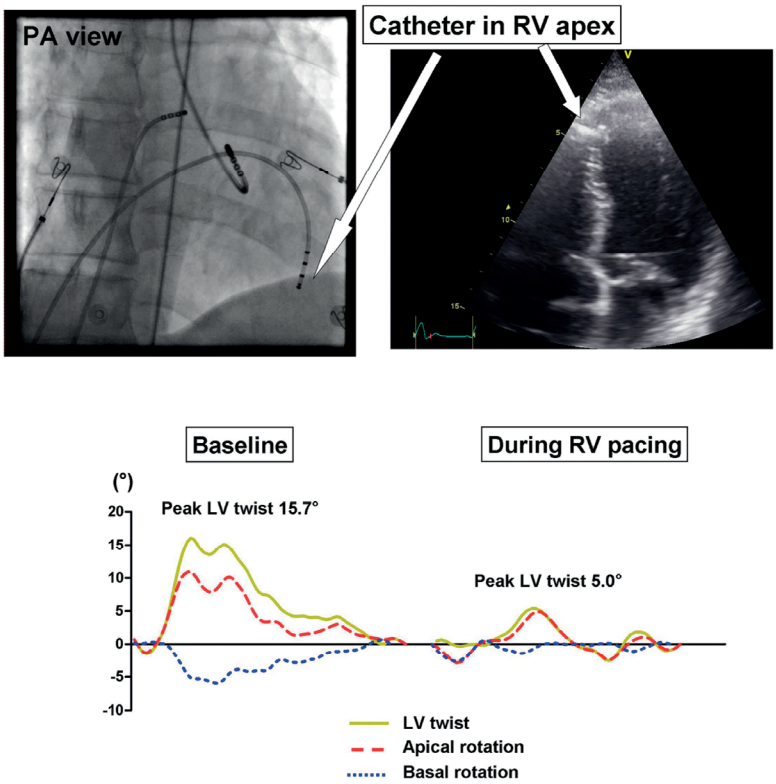

Figure 3. Left ventricular twist during right ventricular pacing.
Example of left ventricular (LV) twist during sinus rhythm (baseline) and during right ventricular (RV) pacing in a patient without structural heart disease.
A standard diagnostic catheter was positioned in the RV apex as illustrated in the postero-anterior (PA) view at fluoroscopy (upper left panel) and the 4-chamber apical view at standard 2-dimensional echocardiography (upper right panel).
The curves of LV rotational parameters at baseline (lower left panel) and during RV pacing (lower right panel). RV pacing induced a severe impairment in LV twist by decreasing both LV apical and basal rotation.

dyssynchronous mechanical activation of the LV, as measured by radial strain (from 21 to 91 ms, p<0.001) and a subsequent significant decrease in LV global longitudinal shortening (from -18.3 ± 3.5% to -11.8 ± 3.6%, p<0.001) and LV twist (from 12.4 ± 3.7° to 9.7 ± 2.6°, p=0.001; Figure 3).

Finally, two recent studies pointed out the relationship between LV-dyssynchrony and LV twist in advanced HF patients with prolonged QRS duration ([18, 30]). A first study showed that the extent of LV-dyssynchrony was inversely related to LV twist ([30]). Subsequently, these results were extended in another study demonstrating that LVEF and LV-dyssynchrony were both independently correlated to LV twist ([18]). This observation further underscores that LV twist is not only a parameter of LV function, but also reflects the extent of LV (dys)synchrony.

LV TWIST IN CRT

As previously indicated, LV mechanics and particularly LV twist are strictly dependent on electro-mechanical activation and are influenced by different pacing modalities ([24, 25, 31]). However, thus far, data on the effects of CRT on LV twist are limited ([18, 30, 32]).

Particularly, abnormal rotational mechanics in advanced HF patients with prolonged QRS duration may result from 2 different conditions that can also co-exist: 1) absolute reduction of LV apical and basal rotation (and consequently of LV twist), due to an impaired myocardial contractility; 2) dyssynchronous contraction of LV apical and basal regions, due to an altered pattern of LV electro-mechanical

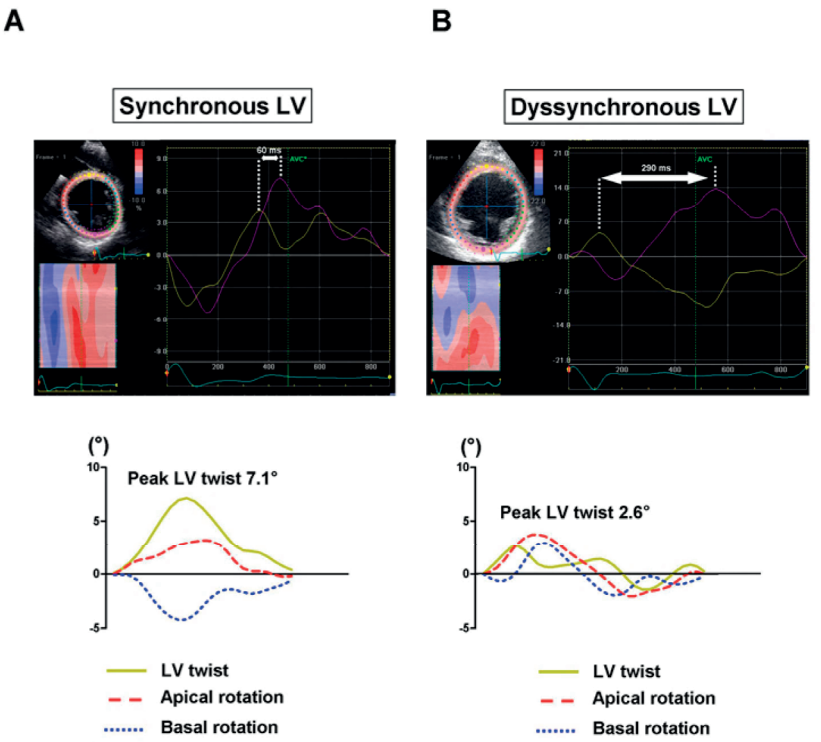

Figure 4. Left ventricular twist in the synchronous and dyssynchronous failing left ventricle.
Example of left ventricular (LV) twist in two patients with dilated cardiomyopathy and severe LV dysfunction (LV ejection fraction <30%).
Example of patients with synchronous (Panel A) and with dyssynchronous LV contraction LV (Panel B).
In both the synchronous (Panel A) and the dyssynchronous LV (Panel B), the curves of the LV rotational parameters reveal reduced LV twist. Of note, the peaks of apical and basal rotation occur almost at the same time interval in the synchronous LV (Panel A), whereas they occur at different time intervals in the dyssynchronous LV (Panel B). In particular, in the dyssynchronous LV (panel B) apical rotation is markedly earlier as compared to the basal rotation, which may result in further worsening of LV twist.

activation (Figure 4). Consequently, CRT, leading to a more physiologic electrical depolarization and mechanical contraction of the myofibers, has the potential to improve rotational mechanics in these patients.

Global Changes in LV twist after CRT

All the available studies are based on 2-dimensional speckle tracking echocardiography that, unlike tagged magnetic resonance imaging, allows the analysis of rotational parameters also after device implantation.

Recently, Zhang et al. ([32]) studied 39 patients scheduled for CRT, measuring LV twist at baseline and 3 months after implantation. At baseline, peak LV twist was significantly reduced in the HF patients as compared to normal controls (6.8 ± 4.2° vs.16.2 ± 5.5°, p <0.001). The authors also noted that in some patients, the presence of apical and/or basal segments showed a paradoxical rotation (clockwise for the apex and counterclockwise for the base), indicating a more compromised rotational mechanics. However, at short-term follow-up the authors could not detect any improvement of LV twist after CRT, although a significant increase of LVEF was observed (from 28.1 ± 6.7% to 35.0 ± 9.4%, p <0.001).

Different findings were reported by Sade et al. ([30]) that studied the acute effect of CRT on 33 patients. At baseline, LV twist was significantly reduced as compared to normal controls either for ischemic and non-ischemic HF patients and correlated well with LVEF and radial dyssynchrony. A significant improvement of LV rotational

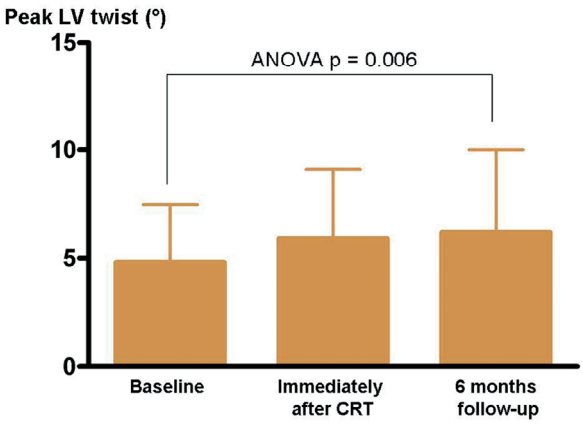

Figure 5. Progressive improvement of LV twist induced by CRT.
A significant and progressive improvement of LV twist was observed immediately after CRT and at 6 months follow-up.

mechanics was observed immediately after CRT. These controversial results may be related to the potential role of the LV lead position in determining LV twist pattern. However, no data about LV lead position were reported in these studies.

A more recent study ([18]) reported the acute and long-term effects of CRT on LV twist exploring also the influence of LV lead position. Specifically, in a group of 80 HF patients candidates to CRT a significant and progressive improvement of LV twist was observed immediately after implantation and at 6 months follow-up (Figure 5).

Responders versus Non-responders

The effect of CRT on rotational mechanics is more evident if the evaluation is performed according to the presence of LV reverse remodeling. Sade et al.([30]) evaluated the changes in LV twist in 33 HF patients treated with CRT. Responder patients (with a reduction in LV end-systolic volume >10%) had an improved LV twist (from 1.5 ± 2.8° to 6.3 ± 3.6°, p<0.0001). Conversely, in non-responders LV twist did not change or tended to worsen (from 5.3 ± 3.1° to 2.0 ± 3.4°). Similarly in a more recent study ([18]), a significant improvement in LV rotational mechanics was noted only in patients who showed LV reverse remodeling (responders), both at the acute and long-term follow-up. In particular, peak LV twist progressively improved in responders during follow-up, whereas in non-responders a gradual deterioration of peak LV twist was observed (Figure 6). Furthermore, at the multivariable logistic regression analysis, in which LV-dyssynchrony and function parameters were included, absolute difference in LV twist immediately after CRT was the strongest predictor of response to CRT at 6 months follow-up (OR = 1.837, 95%CI = 1.378-2.449, p <0.001).

These findings suggest that CRT may (partially) restore LV twist, possibly by providing a more physiologic electrical depolarization and mechanical contraction of the myofibers.

LV twist and LV lead position

LV lead position is considered a potential tool to increase CRT response rate. In clinical scenarios, the optimal site for LV pacing in patients receiving CRT remains controversial. Previous studies indicated that patients with a (postero-)lateral LV lead position and patients with a LV lead located close to the region with the latest mechanical activation do not only derive more benefit in restoring systolic LV function, but also tend to have superior long-term survival after CRT ([33-36]). The different patterns of LV depolarization induced by different LV lead positions may markedly change

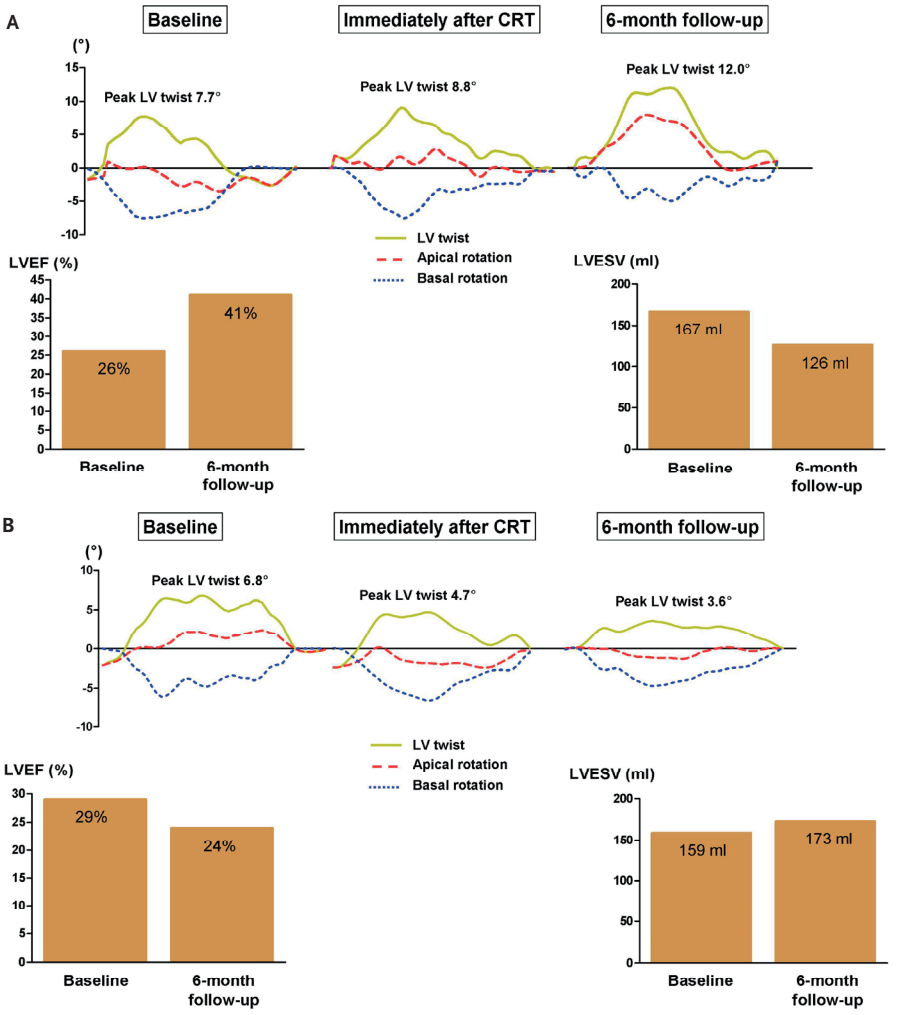

Figure 6. Left ventricular twist changing in CRT responders and non-responders .

Panel A: Example of responder to cardiac resynchronization therapy (CRT). Peak left ventricular (LV) twist increases progressively from baseline to 6-month follow-up. In this example, the improvement of LV twist is mainly due to the improvement of LV apical rotation over time. Immediately after CRT, LV twist increases secondary to an improved electro-mechanical activation of the LV. Further improvement is observed at 6-month follow-up when LV reverse remodeling has also occurred. The lower panel shows the improvement in left ventricular ejection fraction (LVEF) and reduction in left ventricular end-systolic volume (LVESV) after 6-month follow-up.

Panel B. Example of non-responder to CRT. Peak LV twist declines progressively from baseline to 6 months follow-up. In this example, the main determinant of the reduction in LV twist is the deterioration of LV apical rotation. Indeed, the direction of LV apical rotation is reversed (negative red dashed curve) immediately after CRT and at 6 months follow-up. Here, the apical and basal levels have the same direction of rotation which results in a worsening of LV twist. At 6 months follow-up a reduction in LV basal rotation is also observed, which contributes to a further deterioration of LV twist. The lower panel shows the parallel worsening in LVEF and LVESV after 6 months follow-up.

the cardiac mechanics ([12]). Thus, in CRT patients, the magnitude of LV twist may be related to the LV pacing site. However, there is currently minimal data addressing this issue. Firstly, experimental studies showed that LV twist was influenced by the pacing mode (atrial, right and biventricular pacing) ([24, 25, 31]). For example, Sorger et

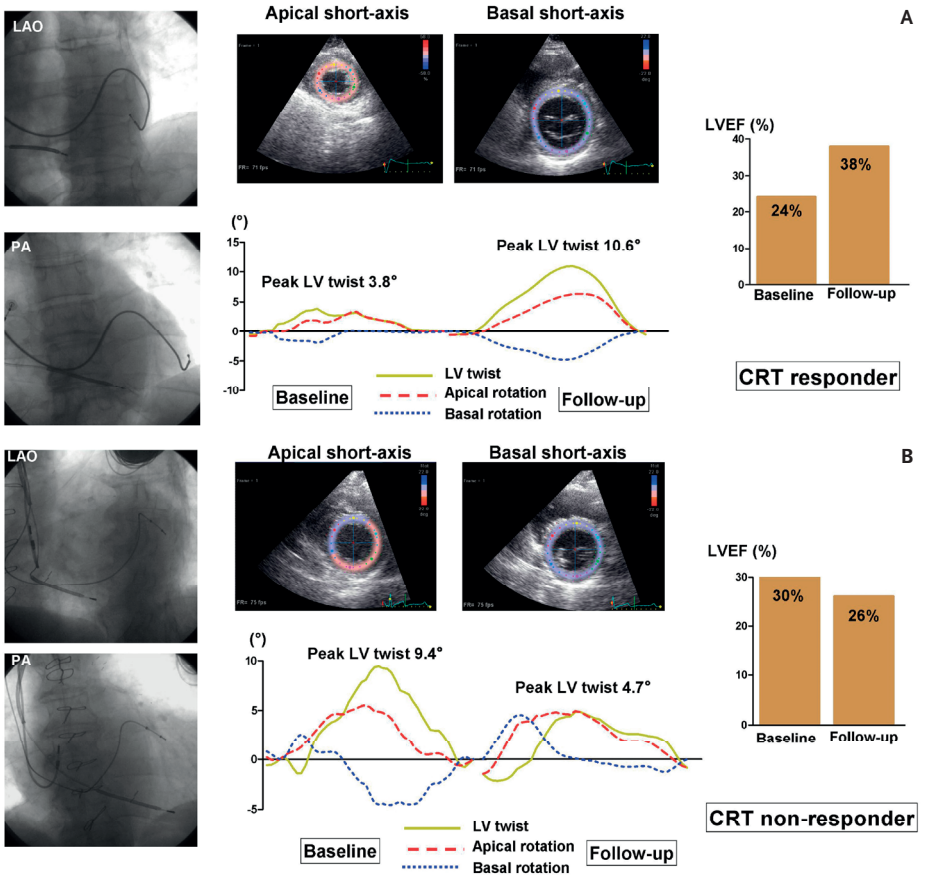

Figure 7. Left ventricular twist versus left ventricular lead position.

Panel A. Example of responder to cardiac resynchronization therapy (CRT) with the left ventricular (LV) lead placed in a (postero-)lateral vein with an apical position. Biplane fluoroscopy (left) displays the LV lead position. Particularly, the left anterior oblique (LAO) view shows the LV lead in the (postero-)lateral vein whereas the postero-anterior (PA) view shows the LV lead in an apical position. Peak LV twist increased from 3.8° at baseline to 10.6° at 6-month follow-up. LV ejection fraction (LVEF) improved from 24% at baseline to 38% at 6-month follow-up. In this patient, pacing close to the LV apical region may produce a more physiological pattern of electro-mechanical activation, resulting in a significant improvement in LV twist.

Panel B. Example of non-responder with the LV lead placed in a lateral vein (LAO view) with a basal position (PA view). Peak LV twist decreased from 9.4° at baseline to 4.7° at 6-month follow-up. LVEF decreased from 30% at baseline to 26% at 6-month follow-up. In this patient, pacing close to the LV basal region may induce a further worsening of the electro-mechanical activation with a significant worsening of LV twist.

al.([25]) evaluated the changes in LV twist during pacing from three different locations: right atrium, right ventricular apex and base of the LV free wall. Biventricular pacing with LV lead placed at the basal level of lateral wall, similarly to apical right ventricular pacing, worsened LV twist as compared to a more physiological electrical stimulation (i.e. right atrial pacing).

A recent study ([18]) explored the change in LV twist after CRT in relation to different LV lead positions in the (postero-)lateral veins. Interestingly, the authors observed that patients with LV leads positioned in mid-ventricular and apical regions exhibited a larger increase in systolic function with a significant increase in LV twist as compared to patients with LV leads positioned in the basal regions of the LV free wall (Figure 7). Possibly, LV pacing sites that yield the largest improvement in LV twist may likely determine a more efficient cardiac contraction with subsequent improvement of LV energetic ([37]). Similar results were obtained in a experimental study in a canine HF model, reporting that the mid-apical part of the LV free wall was the optimal stimulation site ([38]). These findings could be explained by the direction of cardiac depolarization, traveling from the apex towards the base in the normal heart ([12, 39]). Therefore, pacing close to the LV apex may replicate a more physiological pattern of LV depolarization and subsequent mechanical activation, leading to a significant improvement in LV twist ([18, 25]). Furthermore, as the myocardial wall is thinner in the LV apex compared to LV base ([40, 41]), pacing leads positioned near the apex are closer to the Purkinje network. This results in a faster electrical propagation of the cardiac pulse and subsequently a more synchronous LV contraction.

These are early data derived from small experimental and clinical studies, therefore larger multicenter studies are needed to confirm these findings.

FUTURE DIRECTIONS

Thus far, several indices of mechanical dyssynchrony have been proposed to select candidates for CRT. The analysis of LV twist may provide a more comprehensive evaluation of LV mechanics and may help to understand the effects of CRT in HF patients. Moreover, at present, CRT response relies on changes in clinical status, LV reverse remodeling and improvement in LVEF. In this regard, LV twist analysis may be incremental to changes in LV volumes and LVEF to characterize and define CRT response. Recently, Sade et al. ([30]) proposed to quantify the magnitude of LV twist at aortic valve closure timing as good index to predict CRT response, superior to LV-dyssynchrony. Furthermore, pioneer studies showed that an improvement of LV twist early after CRT predicts a reduction of LV volumes after 6 months ([18]). Future studies are warranted to

elucidate whether the magnitude and/or the specific pattern of baseline LV twist and immediate changes in LV twist after CRT may be used as a more sensitive index for the identification of CRT responders.

Currently, 2-dimensional speckle tracking echocardiography permits reliable assessment of LV twist mechanics ([42]). Furthermore, different authors reported a good reproducibility of the assessment of LV twist with 2-dimensional speckle tracking ([18, 43, 44]). However, 2-dimensional speckle tracking echocardiography has some limitations for the assessment of LV twist mainly related to the acquisition of LV apical short-axis images. This may be technically difficult and is highly dependent on the acoustic window and the through-plane motion, particularly at the basal level, that may affect accuracy of the measurement of LV rotational parameters. Recently developed 3-dimensional speckle tracking analysis may partially overcome these limitations and may provide even more global characterization of LV twist mechanics ([45]). Future technical advances will lead to improved accuracy and easier implementation of this technique in the clinical setting.

At present cardiac magnetic resonance remains the referral technique for the assessment of LV twist mechanics although its use is limited by availability and the presence of devices (pacemakers, internal cardioverter-defibrillators).

SUMMARY AND CONCLUSION

LV twist mechanics is a promising tool for characterizing the pathophysiology of HF. In advanced systolic HF, the rotational parameters are severely deteriorated and may be improved by restoring electro-mechanical activation through CRT. An immediate improvement in LV twist after CRT may be a good surrogate of a more physiological LV depolarization, and is independently related to reversal of remodeling after CRT. Finally, LV lead position is important for modifying the extent of LV twist after CRT; in particular pacing sites which provide the greatest improvement of LV twist likely determine the largest reversal of LV remodeling after CRT.

REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119:e21-181.
2. Jeevanantham V, Daubert JP, Zareba W. Cardiac resynchronization therapy in heart failure patients: an update. Cardiol J 2009; 16:197-209.
3. Takeuchi M, Otsuji Y, Lang RM. Evaluation of left ventricular function using left ventricular twist and torsion parameters. Curr Cardiol Rep 2009; 11:225-30.
4. Taber LA, Yang M, Podszus WW. Mechanics of ventricular torsion. J Biomech 1996; 29:745-52.
5. Sengupta PP, Tajik AJ, Chandrasekaran K, Khandheria BK. Twist Mechanics of the Left Ventricle Principles and Application. J Am Coll Cardiol Img 2009; 1:366-76.
6. Sengupta PP, Khandheria BK, Narula J. Twist and untwist mechanics of the left ventricle. Heart Fail Clin 2008; 4:315-24.
7. Notomi Y, Srinath G, Shiota T, et al. Maturational and adaptive modulation of left ventricular torsional biomechanics: Doppler tissue imaging observation from infancy to adulthood. Circulation 2006; 113:2534-41.
8. Bertini M, Nucifora G, Marsan NA, et al. Left ventricular rotational mechanics in acute myocardial infarction and in chronic (ischemic and nonischemic) heart failure patients. Am J Cardiol 2009; 103:1506-12.
9. Kim WJ, Lee BH, Kim YJ, et al. Apical Rotation Assessed by Speckle Tracking Echocardiography as an Index of Global Left Ventricular Contractility. Circ Cardiovasc Imaging 2009; 2:123-31.
10. Ingels NB, Jr. Myocardial fiber architecture and left ventricular function. Technol Health Care 1997; 5:45-52.
11. Sallin EA. Fiber orientation and ejection fraction in the human left ventricle. Biophys J 1969; 9: 954-64.
12. Punske BB, Taccardi B, Steadman B, et al. Effect of fiber orientation on propagation: electrical mapping of genetically altered mouse hearts. J Electrocardiol 2005; 38:40-4.
13. Gjesdal O, Helle-Valle T, Hopp E, et al. Noninvasive Separation of Large, Medium, and Small Myocardial Infarcts in Survivors of Reperfused ST-Elevation Myocardial Infarction: A Comprehensive Tissue Doppler and Speckle-Tracking Echocardiography Study. Circ Cardiovasc Imaging 2009; 1:189-96.
14. Wu MT, Tseng WY, Su MY, et al. Diffusion tensor magnetic resonance imaging mapping the fiber architecture remodeling in human myocardium after infarction: correlation with viability and wall motion. Circulation 2006; 114:1036-45.
15. Kanzaki H, Nakatani S, Yamada N, Urayama S, Miyatake K, Kitakaze M. Impaired systolic torsion in dilated cardiomyopathy: reversal of apical rotation at mid-systole characterized with magnetic resonance tagging method. Basic Res Cardiol 2006; 101:465-70.
16. Setser RM, Kasper JM, Lieber ML, Starling RC, McCarthy PM, White RD. Persistent abnormal left ventricular systolic torsion in dilated cardiomyopathy after partial left ventriculectomy. J Thorac Cardiovasc Surg 2003; 126:48-55.
17. Setser RM, Smedira NG, Lieber ML, Sabo ED, White RD. Left ventricular torsional mechanics after left ventricular reconstruction surgery for ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2007; 134:888-96.
18. Bertini M, Marsan NA, Delgado V, et al. Effects of cardiac resynchronization therapy on left ventricular twist. J Am Coll Cardiol 2009; 54:1317-25.

19. Grosberg A, Gharib M. Modeling the macro-structure of the heart: healthy and diseased. Med Biol Eng Comput 2009.
20. Delhaas T, Arts T, Prinzen FW, Reneman RS. Regional electrical activation and mechanical function in the partially ischemic left ventricle of dogs. Am J Physiol 1996; 271:H2411-H2420.
21. Tibayan FA, Lai DT, Timek TA, et al. Alterations in left ventricular torsion in tachycardia-induced dilated cardiomyopathy. J Thorac Cardiovasc Surg 2002; 124:43-9.
22. Wyman BT, Hunter WC, Prinzen FW, Faris OP, McVeigh ER. Effects of single- and biventricular pacing on temporal and spatial dynamics of ventricular contraction. Am J Physiol Heart Circ Physiol 2002; 282:H372-H379.
23. Ramanathan C, Jia P, Ghanem R, Ryu K, Rudy Y. Activation and repolarization of the normal human heart under complete physiological conditions. Proc Natl Acad Sci U S A 2006; 103:6309-14.
24. Buchalter MB, Rademakers FE, Weiss JL, Rogers WJ, Weisfeldt ML, Shapiro EP. Rotational deformation of the canine left ventricle measured by magnetic resonance tagging: effects of catecholamines, ischaemia, and pacing. Cardiovasc Res 1994; 28:629-35.
25. Sorger JM, Wyman BT, Faris OP, Hunter WC, McVeigh ER. Torsion of the left ventricle during pacing with MRI tagging. J Cardiovasc Magn Reson 2003; 5:521-30.
26. Prinzen FW, Augustijn CH, Allessie MA, Arts T, Delhaas T, Reneman RS. The time sequence of electrical and mechanical activation during spontaneous beating and ectopic stimulation. Eur Heart J 1992; 13:535-43.
27. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999; 33:1735-42.
28. Wang J, Nagueh SF, Mathuria NS, Shih HT, Panescu D, Khoury DS. Left ventricular twist mechanics in a canine model of reversible congestive heart failure: a pilot study. J Am Soc Echocardiogr 2009; 22:95-8.
29. Delgado V, Tops LF, Trines S, et al. Acute effects of right ventricular apical pacing on left ventricular synchrony and mechanics . Circ Arrhythmia and Electrophysiology 2009; 2:135-45.
30. Sade LE, Demir O, Atar I, Muderrisoglu H, Ozin B. Effect of mechanical dyssynchrony and cardiac resynchronization therapy on left ventricular rotational mechanics. Am J Cardiol 2008; 101:1163-9.
31. Notomi Y, Popovic ZB, Yamada H, et al. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. Am J Physiol Heart Circ Physiol 2008; 294:H505-H513.
32. Zhang Q, Fung JW, Yip GW, et al. Improvement of left ventricular myocardial short-axis, but not long-axis function or torsion after cardiac resynchronisation therapy: an assessment by two-dimensional speckle tracking. Heart 2008; 94:1464-71.
33. Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001; 104:3026-9.
34. Delnoy PP, Ottervanger JP, Luttikhuis HO, et al. Pressure-volume loop analysis during implantation of biventricular pacemaker/cardiac resynchronization therapy device to optimize right and left ventricular pacing sites. Eur Heart J 2009.
35. Wilton SB, Shibata MA, Sondergaard R, Cowan K, Semeniuk L, Exner DV. Relationship between left ventricular lead position using a simple radiographic classification scheme and long-term outcome with resynchronization therapy. J Interv Card Electrophysiol 2008; 23:219-27.
36. Ypenburg C, van Bommel RJ, Delgado V, et al. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. J Am Coll Cardiol 2008; 52:1402-9.

37. Beyar R, Sideman S. Left ventricular mechanics related to the local distribution of oxygen demand throughout the wall. Circ Res 1986; 58:664-77.
38. Helm RH, Byrne M, Helm PA, et al. Three-dimensional mapping of optimal left ventricular pacing site for cardiac resynchronization. Circulation 2007; 115:953-61.
39. Sengupta PP, Khandheria BK, Korinek J, et al. Apex-to-base dispersion in regional timing of left ventricular shortening and lengthening. J Am Coll Cardiol 2006; 47:163-72.
40. Bogaert J, Rademakers FE. Regional nonuniformity of normal adult human left ventricle. Am J Physiol Heart Circ Physiol 2001; 280:H610-H620.
41. Vanagt WY, Prinzen FW, Delhaas T. Physiology of cardiac pacing in children: the importance of the ventricular pacing site. Pacing Clin Electrophysiol 2008; 31 Suppl 1:S24-S27.
42. Notomi Y, Lysyansky P, Setser RM, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol 2005; 45:2034-41.
43. Park SJ, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK. Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. J Am Soc Echocardiogr 2008; 21:1129-37.
44. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009; 54:36-46.
45. Saito K, Okura H, Watanabe N, et al. Comprehensive Evaluation of Left Ventricular Strain Using Speckle Tracking Echocardiography in Normal Adults: Comparison of Three-Dimensional and Two-Dimensional Approaches. J Am Soc Echocardiogr 2009.

CHAPTER 3

Left ventricular rotational mechanics in acute myocardial infarction and in chronic (ischemic and nonischemic) heart failure patients.

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ABSTRACT

Left ventricular (LV) twist and untwisting rate are emerging as global and thorough parameters for the assessment of LV function. This study explored the differences of LV twist and untwisting rate among acute myocardial infarction (AMI) patients and ischemic and non-ischemic chronic heart failure (HF) patients. A total of 50 AMI patients, 49 ischemic HF and 38 non-ischemic HF patients were studied. As a control group, 28 normal subjects were included. Speckle tracking analysis was applied to LV short-axis images at basal and apical level. LV twist was defined as the net difference of apical and basal rotation at isochronal time points. The first time derivative of LV untwist was defined as LV untwisting rate. As compared to normal subjects, peak LV twist was reduced in AMI patients and extremely reduced in HF patients (ANOVA p value <0.001). A strong correlation (r=0.87, p<0.001) was found between peak LV twist and LV ejection fraction in the overall study population. LV untwisting rate was progressively reduced in AMI and HF patients as compared to normal subjects (ANOVA p value <0.001). A moderate correlation (r=0.56, p<0.001) was noted between peak LV untwisting rate and the grade of diastolic dysfunction in the overall study population. In conclusions LV twist and untwisting rate are strongly related with LV systolic and diastolic function, respectively. The impairment of LV function observed in AMI and HF patients is associated with a reduction of LV twist and untwisting rate.

INTRODUCTION

Recently, novel speckle tracking analysis has become available as a simple echocardiographic modality to assess LV twist and the untwisting rate. This technique has been validated against sonomicrometry and tagged magnetic resonance imaging, which are currently considered the gold standards for the assessment of rotational parameters.[1, 2] Initial studies evaluated LV twist and the untwisting rate in patients with myocardial infarction and heart failure (HF),[3-5] but thus far, the impact of these different diseases on rotational mechanics has never been systematically evaluated. The present study assesses the differences of LV twist and the untwisting rate between patients with acute myocardial infarction (AMI) and chronic HF.

METHODS

A total of 137 consecutive patients were enrolled: 50 AMI patients, 49 patients with chronic ischemic HF and 38 with non-ischemic HF. The diagnosis of AMI was based on the presence of symptoms consistent with myocardial ischemia lasting ≥30 minutes and ≥2 mm ST-segment elevation in ≥2 contiguous electrocardiographic (ECG) leads.[6] All AMI patients underwent urgent coronary angiography, followed by primary percutaneous coronary intervention, and the echocardiographic examination was performed within 48 hours after AMI. Etiology of HF was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or the history of AMI or previous revascularization.

In addition, 28 subjects without evidence of structural heart disease, matched for age and gender were included as a normal control group. The clinical echocardiographic analysis included standard 2-dimensional echocardiography to assess LV systolic and diastolic function. Furthermore, speckle tracking analysis was applied to assess LV rotational parameters (the twist and untwisting rate).

All patients were imaged in the left lateral decubitus position with a commercially available system (Vingmed Vivid 7, General Electric-Medical Systems, Milwaukee, Wisconsin, USA) equipped with a 3.5-MHz transducer. Standard 2-dimensional images and Doppler and color-Doppler data acquired from the parasternal and apical views (2-, 3-, and 4-chamber) were digitally stored in cine-loop format; analyses were subsequently performed offline using EchoPAC version 7.0.0 (General Electric-Medical Systems).

Left ventricular (LV) end-diastolic (EDV) and end-systolic (ESV) volumes were measured according to the Simpson's biplane method and LV ejection fraction (EF) was calculated as [(EDV-ESV)/EDV] x100.[7]

Transmitral and pulmonary vein pulsed-wave Doppler tracings, obtained in accordance to the recommendations of the American Society of Echocardiography,[8] were used to classify diastolic function as follows: 1) normal, when the E/A ratio = 0.9-1.5, deceleration time = 160-240 ms and pulmonary vein systolic velocity (PVs) ≥ pulmonary vein diastolic velocity (PVd); 2) diastolic dysfunction grade 1 (mild), when the E/A ratio was <0.9, deceleration time >240 ms and PVs >> PVd; 3) diastolic dysfunction grade 2 (moderate), when the E/A ratio = 0.9-1.5, deceleration time = 160-240 ms and PVs < PVd; 4) diastolic dysfunction grade 3 (severe), when the E/A ratio >2.0, deceleration time <160 ms and PVs << PVd; 5) diastolic dysfunction grade 4 (severe), when the E/A ratio >2.5, deceleration time <130 ms and PVs << PVd.[9]

Speckle tracking analysis is based on tracking of natural acoustic markers, or speckles, on standard gray scale images. This novel technique is angle independent and permits evaluation of myocardial contraction/relaxation along the circumferential, longitudinal and radial direction.[10, 11]

In the present evaluation, speckle tracking analysis was applied to determine the LV twist and LV untwisting rate. Parasternal short-axis images were acquired at 2 distinct levels: 1) basal level, identified by the mitral valve; 2) apical level, defined as the smallest cavity achievable distally to the papillary muscles (moving the probe down and slightly laterally, if needed). The frame rate ranged from 45 to 100 frame/s and 3 cardiac cycles for each parasternal short-axis level were stored in cine-loop format for the offline analysis. The endocardial border was traced at an end-systolic frame and the region of interest (ROI) was chosen to fit the entire myocardium. The software allows the operator to check and validate the tracking quality and to adjust the endocardial border or modify the width of the ROI, if needed. Furthermore, each short-axis image was automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior.

Subsequently, the speckle-tracking software calculates LV rotation from the apical and basal short-axis images as the average angular displacement of the 6 standard segments referring to the ventricular centroid, frame by frame. Counter-clockwise rotation was marked as positive value and clockwise rotation as negative value when viewed from the LV apex. The software automatically calculates LV twist, defined as the net difference (in degrees) of apical and basal rotation at isochronal time points. The opposite rotation following LV twist was defined as LV untwist and the time derivative of LV untwist was defined as LV untwisting rate (in °/s) (Figure 1).

The following measurements were obtained:

1) peak apical and basal rotation,
2) peak LV twist and peak LV untwisting rate,
3) time to peak apical and basal rotation,
4) time to peak LV twist and untwisting rate.

A pulsed-wave Doppler tracing obtained from the LV outflow tract was used to identify the timing of aortic valve opening and closure. All the timings were expressed as percentage of systolic phase.

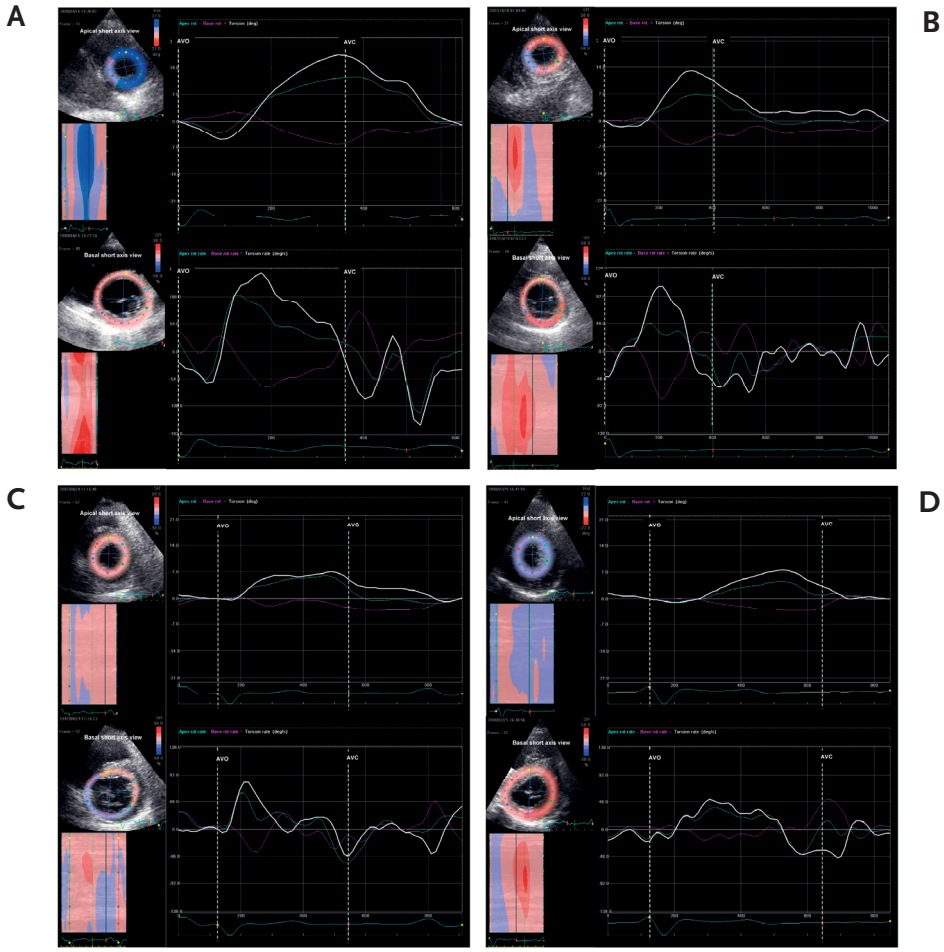

Figure 1 Left ventricular twist and untwisting rate in a normal control (Panel A), AMI patient (Panel B), ischemic HF patient (Panel C) and non-ischemic HF patient (Panel D).
The green line represents apical rotation (upper) and apical rotation rate (lower); the purple line represents basal rotation (upper) and basal rotation rate (lower); the white line represents left ventricular twist/untwist (upper) and left ventricular twisting/untwisting rate (lower).
AMI: acute myocardial infarction, AVC: aortic valve closure. AVO: aortic valve opening, HF: heart failure.

To assess the reproducibility of peak LV twist and peak LV untwisting rate measurements, 20 patients were randomly selected. Bland-Altman analysis was performed to evaluate the intra- and inter-observer agreement repeating the analysis 1 week later by the same observer and by a second independent observer. Bland-Altman analysis demonstrated good intra-observer and inter-observer agreement, with small bias not significantly different from zero. Mean differences ± 2 standard deviation (SD) for peak LV twist and peak LV untwisting rate were 0.05±0.43° and -1.93±15.97°/s, for intra-observer agreement and 0.17±1.51° and -3.97±35.63°/s for inter-observer agreement.

Continuous variables are expressed as mean ±SD. Categorical data are presented as absolute numbers and percentages. One-way ANOVA test was used to assess differences in continuous variables between the different groups of patients; if the result of the analysis was significant, Bonferroni's post-hoc test was applied. The differences in categorical variables were analyzed using Chi-square tests or Fischer's exact tests, as appropriate. Linear regression analysis was used to determine the relations between peak LV twist and LVEF, between peak LV untwisting rate and the grade of diastolic dysfunction, and , between peak LV untwisting rate and LVESV. In order to identify independent determinants of peak LV untwisting rate, a multivariable linear regression analysis was performed including LVESV and the grade of diastolic dysfunction as covariates. All statistical tests were 2-sided, and a p value <0.05 was considered significant. Statistical analysis was performed using the SPSS software package (SPSS 14.0, Chicago, Illinois).

RESULTS

Table 1 summarizes clinical and echocardiographic characteristics of the different patient groups and the normal controls.

As compared to normal controls, AMI patients had significantly lower values of LV apical rotation (9.8±3.0° vs. 7.6±3.8°, p = 0.007), LV basal rotation (-6.3±2.4° vs. -4.9±2.1°, p = 0.04), and LV twist (15.7±3.1° vs. 11.6±3.8°, p <0.001).

LV rotational parameters were not significantly different between ischemic HF and non-ischemic HF patients, but were significantly impaired as compared to AMI patients; peak apical rotation was 2.5±1.9° and 2.4±1.8°, respectively (p <0.001 as compared to AMI patients) and peak basal rotation was -3.4±2.0° and -2.8±2.2°, respectively (p = 0.003 and p <0.001, respectively, as compared to AMI patients). Consequently, the peak LV twist was 5.2±2.2° and 4.0±2.9°, respectively (p <0.001 as compared to AMI patients) (Table 1).

Table 1. Clinical, echocardiographic and rotational parameters of the different groups: normal controls, AMI patients, ischemic HF patients and non-ischemic HF patients

Variable	Normal Controls (n = 28)	AMI patients (n = 50)	Ischemic HF patients (n = 49)	Non-ischemic HF patients (n = 38)	ANOVA p value
Age (years)	60±11	60±11	64±11	65±13	0.084
Men	21 (75%)	38 (76%)	43 (88%)	28 (74%)	0.16
LV end-diastolic volume (ml)	87±26*	103±28*	179±67¶	214±74	<0.001
LV end-systolic volume (ml)	34±12*	55±21*	130±52¶	164±61	<0.001
LV ejection fraction (%)	62±6†	47±10*	28±5¶	24±6	<0.001
Diastolic function	†	§			<0.001
Grade 0	28 (100%)	7 (14%)	0	0	
Grade 1	0	19 (38%)	12 (24%)	8 (21%)	
Grade 2	0	14 (28%)	13 (26%)	6 (16%)	
Grade 3-4	0	10 (20%)	24 (49%)	24 (63%)	
Peak LV twist (°)	15.7±3.1†	11.6±3.8*	5.2±2.2	4.0±2.9	<0.001
Peak LV untwisting rate (°/s)	-107±29*‡	-78±35‖¶	-58±34	-59±32	<0.001
Time peak LV twist (% systole)	98±8§‡	83±14	83±19	75±27	<0.001
Time peak LV untwisting (% systole)	114±9	118±17	116±17	116±23	0.75

*= p <0.001 vs. ischemic and non-ischemic heart failure
†= p <0.001 vs. acute myocardial infarction, ischemic and non-ischemic heart failure
¶= p <0.05 vs. non-ischemic heart failure
‡= p <0.01 vs. acute myocardial infarction
§= p <0.01 vs. , ischemic and non-ischemic heart failure
‖= p <0.05 vs. , ischemic heart failure
AMI: acute myocardial infarction, HF: heart failure, LV: left ventricular.

Figure 2 shows the progressive reduction of peak LV twist and LVEF among the 4 different groups. In particular, a strong correlation (r = 0.87, p <0.001) was found between peak LV twist and LVEF (Figure 3) and between peak LV apical rotation and LVEF (r = 0.79, p <0.001) in the overall study population; conversely, only a modest relation was found between peak LV basal rotation and LVEF (r = -0.48, p <0.001). Furthermore, time to peak LV twist occurred earlier in AMI, ischemic HF and non-ischemic HF patients as compared to normal controls (ANOVA p value <0.001, Table 1).

As compared to normal controls, AMI patients had significantly lower values of peak LV untwisting rate (-107±29°/s vs. -78±35°/s, p = 0.002).

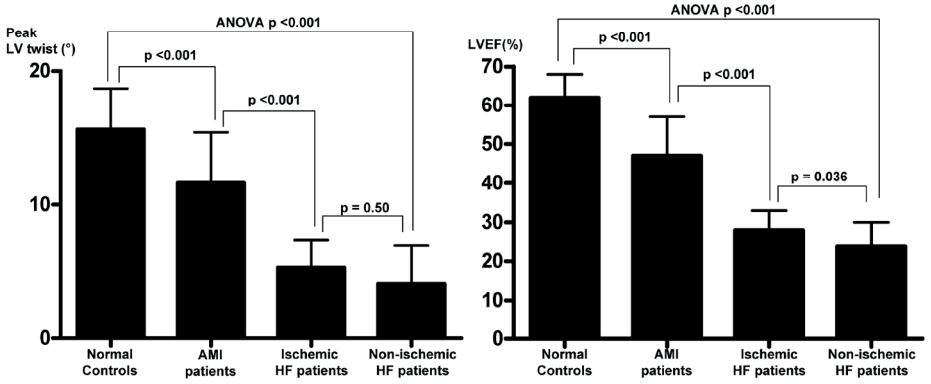

Figure 2: Peak LV twist (left panel) and LVEF (right panel) in normal controls, AMI patients, ischemic HF and non-ischemic HF patients.
AMI: acute myocardial infarction, EF: ejection fraction, HF: heart failure failure, LV: left ventricular.

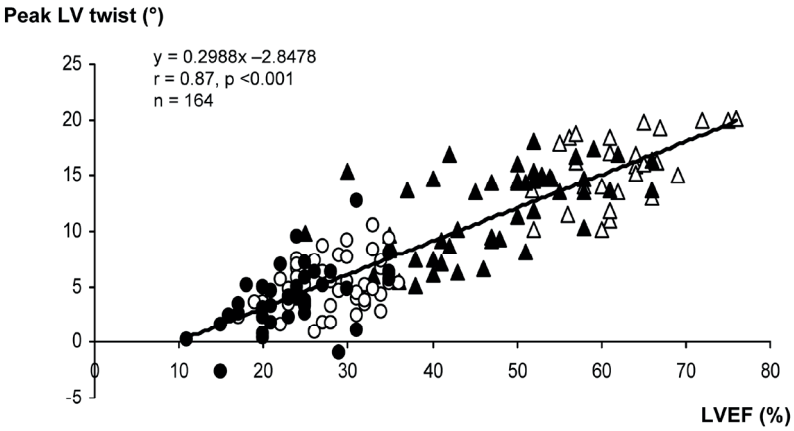

Figure 3. Correlation between LVEF and peak LV twist in the entire study population including normal controls (white triangle), AMI patients (black triangle), ischemic HF patients (white circles) and non-ischemic HF patients (black circles).
AMI: acute myocardial infarction, EF: ejection fraction, HF: heart failure, LV: left ventricular.

Peak LV untwisting rate was not significantly different between ischemic HF and non-ischemic HF patients with lower values as compared to AMI patients: -58±34°/s in ischemic HF patients (p = 0.018) and -59±32°/s in non-ischemic HF patients (p = 0.036) (Table1).

Peak LV untwisting rate and the grade of diastolic dysfunction among the 4 groups are shown in Figure 4. A moderate correlation (r = 0.56, p <0.001) was noted between peak LV untwisting rate and the grade of diastolic dysfunction in the overall study population (Figure 5). Furthermore, peak LV untwisting rate was significantly

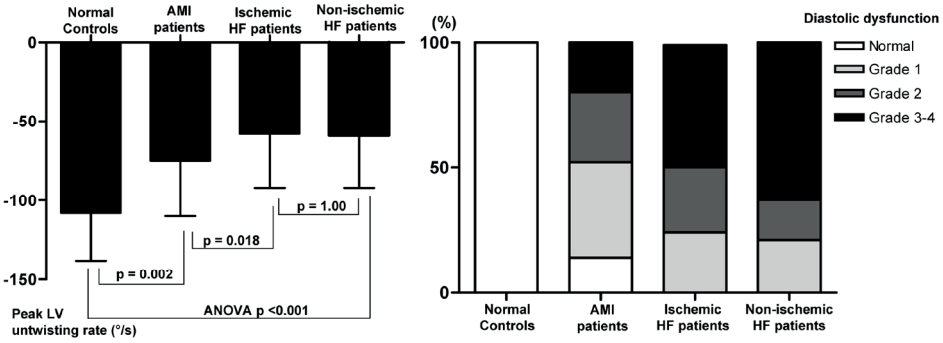

Figure 4: Left panel: A reduced peak LV untwisting rate is observed in AMI patients, IHF and NIHF patients as compared to normal controls. Right panel: The distribution of the different grades of diastolic dysfunction in normal controls, AMI patients, ischemic HF and non-ischemic HF patients is shown.
AMI: acute myocardial infarction, EF: ejection fraction, HF: heart failure, LV: left ventricular.

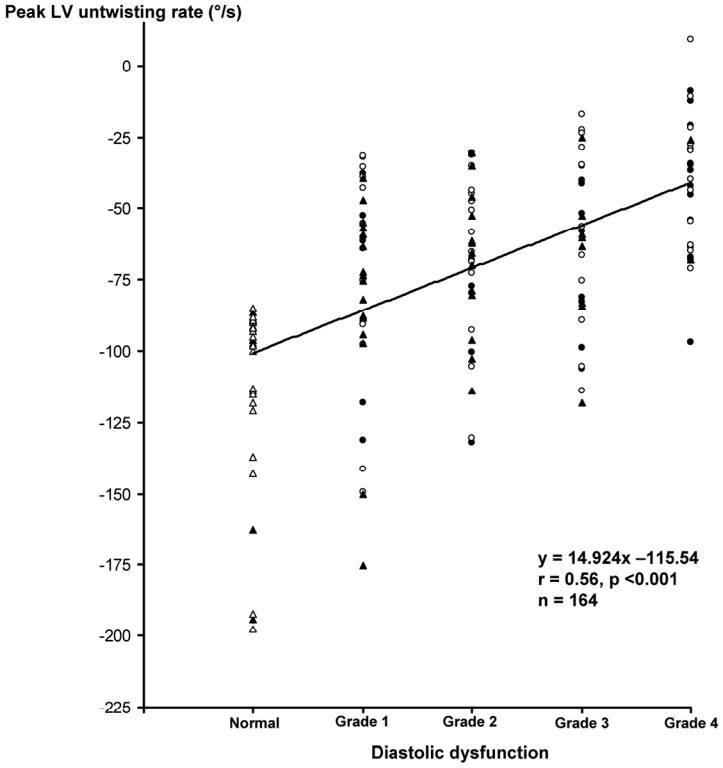

Figure 5: Correlation between the grades of diastolic dysfunction (see definition in the text) and peak LV untwisting rate in the entire study population: normal controls (white triangle), AMI patients (black triangle), ischemic HF patients (white circles) and non-ischemic HF patients (black circles).
AMI: acute myocardial infarction, EF: ejection fraction, HF: heart failure, LV: left ventricular

related to LVESV (r = 0.42, p <0.001). At multivariable linear regression analysis both LVESV (β = 0.16, p = 0.047) and the grade of diastolic dysfunction (β = 0.47, p <0.001) were independently related to peak LV untwisting rate.

No significant differences were found among the different groups for time to peak LV untwisting rate (Table 1).

DISCUSSION

The current study comprehensively evaluated the differences in LV twist and untwisting rate among AMI, ischemic and non-ischemic HF patients, providing new insight in the relationship between LV rotational mechanics and LV function. The main findings can be summarized as follows: 1) LV twist is strongly related to LV systolic function and LV untwisting rate is modestly, but significantly related to diastolic function; 2) impairment of LV function is associated not only with a reduction of LV twist and untwisting rate, but also with an earlier peak of LV twist during systole.

As previously demonstrated in a mathematical model, LV twist distributes equally LV fiber stress and shortening across the LV wall.[12] Accordingly, LV twist increases the efficiency of sarcomere shortening, and improves myocardial deformation during LV ejection.[12] In the current study, a significant impairment of LV twist was observed in AMI and HF patients, compared to normal controls. Moreover, a strong relationship between the degree of impairment of LV twist and the observed impairment of LVEF was noted, confirming the previous findings demonstrating a relation between LV twist and LVEF.[4, 5, 13] The strong correlation found between LV apical rotation and LVEF is not surprising, since LV apical rotation contributes more to LV twist than LV basal rotation.[14] The different impact of acute myocardial infarction and chronic LV remodeling (in HF) on LV twist was also explored. LV twist was more reduced in chronic HF as compared to AMI patients. These findings may be explained by different mechanisms underlying a reduction in LV twist. In HF patients, LV twist impairment is probably the result of a long-lasting process, with a rearrangement of LV myofibers with a consequent loss of the specific LV architecture responsible for the wringing motion.[4, 15, 16] Conversely, in AMI patients the reduction of LV twist may result from an acute impairment in rotation of the LV region involved in the infarction.[3, 17] The severity of this impairment appears related to the transmurality of the infarction and to the extent of dysfunctional myocardial segments.[13, 18]

Intriguingly, the time to peak LV twist occurred earlier in both AMI and HF patients as compared to normal controls. The impaired LV rotational mechanics observed in AMI and HF most likely explains this finding; less time is needed to reach peak

LV twist because of the reduced contraction and rotation of the LV myofibers. In addition, the diseased LV myofibers are not able to fully counteract the systolic ventricular pressure, preventing further myocardial shortening and, consequently, leading to earlier peak LV twist.[18]

LV systolic twist comprehends a deformation of the interstitial matrix resulting in storage of potential energy; the rapid release of the potential energy stored during systole in the isovolumic relaxation time leads to LV untwisting.[19] In turn, LV untwisting generates an intraventricular pressure gradient facilitating diastolic LV filling.[19] Indeed, the LV untwisting rate is emerging as an index of diastolic function.[20-22] Particularly, LV untwisting rate was related to the time constant of LV pressure decay (Tau) and the intraventricular pressure gradient.[21] In the present study, a good relation between the LV untwisting rate and global diastolic function was observed. The relation was not perfect, probably since the LV untwisting rate is a marker of diastolic suction rather than global diastolic function. LV untwisting rate was also independently related with LVESV; however, on multivariable linear regression analysis, the grade of diastolic dysfunction was the strongest determinant of LV untwisting rate.

A significant impairment of LV untwisting rate was observed in AMI and HF patients as compared to control subjects. In AMI patients, the impairment in LV untwisting rate may be related to the increased ventricular stiffness and consequent diastolic dysfunction due to recent acute ischemia and infarction.[23] In HF patients, the LV untwisting rate was even more reduced as compared to AMI patients. This observation may be explained by the presence of extensive, diffuse LV fibrosis as encountered in HF patients, which is not (yet) present early after AMI.[24]

Finally, although groups of patients with different grades of diastolic dysfunction were studied, no significant differences in time to peak LV untwisting rate were noted. This finding is in line with previous experimental and clinical studies in which only the peak of untwisting rate but not the time to peak untwisting rate was affected by the grade of diastolic dysfunction.[21, 25]

As limitations, the acquisition of the LV apical short-axis images (highly dependent on the acoustic window) and through-plane motion, particularly at the basal level, could have affected the accuracy of the measurement of LV rotational parameters.

REFERENCES

(1) Helle-Valle T, Crosby J, Edvardsen T, Lyseggen E, Amundsen BH, Smith HJ, Rosen BD, Lima JA, Torp H, Ihlen H, Smiseth OA. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation* 2005;112:3149-3156.

(2) Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, Thomas JD. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol* 2005;45:2034-2041.

(3) Bansal M, Leano RL, Marwick TH. Clinical assessment of left ventricular systolic torsion: effects of myocardial infarction and ischemia. *J Am Soc Echocardiogr* 2008;21:887-894.

(4) Kanzaki H, Nakatani S, Yamada N, Urayama S, Miyatake K, Kitakaze M. Impaired systolic torsion in dilated cardiomyopathy: reversal of apical rotation at mid-systole characterized with magnetic resonance tagging method. *Basic Res Cardiol* 2006;101:465-470.

(5) Sade LE, Demir O, Atar I, Muderrisoglu H, Ozin B. Effect of mechanical dyssynchrony and cardiac resynchronization therapy on left ventricular rotational mechanics. *Am J Cardiol* 2008;101:1163-1169.

(6) Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernandez-Aviles F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De CR, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation* 2007;116:2634-2653.

(7) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.

(8) Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167-184.

(9) Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. *J Am Coll Cardiol* 2008;51:679-689.

(10) Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-1029.

(11) Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004;17:630-633.

(12) Beyar R, Sideman S. Left ventricular mechanics related to the local distribution of oxygen demand throughout the wall. *Circ Res* 1986;58:664-677.

(13) Garot J, Pascal O, Diebold B, Derumeaux G, Gerber BL, Dubois-Rande JL, Lima JA, Gueret P. Alterations of systolic left ventricular twist after acute myocardial infarction. *Am J Physiol Heart Circ Physiol* 2002;282:H357-H362.

(14) Opdahl A, Helle-Valle T, Remme EW, Vartdal T, Pettersen E, Lunde K, Edvardsen T, Smiseth OA. Apical Rotation by Speckle Tracking Echocardiography: A Simplified Bedside Index of Left Ventricular Twist. *J Am Soc Echocardiogr* 2008.

(15) Setser RM, Kasper JM, Lieber ML, Starling RC, McCarthy PM, White RD. Persistent abnormal left ventricular systolic torsion in dilated cardiomyopathy after partial left ventriculectomy. *J Thorac Cardiovasc Surg* 2003;126:48-55.

(16) Athanasuleas CL, Buckberg GD. Surgical restoration of the postinfarction dilated ventricle. *Heart Fail Clin* 2008;4:361-370.

(17) Sun JP, Niu J, Chou D, Chuang HH, Wang K, Drinko J, Borowski A, Stewart WJ, Thomas JD. Alterations of regional myocardial function in a swine model of myocardial infarction assessed by echocardiographic 2-dimensional strain imaging. *J Am Soc Echocardiogr* 2007;20:498-504.

(18) Knudtson ML, Galbraith PD, Hildebrand KL, Tyberg JV, Beyar R. Dynamics of left ventricular apex rotation during angioplasty: a sensitive index of ischemic dysfunction. *Circulation* 1997;96: 801-808.

(19) Sengupta PP, Khandheria BK, Narula J. Twist and untwist mechanics of the left ventricle. *Heart Fail Clin* 2008;4:315-324.

(20) Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, Garcia MJ, Greenberg NL, Thomas JD. Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 2006;113:2524-2533.

(21) Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, Thomas JD. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 2008;294:H505-H513.

(22) Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Left ventricular untwisting rate by speckle tracking echocardiography. *Circulation* 2007;116:2580-2586.

(23) Ross J, Jr. Is there a true increase in myocardial stiffness with acute ischemia? *Am J Cardiol* 1989; 63:87E-91E.

(24) Weber KT. Extracellular matrix remodeling in heart failure: a role for de novo angiotensin II generation. *Circulation* 1997;96:4065-4082.

(25) Park SJ, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK. Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. *J Am Soc Echocardiogr* 2008;21:1129-1137.

CHAPTER 4

Effects of cardiac resynchronization therapy on left ventricular twist.

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ABSTRACT

Objectives. This study explored the effects of cardiac resynchronization therapy (CRT) on left ventricular (LV) twist, particularly in relation to LV lead position.

Background. LV twist is emerging as a comprehensive index of LV function.

Methods. Eighty heart failure (HF) patients were included. 2D-echocardiography was performed at baseline, immediately after CRT, and at 6 months follow-up. Speckle-tracking analysis was applied to assess LV twist. LV lead was placed preferably in a (postero-)lateral vein and at fluoroscopy, the position was classified as basal, mid-ventricular or apical. Response to CRT was defined as reduction of LV end-systolic volume ≥15% at 6 months follow-up. A control group comprised 30 normal subjects.

Results. Peak LV twist in HF patients was 4.8±2.6° compared to 15.0±3.6° of the controls ($p<0.001$). At 6 months follow-up, peak LV twist significantly improved only in responders (56%), from 4.3±2.4° to 8.5±3.2° ($p<0.001$). The strongest predictor of response to CRT was the improvement of peak LV twist immediately after CRT (odds ratio 1.899, 95% confidence intervals 1.334-2.703, $p<0.001$). Furthermore, LV twist significantly improved in patients with an apical (from 4.3±3.1° to 8.6±3.0°, $p=0.001$) and mid-ventricular (from 4.8±2.2° to 6.4±3.9°, $p=0.038$) but not with a basal (5.0±3.3 vs. 4.1±3.2, $p=0.28$) LV lead position. Similarly LVEF significantly increased in patients with an apical (from 26±7% to 37±7%, $p<0.001$) and mid-ventricular (from 26±6% to 33±8%, $p<0.001$) but not with a basal (26±5% vs. 28±8%, $p=0.30$) LV lead position.

Conclusions. An immediate improvement of LV twist after CRT predicts LV reverse remodeling at 6 months follow-up.

INTRODUCTION

The human heart has a specific helical arrangement of the myofibers with a right-hand orientation from the base towards the apex in the endocardial layers and a left-hand orientation in the epicardial layers. This spiral architecture of the myofibers leads to a left ventricular (LV) systolic wringing motion as a result of an opposite rotation of LV apex and base (1, 2). The gradient between apex and base in the rotation angle along LV longitudinal axis is called twist and contributes significantly to LV systolic function, in addition to myocardial shortening and thickening (3-5).

In heart failure (HF) patients, LV twist is significantly reduced (6). Cardiac resynchronization therapy (CRT) is considered a major therapeutic breakthrough for HF patients, and recent large randomized trials have shown that CRT has beneficial effects on HF symptoms, LV systolic function and survival (7, 8). At present, minimal data are available about the effect of CRT on LV twist (9, 10).

In the current study, the effect of CRT on LV twist was assessed using speckle-tracking echocardiography. Furthermore, the relationship between the change in LV twist and LV reverse remodeling at 6 months follow-up was investigated. Finally, the influence of the LV lead position on the improvement in LV twist and response to CRT was explored.

METHODS

Study population and protocol

A total of 87 consecutive HF patients scheduled for CRT were prospectively included. According to current guidelines, the inclusion criteria were: New York Heart Association (NYHA) functional class III-IV, sinus rhythm, LV ejection fraction (LVEF) ≤35%, QRS duration ≥120 ms (11). Etiology of HF was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization.

The clinical evaluation consists of: 1) assessment of clinical status: NYHA functional class, quality of life (using the Minnesota Living with Heart Failure questionnaire) (12), and 6-minute walk distance (13) at baseline and 6 months follow-up; 2) assessment of LV volumes, function, dyssynchrony and twist, using standard echocardiography and speckle-tracking analysis at baseline, within 48 hours (immediately after CRT) and at 6 months follow-up.

In addition, 30 subjects without evidence of structural heart disease, frequency-matched for age, gender and body surface area, were included as a normal control group, selected from an echocardiographic data base. These subjects were referred for the echocardiographic evaluation because of atypical chest pain, palpitations or syncope without murmur.

Standard echocardiography

All patients were imaged in left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwakee, Wisconsin, USA). Standard 2-dimensional images were obtained using a 3.5-MHz transducer and digitally stored in cine-loop format; the analysis was performed offline using EchoPAC version 6.0.1 (General Electric-Vingmed).

From the standard apical views (4- and 2-chamber) LV volumes and LVEF were calculated according to the American Society of Echocardiography guidelines (14). At 6 months follow-up, patients were classified as echocardiographic responders based on a reduction ≥15% of LV end-systolic volume (LVESV) (15).

Segmental wall motion was assessed according to American Society of Echocardiography in order to evaluate the presence of scarred segments within ischemic HF patients (14). Akinetic and diskinetic segments (wall motion score 3 and 4) were classified as scarred segments (16).

Speckle-tracking analysis

The speckle-tracking software tracks frame-to-frame the movement of natural myocardial acoustic markers, or speckles, on standard gray scale images. Speckles are randomly distributed and each region of the myocardium has a distinguishing pattern, a fingerprint. Furthermore, speckle-tracking analysis is angle independent and allows the evaluation of myocardial contraction/relaxation along the circumferential, longitudinal and radial direction (17, 18).

In the current study, speckle-tracking analysis was applied to evaluate LV dyssynchrony (based on radial strain analysis) and LV twist. Parasternal short-axis images were acquired at 3 distinct levels: 1) basal level, identified by the mitral valve; 2) papillary muscle level; 3) apical level (the smallest cavity achievable distally to the papillary muscles, moving the probe down and slightly laterally, if needed). Frame rate ranged from 45 to 100 frame/s and 3 cardiac cycles for each parasternal short-axis level were stored in cine-loop format for the offline analysis (EchoPAC). The endocardial border

was traced at an end-systolic frame and the region of interest (ROI) was chosen to fit the whole myocardium. The software allows the operator to check and validate the tracking quality and to adjust the endocardial border or modify the width of the ROI, if needed. Furthermore, each short-axis image was automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior.

Aortic valve opening and closure were identified on pulsed-wave Doppler tracings obtained from the LV outflow tract.

LV dyssynchrony analysis

LV dyssynchrony was derived from the radial strain curves obtained from the papillary muscle short-axis view. As previously described, LV dyssynchrony was defined as the time difference of peak radial strain between the anteroseptal and posterior segments (19).

LV twist analysis

The speckle-tracking software calculates LV rotation from the apical and basal short-axis images as the average angular displacement of the 6 standard segments referring to the ventricular centroid, frame by frame. Counterclockwise rotation was marked as positive value and clockwise rotation as negative value when viewed from the LV apex. LV twist was defined as the net difference (in degrees) of apical and basal rotation at isochronal time points. For the calculation of LV twist, averaged apical and basal rotation data were exported to a spreadsheet program (Excel 2003; Microsoft Corporation, Redmond, Washington) (Figure 1) (20, 21). The following measurements were derived: peak apical and basal rotation, peak LV twist.

Reproducibility

Reproducibility of LV end-diastolic volume (LVEDV), LVESV, LVEF and peak LV twist was assessed on 20 randomly selected HF patients. Bland-Altman analysis was performed to evaluate the intra- and inter-observer agreement repeating the analysis few days later by the same observer and by a second independent observer. The results were expressed as absolute mean difference ± 2 standard deviation (SD).

The intra-observer agreement for LVEDV, LVESV, LVEF and peak LV twist were 7.4 ± 11.2 ml, 7.0 ± 10.1 ml, 1.9 ± 4.4%, and 0.2 ± 0.3°, respectively.

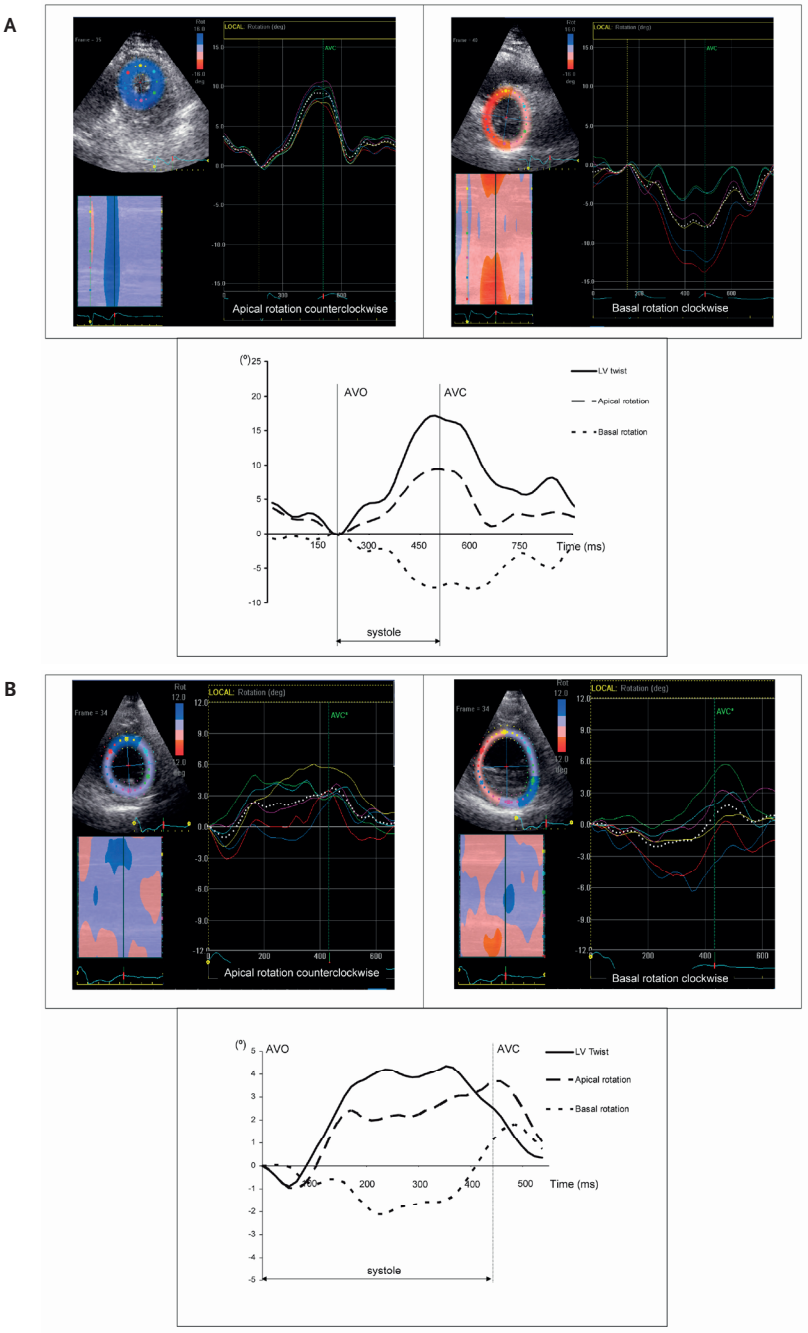

Figure 1 (Assessment of LV twist). Examples of left ventricular (LV) twist in normal control (panel A) and in heart failure patient (panel B). In both panels, the upper parts represent apical and basal rotations and the lower parts represent LV twist calculation after exporting the data to a spreadsheet program (Excel 2003; Microsoft Corporation, Redmond, Washington). AVC: aortic valve closure. AVO: aortic valve opening.

The inter-observer agreement for LVEDV, LVESV, LVEF and peak LV twist were 12.9 ± 14.7 ml, 11.3 ± 13.9 ml, 2.5 ± 4.9%, and 0.7 ± 0.8°, respectively.

CRT implantation

All patients received a biventricular pacemaker with cardioverter-defibrillator function (Contak Renewal 4RF, Boston Scientific St. Paul, Minnesota; or InSync Sentry, Medtronic Inc. Minneapolis, Minnesota; Lumax 340 HF-T, Biotronik, Berlin). The right atrial and ventricular leads were positioned conventionally. All LV leads were implanted transvenously, and positioned preferably in a (postero-)lateral vein. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to place the LV lead (Easytrak, Boston Scientific, or Attain-SD, Medtronic, or Corox OTW Biotronik) in the coronary sinus.

LV lead position

Target veins were lateral or postero-lateral veins. The LV lead position was determined using biplane fluoroscopy classification (22). In the right anterior oblique view and/or in the postero-anterior view, the distance between the coronary sinus/mitral plane and the cardiac apex was divided in 3 parts and the LV lead position was classified in 3 groups: basal, mid-ventricular and apical.

Statistical analysis

All continuous variables had a normal distribution (as evaluated with Kolmogorov-Smirnov tests). Summary statistics for these data are therefore presented as mean ± SD. Categorical data are presented as numbers and percentages. Paired T test was used for the comparison between continuous variables at baseline and immediately after CRT and between baseline and at 6 months follow-up. Unpaired T test was performed to compare continuous variables between normal controls and HF patients and between CRT responders and non-responders. *Chi*-square/Fischer's exact tests were computed to test for differences in categorical variables. Linear regression analysis was performed to determine the relations between LV twist, LVEF and LV dyssynchrony. In order to identify independent determinants of LV twist, a multivariable linear regression analysis using the enter model was performed including as covariates LVEF and LV dyssynchrony. Linear regression analysis was used to assess the relation between the

Δ (difference between immediately after CRT and baseline) peak LV twist and Δ LVEF. The differences in peak LV twist during follow-up in responders and non-responders were assessed using ANOVA for repeated measurements. In order to identify variables related to a positive response to CRT, univariable and multivariable logistic regression analysis were performed including clinical (age, gender, etiology, QRS duration at baseline and 6-minute walk distance at baseline) and echocardiographic (LVESV at baseline, Δ LVESV, LV dyssynchrony at baseline, Δ LV dyssynchrony, peak LV twist at baseline, Δ peak LV twist) characteristics of the patients. Only, significant ($p < 0.05$) univariable predictors were entered as covariates in the multivariable logistic regression analysis which was performed using the enter model. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Model discrimination was assessed using c-statistic and model calibration was assessed using Hosmer-Lemeshow statistic. The differences in peak LV twist and LVEF between the groups of patients with different LV lead position were assessed by one-way ANOVA. All statistical tests were 2-sided, and a p value <0.05 was considered significant. A statistical software program SPSS 14.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

RESULTS

Study population

Reliable speckle-tracking for rotation analysis was obtained in all normal controls and in 80 (92%) HF patients. Consequently, 7 (8%) patients were excluded from the study. Of the 80 HF patients enrolled, 9 did not complete the 6 months follow-up; 3 patients died of worsening HF, 1 had LV pacing switched off due to intolerable phrenic stimulation, 1 had CRT device explantation secondary to infection, and 4 were lost to follow-up. Therefore, data at baseline and immediately after CRT were collected for 80 patients and data at 6 month follow-up were collected for 71 patients.

Baseline characteristics of normal controls and the HF patients are listed in Table 1.

LV twist baseline

As shown in Table 1, peak apical rotation, peak basal rotation and peak LV twist were severely reduced in HF patients compared to normal controls: 2.4 ± 1.8° vs. 9.4 ± 3.2° ($p < 0.001$), -3.3 ± 2.0° vs. -6.1 ± 2.4° ($p < 0.001$) and 4.8 ± 2.6° vs. 15.0 ± 3.6° ($p < 0.001$), respectively.

Table 1. Baseline characteristics of normal controls and heart failure (HF) patients.

	Normal controls (n = 30)	HF patients (n = 80)	p value
Age (years)	61 ± 11	64 ± 11	0.091
Gender (male/female)	22/8	61/19	0.46
NYHA class	-	3.0 ± 0.4	-
QoL	-	34 ± 20	-
6-minute walk distance (m)	-	321 ± 109	-
QRS duration (ms)	91 ± 9	148 ± 30	<0.001
Etiology, n (%)			
Ischemic	-	45 (56)	-
Non-ischemic	-	35 (44)	-
Medication, n (%)			
ACE Inhibitors	-	74 (92)	-
β-blockers	-	69 (86)	-
Diuretics and/or Spironolactone	-	67 (84)	-
LVEDV (ml)	86 ± 26	196 ± 74	<0.001
LVESV (ml)	34 ± 11	146 ± 60	<0.001
LVEF (%)	62 ± 7	26 ± 6	<0.001
LV dyssynchrony (ms)	14 ± 9	146 ± 81	<0.001
Peak apical rotation (°)	9.4 ± 3.2	2.4 ± 1.8	<0.001
Peak basal rotation (°)	-6.1 ± 2.4	-3.3 ± 2.0	<0.001
Peak LV twist (°)	15.0 ± 3.6	4.8 ± 2.6	<0.001

LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume, NYHA: New York Heart Association, QoL: Score on the Minnesota Living with Heart Failure Questionnaire

A significant relation (r = 0.53, p <0.001) was observed between peak LV twist and LVEF in HF patients. This relation was stronger in non-ischemic (r = 0.60, p <0.001) than in ischemic HF patients (r = 0.34, p = 0.020) (Figure 2A). Moreover, a modest relation (r = -0.33, p = 0.003) was observed between peak LV twist and LV dyssynchrony in HF patients.

At multivariable linear regression analysis, LVEF (β = 0.47, p <0.001) and LV dyssynchrony (β = -0.21, p = 0.032) were independent determinants of LV twist.

LV twist after CRT

Immediately after CRT

Immediately after CRT, peak LV twist increased from 4.8 ± 2.6° to 5.9 ± 3.2° (p = 0.007). In particular, Δ peak LV twist was strongly related to Δ LVEF (r = 0.83, p <0.001) and this relation was good in both non-ischemic (r = 0.85, p <0.001) and ischemic HF patients (r = 0.82, p <0.001) (Figure 2B). Furthermore, the relations between Δ peak LV twist and Δ LV dyssynchrony (r = -0.57, p <0.001) and between Δ LV dyssynchrony and Δ LVEF (r = -0.63, p <0.001) were good but less strong than the previous relation between Δ peak LV twist and Δ LVEF.

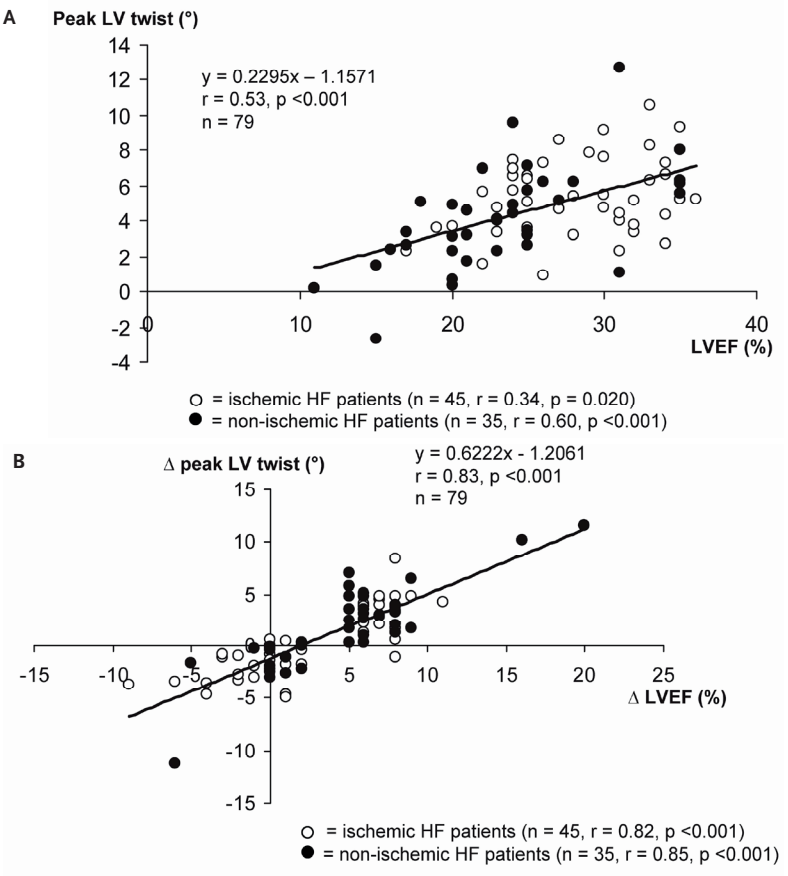

Figure 2 (LV twist and LV systolic function). Panel A: Correlation between baseline peak LV twist and LVEF in heart failure patients (ischemic, white circles, and non-ischemic, black circles). **Panel B:** Correlation between Δ peak LV twist and Δ LVEF immediately after CRT in heart failure patients (ischemic, white circles, and non-ischemic, black circles).

Six months follow-up

At 6 months follow-up, 40 of 71 (56%) patients were classified as echocardiographic responders to CRT (defined as a decrease in LVESV ≥15%).

No significant differences in the baseline clinical characteristics were found between responders and non-responders (Table 2). At 6 months follow-up, significant improvement in NYHA class (from 3.0 ± 0.5 to 2.0 ± 0.7, p <0.001), quality of life

Table 2. Clinical characteristics of responders vs. non-responders at baseline and 6 months follow-up.

	Responders (n = 40)	**Non-responders** (n = 31)	**p value**
Age (years)	66 ± 10	66 ± 11	0.88
Gender (male/female)	32/8	20/11	0.18
Medication, n (%)			
ACE Inhibitors	37 (92)	29 (93)	0.77
β-blockers	35 (87)	27 (86)	0.82
Diuretics and/or			
Spironolactone	34 (84)	26 (84)	0.82
Etiology, n (%)			
Ischemic	20 (50)	18 (58)	
Non-ischemic	20 (50)	13 (42)	0.63
QRS duration (ms)	149 ± 32	149 ± 30	0.97
NYHA class			
Baseline	3.0 ± 0.5	3.0 ± 0.5	0.92
6 months follow-up	2.0 ± 0.7*	2.7 ± 0.6†	<0.001
QoL			
Baseline	35 ± 23	32 ± 15	0.51
6 months follow-up	20 ± 20*	29 ± 19	0.065
6-minute walk distance (m)			
Baseline	306 ± 106	330 ± 107	0.34
6 months follow-up	363 ± 109*	327 ± 110	0.17

* = p <0.001 baseline vs. 6 month follow-up; † = p<0.05 baseline vs. 6 month follow-up.
Abbreviations see Table 1.

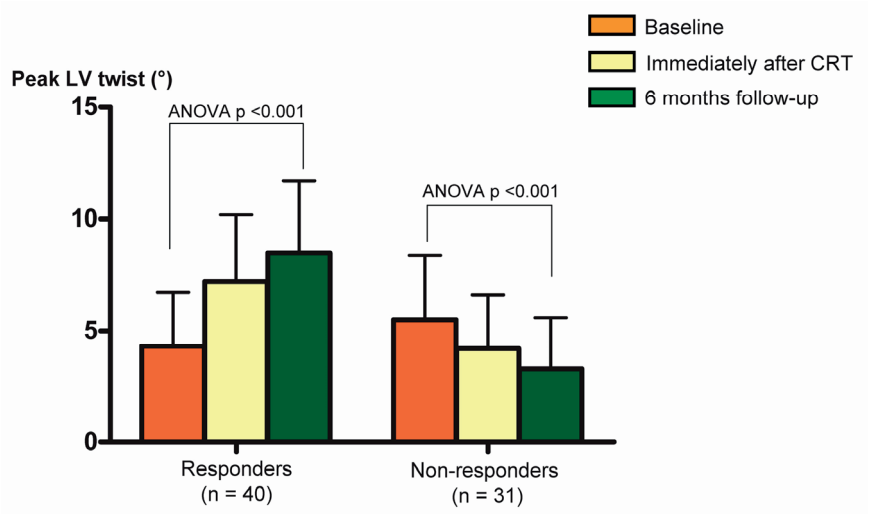

Figure 3 (LV twist in responders and non-responders). Peak LV twist in responders and non-responders at baseline, immediately after CRT and at 6 months follow-up.

(from 35 ± 23 to 20 ± 20, p <0.001), and 6-minute walk distance (from 306 ± 106 m to 363 ± 109 m, p <0.001) were observed in CRT responders only (Table 2).

Baseline echocardiographic characteristics were also similar between the 2 groups, except for LV dyssynchrony (Table 3) that was larger in responders compared to non-responders (182 ± 71 ms vs. 116 ± 83 ms, p = 0.003). A trend towards lower values of peak LV twist were noted in responders as compared to non-responders (4.3 ± 2.4° vs. 5.4 ± 2.9°, p = 0.072). At 6 months follow-up, LV dyssynchrony improved in CRT responders (from 182 ± 71 ms to 60 ± 45 ms, p <0.001), whereas in non-responders LV dyssynchrony did not change (116 ± 83 ms vs. 136 ± 89 ms, p = 0.30) (Table 3). Importantly, within ischemic HF patients, CRT responders presented significantly lower number of scarred segments at 2D-echocardiography as compared to non-responders (2.7 ± 0.9 vs. 4.2 ± 2.2, p = 0.016).

Concerning the rotational parameters, in responders peak LV twist progressively improved during follow-up (ANOVA p value <0.001), whereas in non-responders a progressive deterioration of peak LV twist was noted (ANOVA p value <0.001) (Figure 3). Particularly, both apical and basal rotation significantly improved in responders (from 2.3 ± 1.7° to 5.0 ± 3.0°, p <0.001 and from -3.2 ± 2.2° to -4.3 ± 1.9°, p = 0.006), whereas only basal rotation significantly deteriorated in non-responders (from -3.5 ± 1.7 to -2.1 ± 2.2, p = 0.001) (Table 3).

Table 3. Standard echocardiographic variables and rotational parameters in responders vs. non-responders at baseline and 6 months follow-up.

	Responders (n = 40)	**Non-responders** (n = 31)	**p value** (responders vs. non-responders)
LVESV (ml)			
Baseline	144 ± 58	153 ± 67	0.56
6 months follow-up	110 ± 43*	164 ± 72‡	0.001
LVEF (%)			
Baseline	26 ± 6	26 ± 6	0.91
6 months follow-up	37 ± 7*	26 ± 6	<0.001
LV dyssynchrony (ms)			
Baseline	182 ± 71	116 ± 83	0.003
6 months follow-up	60 ± 45*	136 ± 89	<0.001
Peak apical rotation (°)			
Baseline	2.3 ± 1.7	2.8 ± 2.1	0.32
6 months follow-up	5.0 ± 3.0*	2.1 ± 2.3	<0.001
Peak basal rotation (°)			
Baseline	-3.2 ± 2.2	-3.5 ± 1.7	0.51
6 months follow-up	-4.3 ± 1.9†	-2.1 ± 2.2†	<0.001
Peak LV twist (°)			
Baseline	4.3 ± 2.4	5.4 ± 2.9	0.072
6 months follow-up	8.5 ± 3.2*	3.3 ± 2.2*	<0.001

* = p <0.001 baseline vs. 6 month follow-up; † = p <0.01 baseline vs. 6 month follow-up; ‡ = p<0.05 baseline vs. 6 month follow-up.
Abbreviations see Table 1.

Prediction of LV reverse remodeling

At univariable logistic regression, LV dyssynchrony at baseline, Δ LV dyssynchrony, Δ LVESV and Δ peak LV twist were significantly related to LV reverse remodeling at 6 months follow-up (Table 4). At multivariable logistic regression analysis, Δ peak LV twist was the strongest predictor of response to CRT at 6 months follow-up (OR = 1.899, 95%CI = 1.334-2.703, p <0.001) (Table 4).

Table 4. Univariable and multivariable logistic regression analysis for prediction of response to CRT (defined as reduction in LVESV ≥15%)

Dependent variable: Response to CRT at 6 months follow-up	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Independent variables				
Age	1.003 (0.958-1.050)	0.90		
Female gender	2.198 (0.756-6.404)	0.15		
Ischemic etiology	0.722 (0.281-1.858)	0.50		
QRS width at baseline	1.000 (0.985-1.016)	0.97		
6 minutes walking test at baseline	0.998 (0.993-1.002)	0.34		
LVESV at baseline	0.998 (0.990-1.005)	0.56		
Δ LVESV immediately after CRT	0.949 (0.915-0.984)	0.005	0.998 (0.950-1.049)	0.94
LV dyssynchrony at baseline	1.013 (1.005-1.021)	0.002	1.011 (1.001-1.022)	0.037
Δ LV dyssynchrony immediately after CRT	0.992 (0.986-0.998)	0.010	1.007 (0.996-1.017)	0.21
Peak LV twist at baseline	0.844 (0.698-1.019)	0.078		
Δ peak LV twist immediately after CRT	1.837 (1.378-2.449)	<0.001	1.899 (1.334-2.703)	<0.001

c-statistic: 0.885

CI: confidence intervals; CRT: cardiac resynchronization therapy; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; OR: odds ratio.

LV twist in relation to LV lead position

Considering the 71 patients with 6 months follow-up, 68 patients had the LV lead placed in a (postero-)lateral vein and 3 in an anterior vein. The 3 patients with the LV lead positioned in an anterior vein were non-responders at 6 months follow-up. Of the remaining 68 patients, the LV lead position was classified (from the right anterior oblique/postero-anterior view on fluoroscopy) as basal in 17 (25%), mid-ventricular in 34 (50%), and apical in 17 (25%) patients. At baseline, peak LV twist was not significantly different between patients with apical, mid-ventricular and basal LV lead position, (ANOVA p value = 0.68). However, at 6 months follow-up, peak LV twist showed a significant improvement in patients with apical (from 4.3 ± 3.1° to 8.6 ± 3.0°, p = 0.001) and mid-ventricular (from 4.8 ± 2.2° to 6.4 ± 3.9°, p = 0.038) LV lead position, whereas in patients with a basal LV lead position, peak LV twist did not change significantly (5.0 ± 3.3° vs. 4.1 ± 3.2°, p = 0.28) (Figure 4A). Similarly, LVEF

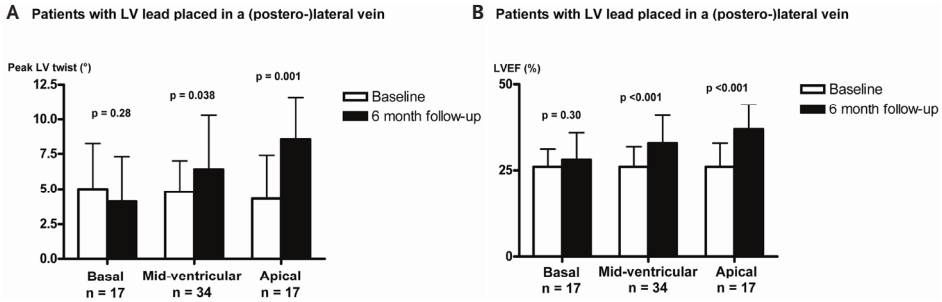

Figure 4 (LV twist and LVEF in relation to LV lead position). Panel A. Peak LV twist at baseline and 6 months follow-up in patients with basal, mid-ventricular and apical LV lead position. Significant improvement was observed in patients with an apical or mid-ventricular LV lead position but not in patients with basal LV lead position. **Panel B.** LVEF at baseline and 6 months follow-up in patients with basal, mid-ventricular and apical LV lead position. Significant improvement was observed in patients with an apical or mid-ventricular LV lead position but not in patients with basal LV lead position.
LV: left ventricular; LVEF: left ventricular ejection fraction

increased significantly in patients with an apical (from 26 ± 7% to 37 ± 7%, p <0.001) and mid-ventricular (from 26 ± 6% to 33 ± 8%, p <0.001) but not with a basal (26 ± 5% vs. 28 ± 8%, p = 0.30) LV lead position (Figure 4B).

Figure 5 shows an example of responder with the LV lead placed in an apical position of a postero-lateral vein and significant improvement in peak LV twist and LVEF after CRT (both immediately after CRT implantation and at 6 months follow-up).

DISCUSSION

The current study evaluated the effects of CRT on LV twist and provides new insights on the relationship between LV rotational mechanics, CRT response and LV lead position. The main findings can be summarized as follows: 1) LV twist was significantly reduced in HF patients; 2) LV twist improved in responders and worsened in non-responders to CRT; 3) the strongest predictor of LV reverse remodeling at 6 months follow-up was Δ peak LV twist (immediate change in LV twist after CRT); 4) an LV lead placed in a (postero-)lateral vein with apical or mid-ventricular position was associated with the greatest improvement of LV twist after CRT and with the highest response rate to CRT.

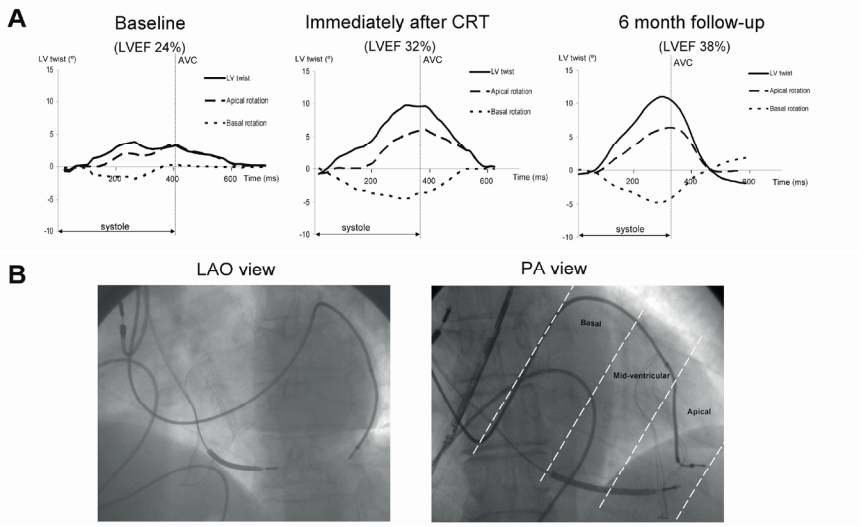

Figure 5. Example of a CRT responder with LV lead in an apical position. **Panel A.** Peak LV twist improved from 3.9° at baseline to 9.7° immediately after CRT implantation. Peak LV twist further improved at 6 months follow-up (peak LV twist 10.9°). AVC: aortic valve closure. **Panel B.** Biplane fluoroscopy: the left anterior oblique (LAO) view shows the LV lead in a posterolateral cardiac vein; in the postero-anterior (PA) view the distance between the coronary sinus/mitral plane and the cardiac apex was divided (dotted lines) in 3 parts (basal, mid-ventricular and apical).

Relationship between LV twist and LV function

Several techniques have been applied for the assessment and quantification of LV twist. For this purpose, tagged cardiac magnetic resonance imaging and sonomicrometry are considered the gold standard, but the most recent speckle-tracking echocardiographic technique, used in the present study, demonstrated a good agreement with these imaging modalities (20, 21). Previous studies, using both tagged cardiac magnetic resonance imaging and speckle-tracking analysis, suggested an important relation between LV twist and LVEF (4, 9). Similarly, in the current study the relation between LV twist and LV systolic function was good ($r = 0.53$, $p < 0.001$), illustrating the potential role of LV twist as comprehensive index of LV systolic function. Furthermore, the results of the present study highlight that the relation between LV systolic function and LV twist was stronger in non-ischemic patients as compared to ischemic patients. A possible reason may be the presence of regional myocardial damage in ischemic patients, involving specifically the apex or the base with a different effect on LV twist (23).

Finally, LV twist was modestly related to LV dyssynchrony ($r = -0.33$, $p < 0.001$), but at multivariable linear regression analysis, LV dyssynchrony was still independently

related to LV twist. This finding points out that LV twist not only is a sensitive and thorough parameter of LV function, but also it may reflect the extent of LV (dys) synchrony.

Relationship between LV twist and CRT response

The effects of CRT on torsional mechanics were different in responders and non-responders. A trend towards more reduced LV twist at baseline in responders as compared to non-responders was observed. In the present study, a significant improvement of LV twist was observed in CRT responders and a significant worsening in non-responders. In contrast, a previous study of Zhang et al. did not show any significant increase of LV twist in responders to CRT (10). The different results may be related to sample size and population characteristics.

In the multivariable model, baseline LV dyssynchrony and an immediate improvement in LV twist after CRT were the only predictors of LV reverse remodeling at 6 months follow-up. The predictive value of LV dyssynchrony has been shown already in previous studies (19, 24). The novelty of the present study is that CRT may (partially) restore LV twist, possibly by providing a more physiologic electrical depolarization and mechanical contraction of the myofibers. Specifically, CRT partially restored LV torsional behavior in responders, by not only improving apical rotation but also basal rotation. In non-responders, the deterioration of LV twist was mainly due to worsening of the basal rotation underscoring the influence of the basal level on LV twist (25).

Relationship between LV twist and LV lead position

Previous studies showed that HF patients treated with CRT showed the best hemodynamic improvement when the LV pacing lead was positioned in (postero-)lateral veins (26). In the current study, 3 patients had the LV lead placed in an anterior vein, and none of them responded to CRT. The remaining 68 patients had the LV lead positioned in the (postero-)lateral vein. In these patients, the optimal position of LV lead inside the target vein was explored. Patients with a mid-ventricular or apical position had the largest systolic improvement, and showed a significant increase in LV twist, whereas patients with a basal LV lead position did not improve systolic function and decreased in LV twist, confirming that pacing site may influence torsional behavior of the LV (27). Similarly, a recent study by Helm et al.(28) reported that the optimal site of stimulation (although in a canine model of HF) was the LV free wall centered

over the mid-apical part. This finding may be related to the fact that normal cardiac depolarization is directed from the apex towards the base (29), and an earlier activation of the LV basal region, altering the normal contraction pattern of the myofibers, may lead to a significant deterioration of LV twist. Another explanation for the findings may be related to the fact that the myocardial wall is thinner towards the apex (30, 31); therefore, the epicardial LV lead in this position is closer to the Purkinje network. Consequently, pacing from this position may generate a cardiac pulse which spreads faster to the entire myocardium with a more physiological activation (32-34).

Conclusion

LV twist is reduced in HF patients and improves in patients who respond to CRT. Particularly, the change in LV twist immediately after CRT predicts LV reverse remodeling at 6 months follow-up.

REFERENCES

1. Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. Br Heart J 1981; 45:248-63.
2. Torrent-Guasp F, Kocica MJ, Corno AF, et al. Towards new understanding of the heart structure and function. Eur J Cardiothorac Surg 2005; 27:191-201.
3. Buchalter MB, Weiss JL, Rogers WJ, et al. Noninvasive quantification of left ventricular rotational deformation in normal humans using magnetic resonance imaging myocardial tagging. Circulation 1990; 81:1236-44.
4. Kanzaki H, Nakatani S, Yamada N, Urayama S, Miyatake K, Kitakaze M. Impaired systolic torsion in dilated cardiomyopathy: reversal of apical rotation at mid-systole characterized with magnetic resonance tagging method. Basic Res Cardiol 2006; 101:465-70.
5. Notomi Y, Martin-Miklovic MG, Oryszak SJ, et al. Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. Circulation 2006; 113:2524-33.
6. Fuchs E, Muller MF, Oswald H, Thony H, Mohacsi P, Hess OM. Cardiac rotation and relaxation in patients with chronic heart failure. Eur J Heart Fail 2004; 6:715-22.
7. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346:1845-53.
8. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352:1539-49.
9. Sade LE, Demir O, Atar I, Muderrisoglu H, Ozin B. Effect of mechanical dyssynchrony and cardiac resynchronization therapy on left ventricular rotational mechanics. Am J Cardiol 2008; 101:1163-9.
10. Zhang Q, Fung JW, Yip GW, et al. Improvement of left ventricular myocardial short-axis, but not long-axis function or torsion after cardiac resynchronisation therapy: an assessment by two-dimensional speckle tracking. Heart 2008; 94:1464-71.
11. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112: e154-e235.
12. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. Am J Cardiol 1993; 71:1106-7.
13. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. Br Med J (Clin Res Ed) 1986; 292:653-5.
14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18:1440-63.
15. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008; 117:2608-16.
16. Schuijf JD, Kaandorp TA, Lamb HJ, et al. Quantification of myocardial infarct size and transmurality by contrast-enhanced magnetic resonance imaging in men. Am J Cardiol 2004; 94:284-8.

17. Leitman M, Lysyansky P, Sidenko S, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 2004; 17:1021-9.
18. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004; 17:630-3.
19. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006; 113:960-8.
20. Helle-Valle T, Crosby J, Edvardsen T, et al. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. Circulation 2005; 112:3149-56.
21. Notomi Y, Lysyansky P, Setser RM, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol 2005; 45:2034-41.
22. Albertsen AE, Nielsen JC, Pedersen AK, Hansen PS, Jensen HK, Mortensen PT. Left ventricular lead performance in cardiac resynchronization therapy: impact of lead localization and complications. Pacing Clin Electrophysiol 2005; 28:483-8.
23. Opdahl A, Helle-Valle T, Remme EW, et al. Apical Rotation by Speckle Tracking Echocardiography: A Simplified Bedside Index of Left Ventricular Twist. J Am Soc Echocardiogr 2008.
24. Delgado V, Ypenburg C, van Bommel RJ, et al. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. J Am Coll Cardiol 2008; 51:1944-52.
25. Notomi Y, Srinath G, Shiota T, et al. Maturational and adaptive modulation of left ventricular torsional biomechanics: Doppler tissue imaging observation from infancy to adulthood. Circulation 2006; 113:2534-41.
26. Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001; 104:3026-9.
27. Notomi Y, Popovic ZB, Yamada H, et al. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. Am J Physiol Heart Circ Physiol 2008; 294:H505-H513.
28. Helm RH, Byrne M, Helm PA, et al. Three-dimensional mapping of optimal left ventricular pacing site for cardiac resynchronization. Circulation 2007; 115:953-61.
29. Sengupta PP, Khandheria BK, Korinek J, et al. Apex-to-base dispersion in regional timing of left ventricular shortening and lengthening. J Am Coll Cardiol 2006; 47:163-72.
30. Bogaert J, Rademakers FE. Regional nonuniformity of normal adult human left ventricle. Am J Physiol Heart Circ Physiol 2001; 280:H610-H620.
31. Sengupta PP, Korinek J, Belohlavek M, et al. Left ventricular structure and function: basic science for cardiac imaging. J Am Coll Cardiol 2006; 48:1988-2001.
32. Peschar M, de Swart H, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. J Am Coll Cardiol 2003; 41:1218-26.
33. Vanagt WY, Prinzen FW, Delhaas T. Reversal of pacing-induced heart failure by left ventricular apical pacing. N Engl J Med 2007; 357:2637-8.
34. Vanagt WY, Prinzen FW, Delhaas T. Physiology of cardiac pacing in children: the importance of the ventricular pacing site. Pacing Clin Electrophysiol 2008; 31 Suppl 1:S24-S27.

CHAPTER 5

Effect of cardiac resynchronization therapy on subendo- and subepicardial left ventricular twist mechanics and relation to favorable outcome.

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ABSTRACT

The analysis of left ventricular (LV) mechanics provides novel insights into the effects of cardiac resynchronization therapy (CRT) on LV performance. Currently, advances in speckle-tracking echocardiography analysis have permitted to characterize subendo- and subepicardial LV twist. This study investigated the role of the acute changes in subendo- and subepicardial LV twist for the prediction of mid-term beneficial effects of CRT.

A total of 84 heart failure patients scheduled for CRT were recruited. All patients underwent echocardiography prior to, within 48 hours after CRT implantation, and at 6 months follow-up. The assessment of LV volumes, ejection fraction (EF) and mechanical dyssynchrony (SDI) was performed with real-time 3D echocardiography. The assessment of subendo- and subepicardial LV twist was performed with 2D speckle-tracking echocardiography. Favorable outcome was defined by the occurrence of reduction ≥15% in LV end-systolic volume associated to improvement ≥1 in NYHA functional class at 6 months follow-up. At 6 months follow-up, 53% of the patients showed a favorable outcome. Ischemic etiology for heart failure, baseline SDI, immediate improvement in LVEF, immediate improvement in SDI, and immediate improvement in subendo- and subepicardial LV twist were significantly related to favorable outcome. However, at multivariable logistic regression analysis, only the immediate improvement of subepicardial LV twist was independently related to favorable outcome (odds ratio=2.31, 95%CI=1.29-4.15, p=0.005). Furthermore, the immediate improvement of subepicardial LV twist had incremental value over established parameters. In conclusion, the immediate improvement in subepicardial LV twist (but not subendocardial LV twist) is independently related to favorable outcome after CRT.

INTRODUCTION

Recent advances in speckle-tracking echocardiography analysis have permitted to characterize subendo- and subepicardial left ventricular (LV) twist.[1-6] The aim of the present study was to investigate the changes induced by cardiac resynchronization therapy (CRT)[7-9] on the rotational mechanics detected with speckle-tracking echocardiography. Specifically, the role of the acute changes in subendo- and subepicardial LV twist for the prediction of mid-term beneficial effects of CRT (LV reverse remodeling associated with clinical improvement at 6 months follow-up), was explored over the classical parameters including mechanical LV dyssynchrony and LV ejection fraction (EF).

METHODS

A total of 106 consecutive heart failure patients scheduled for CRT were included. According to current guidelines, the inclusion criteria were: New York Heart Association (NYHA) functional class III-IV, sinus rhythm, LVEF ≤35% and QRS duration ≥120 ms. Etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization.

All patients underwent complete baseline clinical evaluation, 12-lead surface electrocardiogram and transthoracic echocardiography prior to and within 48 hours after CRT device implantation. Global measures of LV performance were evaluated with real-time 3-dimensional (3D) echocardiography and 2-dimensional (2D) speckle tracking. The assessment of LV volumes, ejection fraction and mechanical dyssynchrony was performed with real-time 3D echocardiography. The assessment of subendo- and subepicardial LV twist was performed with 2D speckle-tracking. In addition, the clinical and echocardiographic evaluation was repeated 6 months after CRT implantation. Favorable outcome was defined by the occurrence of LV reverse remodeling (reduction ≥15% in LV end-systolic volume) associated with clinical improvement (≥1 NYHA functional class) at 6 months follow-up. Finally, the variables related to favorable outcome were investigated and the role of the newest rotational parameters over the established parameters was explored.

All patients were imaged in left lateral decubitus position using a commercially available system (iE33, Philips Medical Systems, Bothell, Washington) equipped with an X3, fully sampled matrix transducer. Apical full-volume data sets were obtained at a frame rate of 20-35 frames/sec and quantitative analysis was performed off-

line using a semiautomated contour tracing algorithm (Q-Lab, version 6.0, Philips Medical Systems), as previously described.[10-12] LV volumes and ejection fraction were measured. In addition, the systolic dyssynchrony index (SDI) was obtained as marker of global LV dyssynchrony, as previously reported.[10-12]

Two-dimensional gray-scale harmonic images were obtained in the left lateral decubitus position using a commercially available ultrasound system (iE33, Philips Medical Systems, Bothell, Washington) equipped with a broadband S5-1 transducer. Parasternal short-axis images were acquired at 2 different levels: 1) basal level, identified by the mitral valve; 2) apical level, defined as the smallest cavity achievable distally to the papillary muscles (just proximal to the level with end-systolic luminal obliteration), moving the probe down and slightly laterally. Patients without appropriate apical level were excluded from the study. Frame rate ranged from 55 to 90 frame/s and 3 cardiac cycles for each parasternal short-axis level were stored in cine-loop format for the off-line analysis (Q-Lab, version 6.0, Philips Medical Systems).

In the current study, 2D speckle-tracking analysis (Q-Lab, version 6.0, Philips Medical Systems) was performed by placing manually several small kernel regions in the subendo- and subepicardial border on an end-diastolic frame. Then, the software tracked the 2 borders frame by frame and the tracking could be adjusted manually, if needed.[4]

The 2D speckle-tracking software calculates LV rotation from the apical and basal short-axis images as the average angular displacement of the 6 standard segments referring to the ventricular centroid, frame by frame. Counterclockwise rotation was marked as positive value and clockwise rotation as negative value when viewed from the LV apex. LV twist was defined as the net difference (in degrees) of apical and basal rotation at isochronal time points. For the calculation of LV twist, averaged apical and basal rotation data were exported to a spreadsheet program (Excel 2003; Microsoft Corporation, Redmond, Washington). The following measurements were derived both for subendo- and subepicardial layers: peak apical and basal rotation, peak LV twist.

All patients received a biventricular pacemaker with cardioverter-defibrillator function (Contak Renewal 4RF, Boston Scientific St. Paul, Minnesota; or InSync Sentry, Medtronic Inc. Minneapolis, Minnesota; Lumax 340 HF-T, Biotronik, Berlin). The right atrial and ventricular leads were positioned conventionally. All LV leads were implanted transvenously, and positioned preferably in a (postero-)lateral vein. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to place the LV lead (Easytrak, Boston Scientific, or Attain-SD, Medtronic, or Corox OTW Biotronik) in the coronary sinus.

All continuous variables are presented as mean ± SD. Categorical data are presented as numbers and percentages. Unpaired T-test was used to compare baseline, immediately after CRT and 6 months follow-up parameters between patients with vs. without favorable outcome. Chi-squared test was used to compare categorical variables between patients with and without favorable outcome. Paired T-test was used to compare baseline and 6 months follow-up data in each group of patients. In order to identify variables related to favorable outcome at 6 months follow-up, uni- and multivariable logistic regression analysis were performed including clinical and echocardiographic characteristics of the patients at baseline and immediately after CRT. Only significant ($p < 0.05$) univariable factors were entered as covariates in the multivariable analysis using backward selection model. Finally, the incremental value of the newest rotational parameters (subendo- and subepicardial LV twist) over other variables was assessed by calculating the global chi-square test for each model. All statistical tests were 2-sided, and a p value <0.05 was considered significant. A statistical software program SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

RESULTS

A total of 22 of 106 (21%) patients were excluded because the image quality did not allow reliable analysis. Therefore, the overall patient population consisted of 84 patients. Of the 84 heart failure patients enrolled, 4 did not complete the 6 months follow-up; 1 patients died of worsening heart failure, 1 had LV pacing switched off due to intolerable phrenic stimulation, and 2 were lost to follow-up.

Baseline characteristics of the overall patient population are listed in Table 1. The mean age was 65 ± 9 years, and all the patients had dilated LV with poor LV function (mean LVEF 26 ± 5%). In addition, the LV rotational parameters were severely reduced in the subendo- and subepicardial layers (peak subendo- and subepicardial LV twist were 4.2 ± 2.9° and 2.3 ± 1.8°, respectively).

At 6 months follow-up, 42 of 80 (53%) patients showed a favorable outcome (LV reverse remodeling associated to clinical improvement at 6 months follow-up).

The baseline parameters of the patients with and without favorable outcome (LV reverse remodeling associated with clinical improvement at 6 months follow-up) are reported in Table 2. The patients with favorable outcome had less frequently ischemic etiology of heart failure ($p = 0.025$). Both groups of patients showed comparable LV volumes and ejection fraction. However, the baseline SDI was significantly larger in the group of patients with favorable outcome (8.1 ± 2.3% vs. 6.4

Table 1. Baseline characteristics of the overall patient population

Variable	Heart failure patients (n = 84)
Age (years)	65 ± 9
Male/female	55/29
Medication	
ACE Inhibitors	76 (91%)
β-blockers	71 (85%)
Diuretics and/or spironolactone	71 (85%)
Etiology of the heart failure	
Ischemic	44 (52%)
Non-ischemic	40 (48%)
NYHA functional class III/IV, n	81/3
QRS duration (ms)	151 ± 29
LV end-diastolic volume (ml)	200 ± 61
LV lead positioned in postero-lateral vein	80 (95%)
LV end-systolic volume (ml)	147 ± 50
LV ejection fraction (%)	26 ± 5
Systolic Dyssynchrony Index (%)	7.3 ± 2.1
Peak subendocardial apical rotation (°)	2.5 ± 2.1
Peak subendocardial basal rotation (°)	-2.5 ± 2.1
Peak subendocardial LV twist (°)	4.2 ± 2.9
Peak subepicardial apical (°)	1.5 ± 1.4
Peak subepicardial basal rotation (°)	-1.7 ± 1.4
Peak subepicardial LV twist (°)	2.3 ± 1.8

ACE: angiotensin-converting enzyme; LV: left ventricular; NYHA: New York Heart Association

± 1.4%, p <0.001). In addition, no differences in baseline subendocardial LV twist (4.0 ± 3.1° vs. 4.5 ± 2.7°, p = 0.45) or subepicardial LV twist (1.9 ± 1.8° vs. 2.6 ± 1.8°, p = 0.10) were observed.

Immediately after CRT, the group of patients with favorable outcome showed a significantly larger improvement in LVEF and SDI than patients without favorable

Table 2. Patients with vs. without favorable outcome (left ventricular reverse remodeling associated to clinical improvement at 6 months follow-up)

	Patients with favorable outcome (n = 42)	Patients without favorable outcome (n = 38)	P value
Ischemic etiology, n (%)	16 (38)	24 (63)	0.025
QRS duration (ms)	152 ± 27	151 ± 31	0.87
NYHA functional class I/II/III/IV, n			
Baseline	0/0/41/1	0/0/36/2	0.50
6 months follow-up	10/31/1/0*	2/8/26/2*	<0.001
LV end systolic-volume (ml)			
Baseline	150 ± 47	143 ± 54	0.50
6 months follow-up	107 ± 39*	149 ± 54	<0.001
LV ejection fraction (%)			
Baseline	26 ± 6	26 ± 5	0.97
6 months follow-up	38 ± 7*	27 ± 7	<0.001
Systolic Dyssynchrony Index (%)			
Baseline	8.1 ± 2.3	6.4 ± 1.4	<0.001
6 months follow-up	5.1 ± 1.8*	8.0 ± 3.8	<0.001
Peak subendocardial LV twist (°)			
Baseline	4.0 ± 3.1	4.5 ± 2.7	0.45
6 months follow-up	5.7 ± 2.9*	3.8 ± 2.8	0.004
Peak subepicardial LV twist (°)			
Baseline	1.9 ± 1.8	2.6 ± 1.8	0.10
6 months follow-up	4.0 ± 2.1*	1.9 ± 1.8†	<0.001

*: p <0.01 vs. baseline; †: p <0.05 vs. baseline
LV: left ventricular; NYHA: New York Heart Association

outcome (delta [Δ] LVEF was 8 ± 6% vs. 3 ± 4%, p <0.001 and Δ SDI was -2.6 ± 2.8% vs. -0.3 ± 2.1%, p <0.001; Figure 1 A, B). Similarly, the improvement in subendo- and subepicardial LV twist immediately after CRT was more pronounced in patients with favorable outcome (Δ subendocardial LV twist was 1.9 ± 2.8° vs. 0.3 ± 2.9°, p = 0.012 and 2.1 ± 2.1° vs. -0.2 ± 1.7°, p <0.001; Figure 1 C, D).

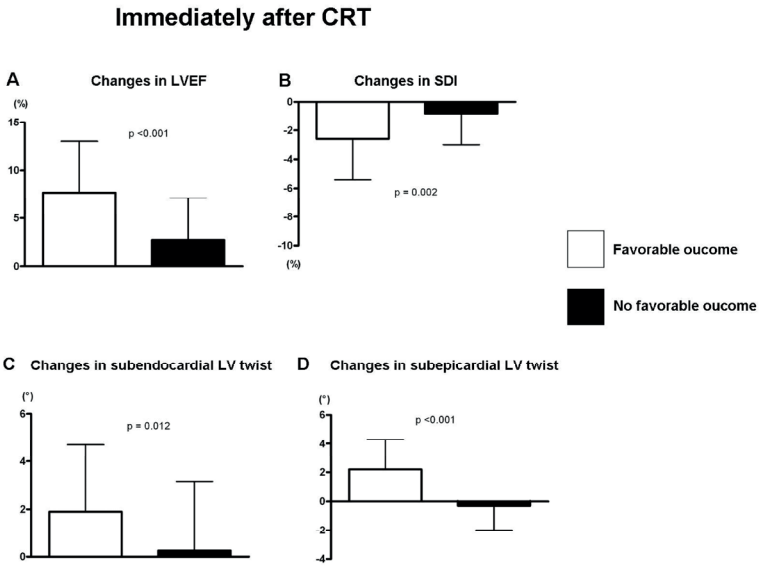

Figure 1. Changes immediately after cardiac resynchronization therapy (CRT) in left ventricular ejection fraction (LVEF; Panel A), systolic dyssynchrony index (SDI; Panel B), subendocardial left ventricular (LV) twist (Panel C) and subepicardial LV twist (Panel D) in patients with favorable outcome (LV reverse remodeling associated to clinical improvement at 6 months follow-up, white bars) and without favorable outcome (no LV reverse remodeling and clinical improvement at 6 months follow-up, black bars).

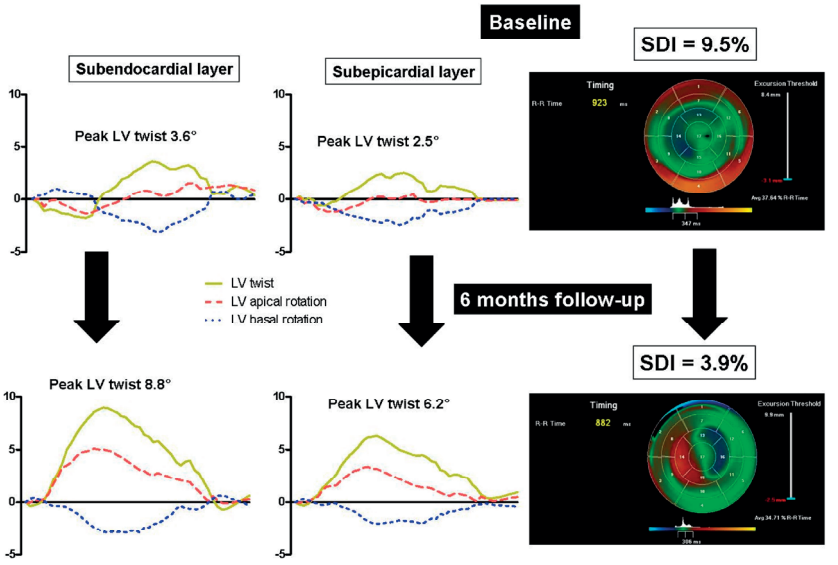

Figure 2. Example of patient with LV reverse remodeling associated to clinical improvement at 6 months follow-up. Subendo- and subepicardial left ventricular (LV) twist were both significantly increased at 6 months follow-up and a parallel reduction of systolic dyssynchrony index (SDI) was observed between baseline and 6 months follow-up.

Finally, at 6 months follow-up, a further improvement in subendo- and subepicardial LV twist was observed in patients showing favorable outcome (from 4.0 ± 3.1° to 5.7 ± 2.9°, p = 0.002 for subendocardial LV twist and from 1.9 ± 1.8° to 4.0 ± 2.1°, p <0.001 for subepicardial LV twist; Table 2). In Figure 2 an example of a patient with favorable outcome (LV reverse remodeling associated to clinical improvement at 6 months follow-up) is shown. In contrast, patients without favorable outcome showed a trend towards a deterioration of subendocardial LV twist (from 4.5 ± 2.7° to 3.8 ± 2.8°, p = 0.11; Table 2), and a significant worsening of subepicardial LV twist, (from 2.6 ± 1.8° to 1.9 ± 1.8°, p = 0.037; Table 2).

At univariable logistic regression, ischemic etiology for heart failure, baseline SDI, immediate improvement in LVEF, immediate improvement in SDI, and immediate improvement in subendo- and subepicardial LV twist were significantly related to favorable outcome. At multivariable logistic regression analysis, only the immediate improvement of subepicardial LV twist was independently related to favorable outcome at 6 months (odds ratio = 2.31, 95%CI = 1.29-4.15, p = 0.005; Table 3). In

Table 3. Variables related to favorable outcome (left ventricular reverse remodeling associated to clinical improvement at 6 months follow-up)

	Univariable analysis		Multivariable analysis	
Dependent variable: favorable outcome	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Baseline independent variables:				
Age (years)	0.98 (0.93-1.03)	0.36	...	...
Male gender	0.52 (0.20-1.36)	0.18	...	...
Ischemic etiology	0.36 (0.14-0.89)	0.027	0.50 (0.16-1.55)	0.23
LV ejection fraction (%)	1.00 (0.92-1.01)	0.97	...	...
Systolic Dyssynchrony Index (%)	1.75 (1.26-2.43)	0.001	1.42 (0.96-2.01)	0.078
Peak subendocardial LV twist (°)	0.94 (0.81-1.02)	0.45	...	...
PeaK subepicardial LV twist (°)	0.81 (0.62-1.05)	0.11	...	...
Immediately after CRT independent variables:				
Δ LV ejection fraction (%)	1.25 (1.11-1.40)	<0.001	1.02 (0.87-1.21)	0.77
Δ Systolic Dyssynchrony Index (%)	0.68 (0.55-0.85)	0.001	...	...
Δ Subendocardial LV twist (°)	1.23 (1.04-1.47)	0.017	0.82 (0.63-1.08)	0.16
Δ Subepicardial LV twist (°)	2.21 (1.50-3.27)	<0.001	**2.31 (1.29-4.15)**	**0.005**

CI: confidence intervals; CRT: cardiac resynchronization therapy; LV: left ventricular; OR: odds ratio; Δ: immediate change (immediately after CRT value – baseline value)

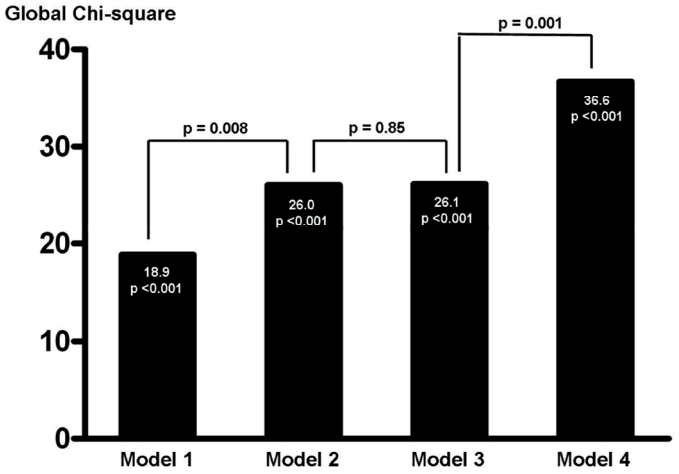

Figure 3. Incremental value of the variables detected immediately after CRT over the baseline variables. Bar graph illustrating the incremental value (depicted by chi-square value on the Y-axis) of the immediate improvement in left ventricular (LV) ejection fraction (LVEF) after cardiac resynchronization therapy (CRT) and of the immediate improvement in subendo- and subepicardial LV twist after CRT for the prediction of favorable outcome (LV reverse remodeling associated to clinical improvement at 6 months follow-up). The addition of the immediate improvement in LVEF provides incremental prognostic information to baseline variables (Model 2). Conversely, the addition of the immediate improvement of subendocardial LV twist does not add further incremental prognostic value (Model 3). Finally, the addition of the immediate improvement of subepicardial LV twist provides significant incremental prognostic information over baseline variables and the immediate improvement in LVEF (Model 4).
Model 1: baseline variables (ischemic etiology and systolic dyssynchrony index).
Model 2: model 1 + immediate improvement in LVEF.
Model 3: model 2 + immediate improvement in subendocardial LV twist.
Model 4: model 3 + immediate improvement in subepicardial LV twist.

particular, the immediate improvement of subepicardial LV twist had incremental prognostic value over baseline SDI and the immediate improvement of LVEF. In contrast, the immediate improvement of subendocardial LV twist did not provide any significant incremental prognostic value over baseline SDI and the immediate changes of LVEF (Figure 3).

DISCUSSION

The current study provides novel insights in the effects of CRT on LV mechanics by demonstrating that the immediate improvement of subepicardial LV twist after CRT was independently related to favorable outcome at 6 months follow-up. Particularly, the immediate improvement of subepicardial LV twist provided incremental prognos-

tic value over immediate improvement of LVEF, whereas the immediate improvement of subendocardial LV twist did not.

The contraction of the subepicardial fibers rotates the LV apex in the counterclockwise direction and the LV base in the clockwise direction.[13] Conversely, shortening of the subendocardial fibers rotates the LV apex and LV base in clockwise and counterclockwise directions, respectively. The larger radius of rotation for the subepicardial layer results in the subepicardial fibers having a mechanical advantage in dominating the overall direction of rotation.[13]

Advanced systolic heart failure patients have extensive LV remodeling with severely deteriorated subendo- and subepicardial LV twist, partially related to the LV dilatation and distortion of the spiral architecture of the myofibers and to the altered LV electromechanical activation.[2, 14-17] Recently, novel speckle-tracking echocardiography analysis has been introduced that permits exploration of subendo- and subepicardial LV twist,[3, 4] and this approach was applied in the current study. A typical patient population was included, characterized by end-stage systolic heart failure, dilated LV and prolonged QRS duration. The patients showed pronounced impairment of rotational parameters, and particularly subendo- and subepicardial LV twist were severely reduced (4.2 ± 2.9° and 2.3 ± 1.8°, respectively) underscoring transmural myocardial dysfunction.

It has recently been shown that CRT can increase global LV twist by restoring a more physiological LV electromechanical activation in advanced heart failure patients.[1, 17] The current findings extend these results by exploring the LV twist in the subendo- and subepicardial layers. In patients with favorable 6 months outcome after CRT (defined as improved symptoms and reverse remodeling), an acute improvement of LV twist was observed in both layers, possibly related to a (partially) restored LV electromechanical activation. These patients showed a further improvement of LV twist in both layers at 6 months follow-up, probably related to LV reverse remodeling with subsequent partial restoration of the spiral architecture of the LV myofibers. It was particularly interesting to note that the immediate improvement in subepicardial LV twist was an independent predictor of favorable outcome at 6 months follow-up, whereas the immediate improvement of subendocardial LV twist was not. Moreover, the immediate improvement in subepicardial LV twist added incremental value over the classical parameters including mechanical LV dyssynchrony and LVEF. This observation underscores that the beneficial effects of CRT at 6 months follow-up may mostly rely on the acute improvement in subepicardial LV twist. Several reasons may explain this important finding. First, subepicardial LV twist may reflect the positive effects of CRT better than subendocardial LV twist, because the subepicardial layer is the major determinant of LV twist.[13] Second, LV pacing in CRT is applied from the epicardial surface which may be more closely

related to mechanical changes in the subepicardial than the subendocardial LV layer. Finally, the immediate changes in subepicardial LV twist is more strongly related to LV energetics and LV dP/dt max than LVEF;[18] therefore, immediate improvement in subepicardial LV twist may identify patients who have better LV energetics after CRT and most likely these patients will improve clinical status and reduce LV volumes.[19]

Accordingly, immediate assessment of changes in rotational mechanics of the subepicardial layer after CRT implantation may be useful to predict a favorable mid-term outcome, although the long-term prognostic value remains to be demonstrated.

Speckle-tracking echocardiography provides reliable values of LV apical rotation, but only when acquisition of the short axis view close to the real LV apex is possible[4]; for this reason, patients without adequate apical acoustic window were excluded in the current study. Moreover, motion throughout the planes of the myocardial regions during the cardiac cycle may reduce the accuracy of speckle tracking analysis in particular at the basal level where this motion is more pronounced.

REFERENCES

(1) Bertini M, Marsan NA, Delgado V, van Bommel RJ, Nucifora G, Borleffs CJW, Boriani G, Biffi M, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Effects of cardiac resynchronization therapy on left ventricular twist. *J Am Coll Cardiol* 2009;54:1317-1325.

(2) Bertini M, Nucifora G, Marsan NA, Delgado V, van Bommel RJ, Boriani G, Biffi M, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Left ventricular rotational mechanics in acute myocardial infarction and in chronic (ischemic and nonischemic) heart failure patients. *Am J Cardiol* 2009; 103:1506-1512.

(3) Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, Weaver JA, Oryszak SJ, Greenberg NL, White RD, Thomas JD. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol* 2005;45:2034-2041.

(4) Goffinet C, Chenot F, Robert A, Pouleur AC, de Waroux JB, Vancrayenest D, Gerard O, Pasquet A, Gerber BL, Vanoverschelde JL. Assessment of subendocardial vs. subepicardial left ventricular rotation and twist using two-dimensional speckle tracking echocardiography: comparison with tagged cardiac magnetic resonance. *Eur Heart J* 2008.

(5) Delgado V, Tops LF, Trines SA, Zeppenfeld K, Marsan NA, Bertini M, Holman ER, Schalij MJ, Bax JJ. Acute effects of right ventricular apical pacing on left ventricular synchrony and mechanics. *Circ Arrhythm Electrophysiol* 2009;2:135-145.

(6) Notomi Y, Popovic ZB, Yamada H, Wallick DW, Martin MG, Oryszak SJ, Shiota T, Greenberg NL, Thomas JD. Ventricular untwisting: a temporal link between left ventricular relaxation and suction. *Am J Physiol Heart Circ Physiol* 2008;294:H505-H513.

(7) Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.

(8) Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-880.

(9) Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352: 1539-1549.

(10) Marsan NA, Bleeker GB, Ypenburg C, van Bommel RJ, Ghio S, Van D, V, Delgado V, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Real-time three-dimensional echocardiography as a novel approach to assess left ventricular and left atrium reverse remodeling and to predict response to cardiac resynchronization therapy. *Heart Rhythm* 2008;5:1257-1264.

(11) Kapetanakis S, Kearney MT, Siva A, Gall N, Cooklin M, Monaghan MJ. Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony. *Circulation* 2005;112:992-1000.

(12) Marsan NA, Bleeker GB, Ypenburg C, Ghio S, Van D, V, Holman ER, van der Wall EE, Tavazzi L, Schalij MJ, Bax JJ. Real-time three-dimensional echocardiography permits quantification of left ventricular mechanical dyssynchrony and predicts acute response to cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2008;19:392-399.

(13) Taber LA, Yang M, Podszus WW. Mechanics of ventricular torsion. *J Biomech* 1996;29:745-752.

(14) Grosberg A, Gharib M. Modeling the macro-structure of the heart: healthy and diseased. *Med Biol Eng Comput* 2009.

(15) Setser RM, Kasper JM, Lieber ML, Starling RC, McCarthy PM, White RD. Persistent abnormal left ventricular systolic torsion in dilated cardiomyopathy after partial left ventriculectomy. *J Thorac Cardiovasc Surg* 2003;126:48-55.

(16) Popescu BA, Beladan CC, Calin A, Muraru D, Deleanu D, Rosca M, Ginghina C. Left ventricular remodelling and torsional dynamics in dilated cardiomyopathy: reversed apical rotation as a marker of disease severity. *Eur J Heart Fail* 2009;11:945-951.

(17) Sade LE, Demir O, Atar I, Muderrisoglu H, Ozin B. Effect of mechanical dyssynchrony and cardiac resynchronization therapy on left ventricular rotational mechanics. *Am J Cardiol* 2008;101:1163-1169.

(18) Kim WJ, Lee BH, Kim YJ, Kang JH, Jung YJ, Song JM, Kang DH, Song JK. Apical Rotation Assessed by Speckle Tracking Echocardiography as an Index of Global Left Ventricular Contractility. *Circ Cardiovasc Imaging* 2009;2:123-131.

(19) Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, Hare JM, Kass DA. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 2000;102:3053-3059.

CHAPTER 6

Prediction of cardiac resynchronization therapy response: value of calibrated integrated backscatter imaging.

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ABSTRACT

Background. Left ventricular (LV) fibrosis is important for the response to cardiac resynchronization therapy (CRT). Calibrated integrated backscatter (IB) derived by 2D-echocardiography quantifies myocardial ultrasound reflectivity which may provide a surrogate of LV fibrosis. The aim of the study was first to investigate the relation of myocardial ultrasound reflectivity assessed with calibrated IB on CRT-response; second to explore the "myocardial ultrasound reflectivity-CRT-response" relation in ischemic and non-ischemic heart failure (HF) patients.

Methods and Results. 159 HF patients referred for CRT underwent an extensive echocardiographic evaluation at baseline and at 6-month follow-up. LV dyssynchrony was derived from speckle-tracking analysis. Calibrated IB was obtained from the parasternal long-axis view. The mean value of calibrated IB of the antero-septal and posterior wall was used to estimate myocardial ultrasound reflectivity. CRT-response was defined as reduction ≥15% of LV end-systolic volume. At baseline LV dyssynchrony was significantly larger in responders as compared to non-responders (188±96ms vs. 115±68ms, $p<0.001$) and CRT-responders showed less myocardial ultrasound reflectivity as compared to non-responders (-20.8±3.0dB vs. -17.0±3.0dB, $p<0.001$). In multivariable logistic regression analysis independent predictors for CRT-response were LV dyssynchrony, renal function and myocardial ultrasound reflectivity. Importantly, myocardial ultrasound reflectivity provided an incremental value to CRT-response (Chi-square change=40, $p<0.001$). Considering ischemic HF patients, the only independent predictor of CRT-response was myocardial ultrasound reflectivity whereas in non-ischemic HF patients independent predictors of LV reverse remodeling were myocardial ultrasound reflectivity, LV dyssynchrony and renal function.

Conclusions. Assessment of myocardial ultrasound reflectivity is important in the prediction of CRT-response in ischemic and non-ischemic patients.

INTRODUCTION

Landmark randomized clinical trials have shown the benefits of cardiac resynchronization therapy (CRT) on heart failure (HF) symptoms, left ventricular (LV) function and survival.[1, 2] Thus far, despite current selection criteria,[3] up to 30% of the patients does not show clinical response to CRT. Furthermore, considering LV reverse remodeling as end-point of the treatment, non-response rate is even higher (40-45%).[4]

Among different reasons proposed to explain the lack of response to CRT, the etiology of HF remains still controversial. In the CARE-HF trial, ischemic HF patients showed a reduction in LV volumes or improvement in LV function to a lesser degree than non-ischemic HF patients.[5, 6] Previous data suggest that the extent and location of LV fibrosis, strongly influence response to CRT in patients with ischemic etiology of HF.[7-12] The presence of LV fibrosis has been also demonstrated in mixed population of ischemic and non-ischemic HF patients.[13] However, particularly in non-ischemic HF patients, little is known about the influence of the LV fibrosis on CRT response. At present, contrast-enhanced cardiac magnetic resonance (CMR) is considered the gold standard to detect LV fibrosis,[14] but its use is limited by low availability.[15] Two-dimensional (2D) echocardiography imaging is more widely available than contrast-enhanced CMR and, ultrasonic integrated backscatter (IB) derived by 2D echocardiography provides information on myocardial ultrasound reflectivity which may be a surrogate for fibrosis of the insonified tissue.[16, 17] Recent studies demonstrated the use of this technique in different groups of patients to characterize myocardial ultrasound reflectivity.[18-20] The echocardiographic assessment of myocardial ultrasound reflectivity along with the evaluation of LV mechanical dyssynchrony may provide more comprehensive and valuable information to select candidates to CRT. In the current study calibrated IB was used to quantify myocardial ultrasound reflectivity in HF candidates for CRT. The aim of the study was twofold: first to investigate the influence of myocardial ultrasound reflectivity on CRT-response in general; second to explore the "myocardial ultrasound reflectivity -CRT response" relation specifically in ischemic and non-ischemic HF patients.

METHODS

Patient population and protocol

A total of 184 consecutive HF patients scheduled for CRT were prospectively included. According to current guidelines, the inclusion criteria were: New York Heart Association (NYHA) functional class III-IV, sinus rhythm, LV ejection fraction (LVEF)≤35% and QRS duration≥120 ms.[3] Etiology of HF was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization.

All patients underwent a clinical and echocardiographic evaluation at baseline and 6 months after CRT assessing NYHA functional class, hemoglobin and renal function,[21] LV volumes and LVEF. Finally, the extent of myocardial ultrasound reflectivity was estimated as the mean of calibrated IB of the antero-septal and posterior walls in order to: 1. determine the role of myocardial ultrasound reflectivity on CRT-response; 2. study the relation between myocardial ultrasound reflectivity and CRT-response in ischemic and non-ischemic HF patients.

Standard echocardiography

All patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwakee, Wisconsin, USA). Standard 2D images were obtained using a 3.5-MHz transducer and, digitally stored in cine-loop format; the analysis was performed offline using EchoPAC version 7.0.0 (General Electric-Vingmed).

From the standard apical views (4- and 2-chamber) LV volumes and LVEF were calculated according to the American Society of Echocardiography guidelines.[22] At 6 months follow-up, patients were classified as echocardiographic responders based on a reduction ≥15% of LV end-systolic volume (LVESV).[4]

Mechanical dyssynchrony

In the current study 2 types of mechanical dyssycnhrony were assessed: the interventricular mechanical dyssynchrony and the intra-LV mechanical dyssynchrony (LV dyssynchrony). Interventricular mechanical dyssynchrony was quantified using the interventricular mechanical dyssynchrony index.[2] LV dyssynchrony was assessed using speckle-tracking echocardiography.[23] LV dyssynchrony was derived from the radial

strain curves obtained at the 2D gray scale images of the mid-ventricular short-axis (frame rate ranged from 45 to 100 frame/s). As previously described, LV dyssynchrony was defined as the time to peak radial strain difference between the antero-septal and posterior segments.[24]

Calibrated integrated backscatter

Calibrated IB is a parameter based on gray-scale 2D images which evaluates myocardial ultrasound reflectivity. In the heart, the pericardium is the anatomic structure with the highest content of fibrosis and with the highest ultrasound reflectivity; whereas blood pool has the lowest ultrasound reflectivity since no fibrous tissue exists. The myocardium shows an intermediate ultrasound reflectivity and this reflectivity may increase together with the amount of fibrosis.[16, 18-20] Gray-scale 2D images were obtained at parasternal long-axis view, with frame rates between 80 and 120 frames/s, depending on the sector width, and 3 cardiac cycles were stored in cine-loop format for the offline analysis (EchoPAC version 7.0.0, General Electric-Vingmed). A fixed 9x9-mm region of interest was positioned in the mid-myocardium of the antero-septal and posterior walls of the LV and a fixed 2x3-mm region of interest was positioned in the pericardium. A measure of myocardial ultrasound reflectivity or tissue density was obtained with calibrated IB by subtracting pericardial IB intensity from myocardial IB intensity of the LV antero-septal and LV posterior walls. The measurements of calibrated IB were performed at a fixed point in the cardiac cycle (peak of the QRS complex) and expressed in decibel (dB).[16, 18-20] The mean value of calibrated IB of the LV antero-septal and posterior walls was calculated to indicate the myocardial ultrasound reflectivity (Figure 1).[16]

CRT implantation

All patients received a biventricular pacemaker with cardioverter-defibrillator function (Contak Renewal, Cognis, Boston Scientific St. Paul, Minnesota; or InSync Sentry, Consulta, Medtronic Inc. Minneapolis, Minnesota; Lumax 340 HF-T, Biotronik, Berlin). The right atrial and ventricular leads were positioned conventionally. All LV leads were implanted transvenously, and placed preferably in a (postero-)lateral vein. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to place the LV lead (Easytrak, Boston Scientific, or Attain-SD, Medtronic, or Corox OTW Biotronik) in the coronary sinus.

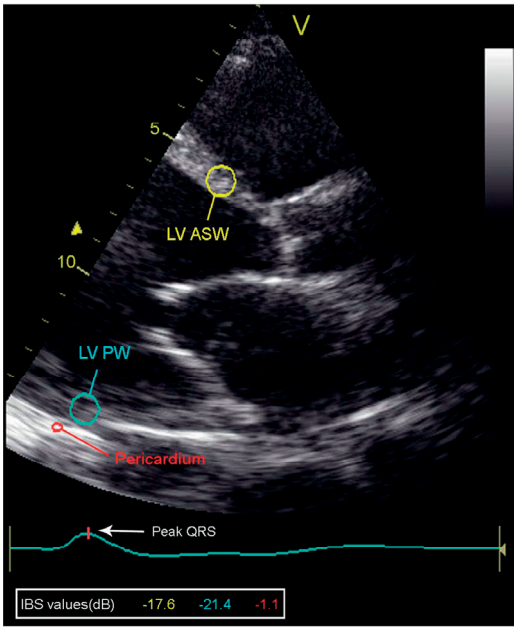

Figure 1: Example of assessment of LV fibrosis in the antero-septal and posterior walls with calibrated IB. A fixed 9x9-pixel region of interest was positioned in the mid-myocardium of the antero-septal (ASW) and posterior wall (PW) and a fixed 2x3-pixel region of interest was positioned in the pericardium. In this patient example, calibrated IB for the ASW is calculated by subtracting the pericardial IB intensity (-1.1dB) from the ASW IB intensity (-17.6dB), and the calibrated IB for the PW is calculated by subtracting the pericardial IB intensity (-1.1dB) from the PW IB intensity (-21.4dB). This results in calibrated IB of the ASW and PW of -16.5dB and -20.3dB, respectively. Accordingly, the mean calibrated IB was -18.4dB.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical data are presented as numbers and percentages. Unpaired T test was used to compare continuous variables between HF patients with vs. without 6 months follow-up, responders vs. non-responders, and ischemic vs. non-ischemic HF patients. Paired T test was used to compare baseline and 6 months follow-up data either in responders and non-responders. Chi-square test was used to compare categorical variables. To determine the reproducibility of calibrated IB, 20 HF patients were randomly selected. For each of the selected patients, the measurements of calibrated IB were repeated by the same observer in a blinded-fashion and at a separate time (1 week later). To evaluate interobserver variability, a second independent observer re-analyzed the same dataset.

Intra- and inter-observer variability were assessed using intraclass correlation co-efficients.

Linear regression analysis was performed to assess the correlation between the relative change of LVESV and calibrated IB in the overall population, in ischemic and non-ischemic HF patients.

In order to identify variables related to a positive response to CRT, uni- and multivariable logistic regression analyses were performed including baseline clinical (age, gender, etiology, NYHA functional class, QRS duration, renal function and hemoglobin) and baseline echocardiographic (LVESV, LVEF, LV dyssynchrony, calibrated IB) characteristics of the patients. Only variables with $p<0.10$ in univariable analysis were entered as covariates in the multivariable model. The multivariable logistic regression analysis was performed using a forward selection method with entry p value <0.05. Model discrimination was assessed using c-statistic and model calibration using Hosmer-Lemeshow statistic. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. To increase clinical utility, OR and 95%CI of continuous variables were reported as per 1 year increase in age, per 10ms increase in QRS width at baseline, per 30ml/min increase in estimated glomerular filtration rate, per 1mmol/ l increase in hemoglobin, per 50ml increase in LVESV, per 5% increase in LVEF, per 50ms increase in LV dyssynchrony, and per 5dB increase in calibrated IB. The incremental value of myocardial ultrasound reflectivity over other variables was assessed by calculating the global chi-square test for each model. In order to identify variables related to a positive response to CRT in the subgroups of patients with ischemic and non-ischemic etiology of heart failure, uni- and multivariable logistic regression analyses were performed including the same baseline variables as indicated above, using the same inclusion criteria for the multivariable logistic regression analysis.

All statistical tests were 2-sided, and a p value<0.05 was considered significant. The statistical software program SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

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

RESULTS

In 13(7%) of 184 patients, calibrated IB analysis was not feasible due to suboptimal gray-scale 2D images with poor differentiation between myocardium and pericardium, and these patients were excluded from the analysis. Furthermore, of the 171 patients included, 12(7%) did not complete the 6 months follow-up; 4 patients died, 2 patients had LV pacing switched off due to intolerable phrenic stimulation and 6 patients were

lost to follow-up. Therefore, baseline and 6 months follow-up data were available for 159 patients.

Patient population

The general characteristics of the overall patient population are summarized in Table 1.

The mean age was 66±10 years and 132 patients were male. Importantly, 58% of the patients had ischemic etiology of HF; the mean LV end-diastolic volume (LVEDV) was 218±81ml and the mean LVEF was 25±7%. No significant differences were observed between HF patients with and without 6 months follow-up data.

Calibrated integrated backscatter

The mean myocardial ultrasound reflectivity of the LV at baseline quantified with calibrated IB was -19.2±3.7dB. The intra- and inter-observer agreements for calibrated IB were 0.91 and 0.92, respectively.

In addition, myocardial ultrasound reflectivity was not related to QRS duration ($r=0.09$, $p=0.24$), whereas a weak but significant inverse relation between myocardial ultrasound reflectivity and renal function ($r=-0.17$, $p=0.039$) was observed.

Responders vs. non-responders

Table 2 shows the baseline clinical characteristics of CRT responders and non-responders. There were no differences in clinical characteristics, although non-responders showed a trend to higher prevalence of ischemic etiology ($p=0.10$). Conversely, QRS duration, estimated glomerular filtration rate and hemoglobin were higher in responders as compared to non-responders. There were no differences in baseline LV volumes and LVEF for responders and non-responders (Table 3). LV dyssynchrony was significantly larger in responders as compared to non-responders (188±96ms vs. 115±68ms, $p<0.001$), whereas only a trend towards a larger interventricular dyssynchrony in responders as compared to non-responders was observed (41±23 ms vs. 35±33ms, $p=0.17$). Finally, CRT responders showed lower myocardial ultrasound reflectivity as compared to non-responders (-20.8±3.0dB in responders vs. -17.0±3.0dB in non-responders, $p<0.001$; Table 3).

Table 1. Baseline characteristics of heart failure (HF) patients.

	Overall HF patients (n=171)	**HF patients with 6 months follow-up** (n=159)	**HF patients without 6 months follow-up** (n=12)	**HF patients with vs. without 6 months follow-up** p value
Age (years)	66±10	66±10	66±10	0.99
Gender (male/female)	132/39	123/36	9/3	0.85 (df=1)
NYHA class (III/IV)	157/14	147/12	10/2	0.27 (df=1)
QRS duration (ms)	154±32	154±32	150±20	0.63
Estimated glomerular filtration rate (ml/min)	70.9±33.2	70.9±33.2	70.8±33.0	0.99
Hemoglobin (mmol/l)	8.2±0.9	8.2±0.9	8.3±0.8	0.64
Etiology, n(%)				
Ischemic	99(58)	93(58)	6(50)	0.57 (df=1)
Non-ischemic	72(42)	66(42)	6(50)	
Medication, n(%)				
ACE Inhibitors	154(90)	144(91)	10(83)	0.69 (df=1)
β-blockers	149(87)	137(86)	12(100)	0.35 (df=1)
Diuretics and/or				
Spironolactone	145(85)	134(84)	11(92)	0.74 (df=1)
(Postero-)lateral LV lead, n(%)	161(94)	151(95)	10(83)	0.28
LVEDV (ml)	218±81	218±81	240±86	0.35
LVESV (ml)	167±71	167±71	190±70	0.28
LVEF (%)	25±7	25±7	22±6	0.12
Interventricular dyssynchrony (ms)	39±28	33±29	33±17	0.96
LV dyssynchrony (ms)	157±92	157±92	155±81	0.96
Calibrated IB (dB)	-19.2± 3.7	-19.2± 3.7	-18.8± 3.0	0.70

dB: decibels, df: degree of freedom; IB: integrated backscatter LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume, NYHA: New York Heart Association.

At 6 months follow-up, only responders showed a significant decrease in LVEDV and LVESV (by definition), with a significant increase in LVEF (Table 3). In addition,

Table 2. Clinical characteristics of responders vs. non-responders at baseline.

	Responders (n=91)	Non-responders (n=68)	p value
Age (years)	65±9	67±11	0.43
Gender (male/female)	71/20	52/16	0.85 (df=1)
Medication, n(%)			
ACE Inhibitors	83(91)	61(90)	0.95 (df=1)
β-blockers	78(86)	59(87)	0.96 (df = 1)
Diuretics and/or			
Spironolactone	77(85)	57(84)	0.96 (df = 1)
Etiology, n(%)			
Ischemic	48(53)	45(66)	
Non-ischemic	43(47)	23(44)	0.10 (df=1)
QRS duration (ms)	159±32	148±32	0.028
Estimated glomerular filtration rate (ml/min)	76±31	64±35	0.023
Hemoglobin (mmol/l)	8.4±0.9	8.0±0.9	0.040
NYHA class (III/IV)	85/6	62/6	0.60 (df=1)

Abbreviations see Table 1.

responders revealed a more synchronous LV contraction after 6 months of CRT whereas in non-responders the LV dyssynchrony remained unchanged (Table 3).

Of note, the relative change in LVESV (delta LVESV %) at 6 months follow-up was significantly related to calibrated IB (r=0.50, p<0.001; Figure 2A).

Prediction of LV reverse remodeling

At univariable logistic regression, ischemic etiology, QRS duration, estimated glomerular filtration rate, hemoglobin, LV dyssynchrony, calibrated IB were significantly related to LV reverse remodeling at 6 months follow-up (Table 4). At multivariable logistic regression analysis, the independent predictors of response to CRT were estimated glomerular filtration rate, LV dyssynchrony and calibrated IB (Table 4). Furthermore, calibrated IB had incremental value over LV dyssynchrony and estimated glomerular filtration rate for prediction of response to CRT (chi-square change=40, p<0.001, degree of freedom=1).

Table 3. Standard echocardiographic variables and calibrated IB in responders vs. non-responders at baseline and 6 months follow-up.

	Responders (n=91)	**Non-responders** (n=68)	**p value** (responders vs. non-responders)
LVEDV (ml)			
Baseline	223± 81	211±80	0.34
6 months follow-up	186±71*	212±84	0.045
LVESV (ml)			
Baseline	173±72	159±69	0.22
6 months follow-up	123±57*	161±73†	0.001
LVEF (%)			
Baseline	24±7	26±7	0.058
6 months follow-up	36±8*	26±7	<0.001
LV dyssynchrony (ms)			
Baseline	188±96	115 ± 68	<0.001
6 months follow-up	80±132*	125 ± 121	0.032
Calibrated IB (dB)			
Baseline	-20.8±3.0	-17.0±3.0	<0.001
6 months follow-up	-21.9±3.2†	-15.6±3.5†	<0.001

*=p<0.001 baseline vs. 6 month follow-up; † =p<0.05 baseline vs. 6 month follow-up.
Abbreviations see Table 1.

Ischemic vs. non-ischemic etiology of heart failure

Of the 159 patients with 6 months follow-up data, 93 patients had ischemic etiology of HF, whereas 66 had a non-ischemic HF. The baseline clinical characteristics were not different between patients with ischemic and non-ischemic cardiomyopathy. Conversely, patients with ischemic cardiomyopathy had significantly higher LVEF (26±7% vs. 23±7%, p<0.001) and less LV dyssynchrony (144±92ms vs. 175±90ms, p=0.036) as compared to patients with non-ischemic cardiomyopathy. In addition, myocardial ultrasound reflectivity estimated with calibrated IB was higher in patients with ischemic as compared to non-ischemic cardiomyopathy (-18.5±3.8dB vs. -20.2± 3.0dB,

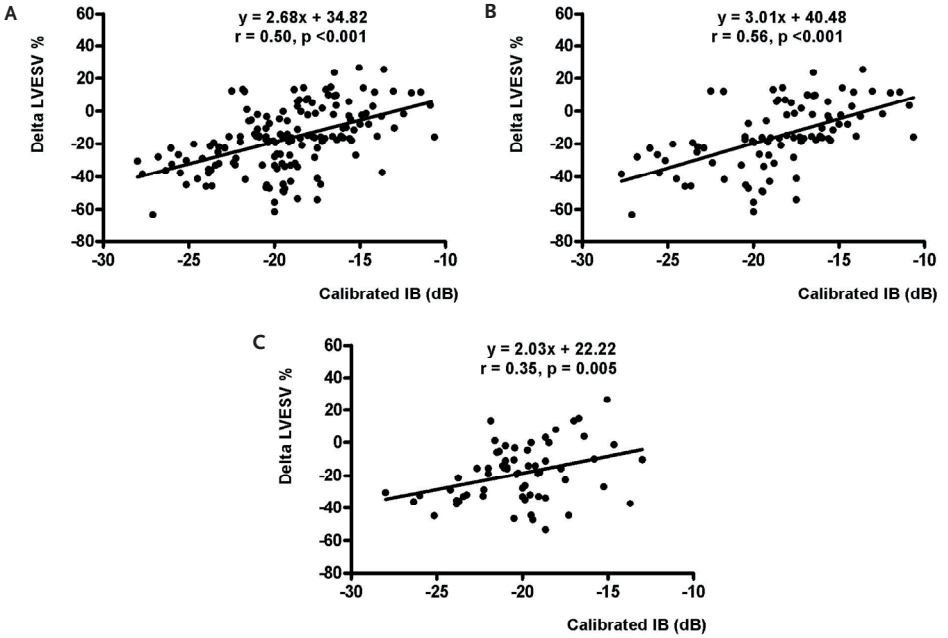

Figure 2A. Panel A: Relation between the relative change of LVESV at 6 months follow-up (delta LVESV) and calibrated integrated backscatter (IB) in the overall population. **Panel B:** Relation between the delta LVESV in ischemic HF patients and calibrated IB. **Panel C:** Relation between the delta LVESV in non-ischemic HF patients and calibrated IB.

p=0.002). Finally, the relationship between the relative change of LVESV at 6 months follow-up and calibrated IB was stronger in patients with ischemic cardiomyopathy (r=0.56, p<0.001; Figure 2B) as compared to patients with non-ischemic HF (r=0.35, p=0.005; Figure 2C).

Prediction of LV reverse remodeling in ischemic etiology

In the subgroup of patients with ischemic HF, in univariable logistic regression, LVEF, LV dyssynchrony, calibrated IB were significantly related to LV reverse remodeling at 6 months follow-up (Table 5). In multivariable logistic regression analysis, the only independent predictor of response to CRT was calibrated IB (Table 5).

Table 4. Multivariable logistic regression analysis for prediction of response to CRT (defined as reduction in LVESV≥15%)

Dependent variable: Response to CRT at 6 months follow-up	**Univariable analysis**		**Multivariable analysis**	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
Independent variables				
Age (per 1 years)	0.98(0.96-1.02)	0.42		
Female gender	1.09(0.52-2.31)	0.82		
Ischemic etiology	0.58(0.30-1.09)	0.09	...	...
NYHA class IV	0.73(0.22-2.37)	0.60		
QRS width at baseline (per 10ms)	1.12(1.01-1.24)	0.029	...	...
Estimated glomerular filtration rate (per 30ml/min)	1.43(1.04-1.96)	0.026	1.93(1.26-2.95)	**0.003**
Hemoglobin (per 1mmol/l)	1.46(1.01-2.12)	0.043	...	...
LVESV at baseline (per 50ml)	1.15(0.92-1.45)	0.22		
LVEF at baseline (per 5%)	0.80(0.63-1.01)	0.060	...	...
LV dyssynchrony at baseline (per 50ms)	1.77(1.38-2.28)	<0.001	1.90(1.39-2.59)	**<0.001**
Calibrated IB (per 5dB)	0.11(0.05-0.24)	<0.001	0.10(0.04-0.25)	**<0.001**

c-statistic: 0.89
Hosmer and Lemeshow Test: chi-square=9.5, p=0.30 (df=8)
CI: confidence intervals; CRT: cardiac resynchronization therapy; df: degree of freedom; IB: integrated backscatter; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; OR: odds ratio.

Prediction of LV reverse remodeling in non-ischemic etiology

In the subgroup of patients with non-ischemic etiology of HF, in univariable logistic regression, estimated glomerular filtration rate, LV dyssynchrony and calibrated IB were significantly related to LV reverse remodeling at 6 months follow-up (Table 6). In multivariable logistic regression analysis, these variables were all independent predictors of response to CRT (Table 6).

Table 5. Univariable and multivariable logistic regression analysis for prediction of response to CRT (defined as reduction in LVESV≥15%) in ischemic heart failure

Dependent variable: Response to CRT at 6 months follow-up	**Univariable analysis**		**Multivariable analysis**	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
Independent variables				
Age (per 1 years)	0.98(0.94-1.03)	0.45		
Female gender	0.68(0.23-2.02)	0.49		
QRS width at baseline (per 10ms)	1.13(1.00-1.27)	0.053	...	...
Estimated glomerular filtration rate (per 30ml/min)	1.30(0.90-1.89)	0.16		
Hemoglobin (per 1mmol/l)	1.51(0.91-2.48)	0.11		
LVESV at baseline (per 50ml)	1.21(0.89-1.66)	0.23		
LVEF at baseline (per 5%)	0.71(0.51-0.99)	0.041	...	...
LV dyssynchrony at baseline (per 50ms)	1.37(1.06-1.78)	0.017	...	...
Calibrated IB (per 5dB)	0.07(0.02-0.23)	<0.001	0.07(0.02-0.23)	**<0.001**

c-statistic: 0.87
Hosmer and Lemeshow Test: chi-square=12.6, p=0.13 (df=8)
Abbreviations as in Table 4

DISCUSSION

The current study investigated the role of LV fibrosis in the prediction of CRT response and demonstrated that: 1) myocardial ultrasound reflectivity assessed with calibrated IB together with LV mechanical dyssynchrony and renal function were the major determinants of LV reverse remodeling after CRT; 2) myocardial ultrasound reflectivity assessed with calibrated IB provided incremental value over LV mechanical dyssynchrony and renal function for prediction of CRT response; 3) myocardial ultrasound reflectivity was the only independent predictor of CRT response in patients with ischemic HF; 4) myocardial ultrasound reflectivity was also an independent determinant of CRT response in non-ischemic HF.

Myocardial ultrasound reflectivity with calibrated IB

Currently, contrast-enhanced CMR provides accurate assessment of the extent of LV fibrosis with high spatial resolution, but CMR remains limited for daily practice.[14] Two-

Table 6. Univariable and multivariable logistic regression analysis for prediction of response to CRT (defined as reduction in LVESV≥15%) in non-ischemic heart failure

Dependent variable: Response to CRT at 6 months follow-up	**Univariable analysis**		**Multivariable analysis**	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
Independent variables				
Age (per 1 years)	0.99(0.94-1.05)	0.86		
Female gender	0.99(0.33-2.95)	0.99		
QRS width at baseline (per 10ms)	1.04(0.85-1.28)	0.67		
Estimated glomerular filtration rate (per 30ml/min)	1.93(1.04-3.56)	0.036	5.76(1.55-21.4)	**0.009**
Hemoglobin (per 1mmol/l)	1.29(0.72-2.29)	0.39		
LVESV at baseline (per 50ml)	1.03(0.73-1.45)	0.86		
LVEF at baseline (per 5%)	1.02(0.70-1.49)	0.87		
LV dyssynchrony at baseline (per 50ms)	4.03(1.90-8.58)	<0.001	6.94(2.14-22.48)	**0.001**
Calibrated IB (per 5dB)	0.20(0.06-0.60)	0.004	0.06(0.01-0.60)	**0.017**

c-statistic: 0.94
Hosmer and Lemeshow Test: chi-square=2.5, p=0.96 (df=8)
Abbreviations as in Table 4

dimensional echocardiography permits assessment of myocardial ultrasound reflectivity or tissue density using calibrated IB analysis. The analysis of myocardial reflectivity with IB relies on the quantification of ultrasonic energy returned to the transducer after interactions with individual scattering elements within the myocardium.[16-20, 25] Picano et al.[16] showed a modest but significant relation (r=0.55, p<0.05) between the percent connective tissue area determined in histologic sections of myocardial biopsies obtained from the LV septum and the ultrasonic reflectivity of the same region of myocardium assessed with 2D echocardiography. Moreover, experimental and clinical studies demonstrated the usefulness of this technique for the detection of subtle alterations of myocardial function and structure.[17-20, 25] In an animal model, Perez et al.[17] found that myocardial areas with increased IB corresponded histologically to discrete fibrocalcific lesions whereas areas with normal IB corresponded to normal myocardium.

The present study explored the value of calibrated IB to estimate myocardial ultrasound reflectivity as a surrogate of LV fibrosis in HF patients who are candidates for CRT. No significant relation was found between myocardial ultrasound reflectivity and QRS duration. Furthermore, although QRS duration was larger in non-ischemic as compared to ischemic HF patients (162±25 ms vs. 149±35ms, p=0.006), myocar-

dial ultrasound reflectivity was higher in ischemic as compared to non-ischemic HF patients (-18.5±3.8dB vs. -20.2±3.0dB, p=0.002). These results extend the findings of previous studies indicating the lack of relation between the QRS duration and fibrosis in dilated cardiomyopathy.[26] Therefore, the extent of fibrosis or a surrogate such as myocardial ultrasound reflectivity can not be estimated by the QRS duration on the surface ECG. In addition, renal function was weakly but significantly related to myocardial ultrasound reflectivity underscoring that worse renal function was associated with higher IB reflectivity (possibly indicating more extensive LV fibrosis).[27]

Myocardial ultrasound reflectivity and CRT response

Previous studies showed that beyond mechanical dyssynchrony, the quantification of myocardial fibrosis is an important pathophysiological determinant of CRT response. In particular, studies performed with nuclear imaging and contrast-enhanced CMR underscored the importance of the assessment of LV fibrosis for clinical and echocardiographic response to CRT.[7, 10-12, 28, 29] For example, White et al.[29] studied 23 HF patients with previous myocardial infarction and demonstrated that the extent of scar tissue in the LV, assessed with contrast-enhanced CMR, was significantly less in CRT responders as compared to non-responders (1.0% vs. 24.7%, p=0.002). Furthermore, a recent study from Bilchick and colleagues[13] used CMR to assess both mechanical dyssynchrony and LV fibrosis in a small group of 20 HF patients with ischemic and non-ischemic etiology referred for CRT. The authors showed that the combined approach (assessment of mechanical dyssynchrony and quantification of LV fibrosis) significantly improved predictive accuracy for clinical CRT response.

In the current study, mechanical dyssynchrony and myocardial ultrasound reflectivity (a potential surrogate of LV fibrosis) were comprehensively evaluated with 2D echocardiography techniques (speckle-tracking imaging and calibrated IB). Myocardial ultrasound reflectivity was larger in non-responders as compared to responders (-17.0±3.0dB vs. -20.8±3.0dB, respectively, p<0.001). Moreover, myocardial ultrasound reflectivity was directly related to the extent of reverse remodeling after CRT and provided incremental value over LV dyssynchrony and renal function for prediction of CRT response, in line with previous studies.[24, 30, 31]

Myocardial ultrasound reflectivity in ischemic and non-ischemic HF patients

Various studies have focused on the relation between LV fibrosis and CRT response in ischemic HF patients.[7, 10-12, 28, 29] In particular, Ypenburg et al.[11] demonstrated in 34

ischemic HF patients the close relation between the total scar burden assessed with contrast-enhanced CMR and LV reverse remodeling after CRT ($r=0.91$, $p<0.05$). In the present study, in ischemic HF patients, the amount of myocardial ultrasound reflectivity was not only significantly related to LV reverse remodeling, but also the strongest independent predictor of LV reverse remodeling. These findings underscore the relevance of this indirect parameter of LV fibrosis for CRT response in the setting of ischemic HF.

Few studies have reported on the presence of LV fibrosis in patients with non-ischemic dilated cardiomyopathy,[14, 32] but none have explored the relation between LV fibrosis and CRT response in patients with non-ischemic HF. The current results demonstrated a significant direct relation between the extent of myocardial ultrasound reflectivity, as a potential surrogate of LV fibrosis, and LV reverse remodeling after CRT. Moreover, in non-ischemic HF patients myocardial ultrasound reflectivity was an important and independent predictor of CRT response. Accordingly, the current findings underscore the role of the assessment of myocardial ultrasound reflectivity to improve CRT response rate in non-ischemic HF patients.

Study limitations

As previously described,[16, 18-20] calibrated IB assessed in the antero-septal and posterior wall was used to detect myocardial ultrasound reflectivity. The measurement of calibrated IB in the antero-septal and posterior wall is dependent on ultrasound machine settings (focus, depth, gain and insonation angle). These settings were adjusted in all patients in order to optimize the image quality for offline analysis. In addition, by correcting calibrated IB of the antero-septal and posterior walls for the calibrated IB of the pericardium, the effect of these technical issues on the accuracy of this analysis may be minimized. In addition, no independent technique as CMR was used to prove the association between myocardial ultrasound reflectivity and fibrosis. However, previous studies showed a potential relation between myocardial ultrasound reflectivity and fibrosis.[16, 17]

CONCLUSIONS

In the current study, myocardial ultrasound reflectivity assessed with calibrated IB was related to CRT-response. In particular, myocardial ultrasound reflectivity provided incremental value to CRT response over mechanical LV dyssynchrony and renal function. Furthermore, myocardial ultrasound reflectivity was a strong determinant of LV reverse remodeling after CRT, both in ischemic and non-ischemic HF patients.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352: 1539-1549.
3. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC, Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005;112: e154-e235.
4. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J, III, St John SM, De SJ, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608-2616.
5. Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am Coll Cardiol* 2008;52:438-445.
6. Wikstrom G, Blomstrom-Lundqvist C, Andren B, Lonnerholm S, Blomstrom P, Freemantle N, Remp T, Cleland JG. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. *Eur Heart J* 2009;30:782-788.
7. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de RA, van der Wall EE, Schalij MJ, Bax JJ. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. *Circulation* 2006;113:969-976.
8. Hummel JP, Lindner JR, Belcik JT, Ferguson JD, Mangrum JM, Bergin JD, Haines DE, Lake DE, DiMarco JP, Mounsey JP. Extent of myocardial viability predicts response to biventricular pacing in ischemic cardiomyopathy. *Heart Rhythm* 2005;2:1211-1217.
9. Rocchi G, Bertini M, Biffi M, Ziacchi M, Biagini E, Gallelli I, Martignani C, Cervi E, Ferlito M, Rapezzi C, Branzi A, Boriani G. Exercise stress echocardiography is superior to rest echocardiography in predicting left ventricular reverse remodelling and functional improvement after cardiac resynchronization therapy. *Eur Heart J* 2009;30:89-97.
10. Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, bbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J* 2007;28:33-41.
11. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de RA, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol* 2007;99:657-660.
12. Chalil S, Foley PW, Muyhaldeen SA, Patel KC, Yousef ZR, Smith RE, Frenneaux MP, Leyva F. Late gadolinium enhancement-cardiovascular magnetic resonance as a predictor of response to

cardiac resynchronization therapy in patients with ischaemic cardiomyopathy. *Europace* 2007;9: 1031-1037.

13. Bilchick KC, Dimaano V, Wu KC, Helm RH, Weiss RG, Lima JA, Berger RD, Tomaselli GF, Bluemke DA, Halperin HR, Abraham T, Kass DA, Lardo AC. Cardiac magnetic resonance assessment of dyssynchrony and myocardial scar predicts function class improvement following cardiac resynchronization therapy. *JACC Cardiovasc Imaging* 2008;1:561-568.
14. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, Kaye DM, Taylor AJ. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol* 2008;52:1574-1580.
15. Abraham TP, Kass D, Tonti G, Tomassoni GF, Abraham WT, Bax JJ, Marwick TH. Imaging Cardiac Resynchronization Therapy. *J Am Coll Cardiol Img* 2009;2:486-497.
16. Picano E, Pelosi G, Marzilli M, Lattanzi F, Benassi A, Landini L, L'Abbate A. In vivo quantitative ultrasonic evaluation of myocardial fibrosis in humans. *Circulation* 1990;81:58-64.
17. Perez JE, Barzilai B, Madaras EI, Glueck RM, Saffitz JE, Johnston P, Miller JG, Sobel BE. Applicability of ultrasonic tissue characterization for longitudinal assessment and differentiation of calcification and fibrosis in cardiomyopathy. *J Am Coll Cardiol* 1984;4:88-95.
18. Mottram PM, Haluska B, Yuda S, Leano R, Marwick TH. Patients with a hypertensive response to exercise have impaired systolic function without diastolic dysfunction or left ventricular hypertrophy. *J Am Coll Cardiol* 2004;43:848-853.
19. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. *Circulation* 2004;110:3081-3087.
20. Yuda S, Fang ZY, Marwick TH. Association of severe coronary stenosis with subclinical left ventricular dysfunction in the absence of infarction. *J Am Soc Echocardiogr* 2003;16:1163-1170.
21. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
22. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.
23. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-1029.
24. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;113:960-968.
25. Logan-Sinclair R, Wong CM, Gibson DG. Clinical application of amplitude processing of echocardiographic images. *Br Heart J* 1981;45:621-627.
26. Yamada T, Fukunami M, Ohmori M, Iwakura K, Kumagai K, Kondoh N, Tsujimura E, Abe Y, Nagareda T, Kotoh K, . New approach to the estimation of the extent of myocardial fibrosis in patients with dilated cardiomyopathy: use of signal-averaged electrocardiography. *Am Heart J* 1993;126:626-631.
27. Salvetti M, Muiesan ML, Paini A, Monteduro C, Bonzi B, Galbassini G, Belotti E, Movilli E, Cancarini G, gabiti-Rosei E. Myocardial ultrasound tissue characterization in patients with chronic renal failure. *J Am Soc Nephrol* 2007;18:1953-1958.

28. Sciagra R, Giaccardi M, Porciani MC, Colella A, Michelucci A, Pieragnoli P, Gensini G, Pupi A, Padeletti L. Myocardial perfusion imaging using gated SPECT in heart failure patients undergoing cardiac resynchronization therapy. *J Nucl Med* 2004;45:164-168.
29. White JA, Yee R, Yuan X, Krahn A, Skanes A, Parker M, Klein G, Drangova M. Delayed enhancement magnetic resonance imaging predicts response to cardiac resynchronization therapy in patients with intraventricular dyssynchrony. *J Am Coll Cardiol* 2006;48:1953-1960.
30. Delgado V, Ypenburg C, van Bommel RJ, Tops LF, Mollema SA, Marsan NA, Bleeker GB, Schalij MJ, Bax JJ. Assessment of left ventricular dyssynchrony by speckle tracking strain imaging comparison between longitudinal, circumferential, and radial strain in cardiac resynchronization therapy. *J Am Coll Cardiol* 2008;51:1944-1952.
31. Fung JW, Szeto CC, Chan JY, Zhang Q, Chan HC, Yip GW, Yu CM. Prognostic value of renal function in patients with cardiac resynchronization therapy. *Int J Cardiol* 2007;122:10-16.
32. Bogun FM, Desjardins B, Good E, Gupta S, Crawford T, Oral H, Ebinger M, Pelosi F, Chugh A, Jongnarangsin K, Morady F. Delayed-enhanced magnetic resonance imaging in nonischemic cardiomyopathy: utility for identifying the ventricular arrhythmia substrate. *J Am Coll Cardiol* 2009; 53:1138-1145.

CHAPTER 7

Why, how and when do we need to optimize the setting of cardiac resynchronization therapy?

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1. INTRODUCTION

At present, up to 40% of patients do not show improvement in left ventricular (LV) performance or clinical symptoms after cardiac resynchronization therapy (CRT).[1] This suboptimal response may be secondary to several pre-implantation and implantation issues such as lack of LV mechanical dyssynchrony, the presence of substantial scar tissue or non-optimal LV lead position.[2] Furthermore, the presence of suboptimal LV filling time (atrioventricular [AV] dyssynchrony) or remaining LV dyssynchrony after CRT may reduce benefit of this therapy.[3] Current CRT devices allow manipulation of the AV and interventricular (VV) timings in order to maximize LV filling and stroke volume. However, multiple single center and few multicenter trials have provided controversial data on the beneficial effects of AV and VV intervals optimization on cardiac performance and clinical status.[4-7] In addition, multiple methodologies have been proposed to optimize AV and VV intervals but no consensus has been reached on which methodology should preferably be used.[4-7] Finally, whether AV and VV intervals may be evaluated and adjusted periodically remains also controversial.[8-10] The present article reviews the clinical evidence on AV and VV interval optimization by addressing why, how and when we need to optimize AV and VV intervals.

2. WHY DO WE NEED TO OPTIMIZE CRT SETTING?

Management of heart failure patients after CRT implantation should include the evaluation of the effects of CRT on LV hemodynamics and mechanics. A suboptimal programming of the AV and/or VV interval may partially contribute to the presence of AV or LV dyssynchrony and, consequently, may curtail the beneficial effects of CRT. The hemodynamic importance of AV interval optimization was first demonstrated in studies with dual chamber pacemakers; next, these benefits were confirmed also in CRT recipients.[3, 11] Auricchio et al. demonstrated in 39 heart failure patients treated with CRT that the maximum rate of increase of LV pressure (dP/dt_{max}) and pulse pressure were measured at different AV and VV intervals. The maximum hemodynamic benefit occurred at the AV interval that provided the optimal LV diastolic filling and did not decrease the LV end-diastolic pressure.[3] In addition, several prospective studies have demonstrated the benefits of tailored optimized sequential biventricular pacing strategies.[12, 13] In 41 heart failure patients receiving CRT, Bordachar et al. evaluated the effect of several sequential VV intervals on LV dyssynchrony, as assessed with pulsed-wave tissue Doppler imaging (TDI) and hemodynamics (cardiac output and mitral regurgitation).[12] Changes in LV dyssynchrony were strongly correlated with changes in

cardiac output and mitral regurgitation. An optimized VV interval provided the most LV synchronous contraction, the largest cardiac output, and significantly reduced the severity of mitral regurgitation.[12]

3. HOW TO OPTIMIZE THE AV AND VV INTERVALS?

3.1 AV interval optimization

About 20-30% of the resting stroke volume in heart failure patients is due to atrial contraction. A too short AV interval results in early LV contraction and mitral valve closure, thereby reducing left atrial contribution to LV filling (resulting in truncation of the A wave on pulsed-wave Doppler transmitral inflow). In contrast a too long AV interval is characterized by early left atrial contraction, with fusion of E and A wave, with reduction of LV filling time and possible induction of diastolic mitral regurgitation. Both these conditions result in impaired LV filling with a reduction in LV perfor-

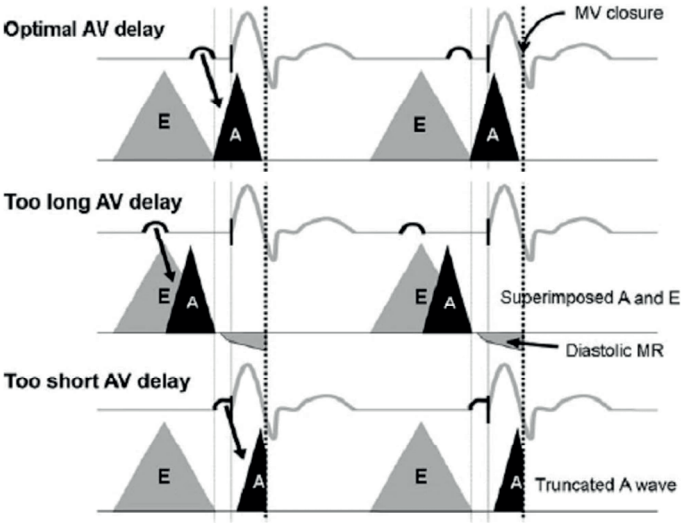


Figure 1. Effect of AV interval programming on echocardiographic pulsed-wave Doppler transmitral inflow. An optimal AV interval (upper panel) permits completion of the left atrial contraction and the mitral valve closes at the end of the A wave. When the AV interval is too long (middle panel), left atrial contraction occurs prematurely, and the A wave is superimposed to the E wave (fusion of E and A wave). The LV diastolic filling time is shortened and diastolic mitral regurgitation can occur. In contrast, when the AV interval is too short (lower panel), LV contraction occurs earlier and the mitral valve closes before completion of left atrial contraction. On pulsed-wave Doppler recordings of the transmitral inflow truncation of the A wave is observed

Table 1. AV interval optimization methods

Echocardiography		Non-echocardiography
Optimization of LV diastolic filling	Optimization of LV systolic function	
• Iterative method • Ritter's method • Mitral inflow VTI • Meluzin's method	• LV dP/dt_{max} • LV outflow tract VTI • Myocardial performance index	• Invasive dP/dt_{max} • Impedance cardiography • Acoustic cardiography • Intracardiac electrograms

Abbreviations = LV = left ventricular; VTI = velocity time integral.

mance.[6] The optimal AV interval is the shortest AV delay that does not compromise left atrial contribution to the LV diastolic filling (Figure 1). Several echocardiographic and non-echocardiographic methods have been proposed to optimize the AV interval (Table 1). Using echocardiography, the AV interval can be optimized by maximizing LV diastolic filling or LV hemodynamics.[7] The **iterative method** evaluates the effects of the AV interval on LV diastolic filling. A long AV interval is first programmed and the LV diastolic filling pattern is evaluated on the pulsed-wave Doppler transmitral inflow. Thereafter the AV interval is shortened by increments of 20 ms until truncation of the A wave occurs. The optimal AV interval is then identified by increasing the AV delay in 10 ms increment until the A wave is not longer truncated (Figure 2). The multicenter, randomized CARE-HF trial optimized the AV interval with this method.[14] However, the effects of performing routinely AV interval optimization on clinical outcome or LV systolic function and remodeling have not been reported. The **Ritter's method** is also based on pulsed-wave Doppler recordings of the transmitral inflow.[7] With this method, two extreme AV intervals are programmed: a long AV interval with A wave attenuation (AV_{long}) and a short AV interval with A wave truncation (AV_{short}). For each

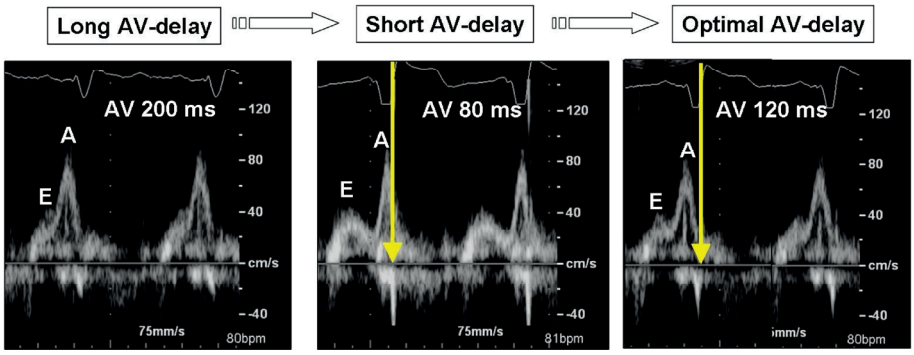
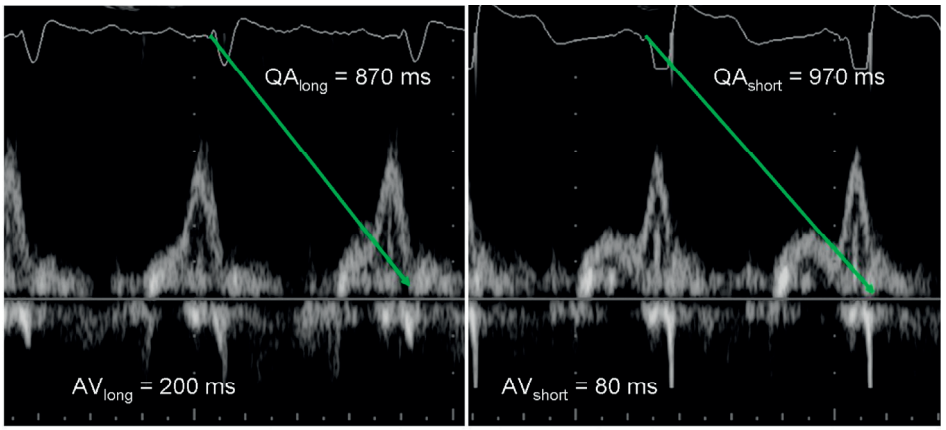


Figure 2. AV interval optimization with the iterative method. From a long AV interval (left panel), the AV interval is shortened by 20 ms steps until the A wave is truncated (middle panel, yellow arrow). Thereafter, the AV interval is increased to obtain the optimal AV interval (the shortest AV interval without truncation of the A wave) (right panel).



$$\text{Optimal AV interval} = AV_{short} + [(AV_{long} + QA_{long}) - (AV_{short} + QA_{short})]$$

$$\text{AV interval} = 80 + [(200 + 870) - (80 + 970)] = 100 \text{ ms}$$

Figure 3. AV interval optimization with the Ritter's method. Two extreme AV intervals are programmed, a long AV interval (AV_{long}) and a short AV interval (AV_{short}). The time difference between the QRS onset to the completion of the A wave is measured at each AV interval. The optimal AV interval is calculated according to the formula.

AV interval, the time between the QRS complex onset to the completion of the A-wave is measured. The optimal AV interval is calculated with the formula: $AV_{short} + [(AV_{long} + QA_{long}) - (AV_{short} + QA_{short})]$ (Figure 3). This method has been used in several multicenter trials (MUSTIC, MIRACLE, InSyncIII).[15-17] However, the clinical use of this method may be limited in patients with high heart rate or with an intrinsic AV interval <150 ms. In addition, **measurement of LV filling volume** may be a useful method to optimize the AV interval. On pulsed-wave Doppler recordings of the transmitral inflow, the measurement of the velocity time integral (VTI) is a surrogate for LV filling volume (Figure 4). The optimal AV interval is defined by the largest VTI. Another method to optimize AV interval is the method described by **Meluzin**.[18] The AV interval is optimized by aligning the end of LV filling and the onset of ventricular contraction. On pulsed-wave Doppler recordings of the transmitral inflow, a long AV interval is defined as the maximum AV delay that allows full ventricular capture (lowered by 5-10 s). Thereafter, the time between the end of the A wave and the onset of the mitral regurgitation spectral signal is measured (t1). The difference between the long AV interval and the t1 yields the optimal AV interval. The use of this method in clinical practice may be limited by the need for detectable mitral regurgitation signal. Echocardiographic methods that optimize AV interval based on LV hemodynamics include **measurement of stroke volume** on pulsed- or continuous-wave Doppler recordings of the LV outflow tract (LVOT) or the non-invasive **measurement of LV dP/dt$_{max}$** on continuous-wave Doppler spectral

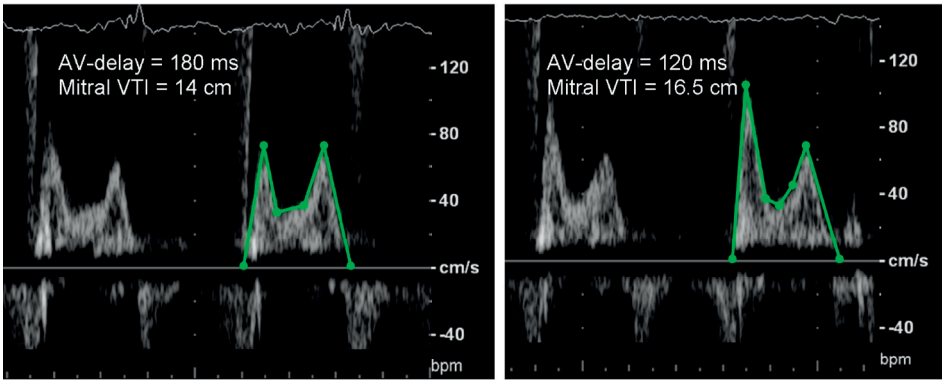


Figure 4. Mitral inflow velocity time integral to optimize the AV interval. The mitral inflow velocity time integral (VTI) is a surrogate for LV filling volume, assuming a constant mitral valve area. The optimal AV interval yields the largest mitral VTI.

signal of mitral regurgitation (Figure 5).[7] The product of the LVOT cross-sectional area and VTI measured on the pulsed- or continuous-wave Doppler recordings of the LVOT or aortic valve yields the stroke volume.[19, 20] The optimal AV interval is defined by the largest stroke volume. The measurement of the LV dP/dt_{max} provides information on LV contractility. Non-invasive measurement of this parameter is performed on the continuous-wave Doppler spectral signal of the mitral regurgitation. First, the time

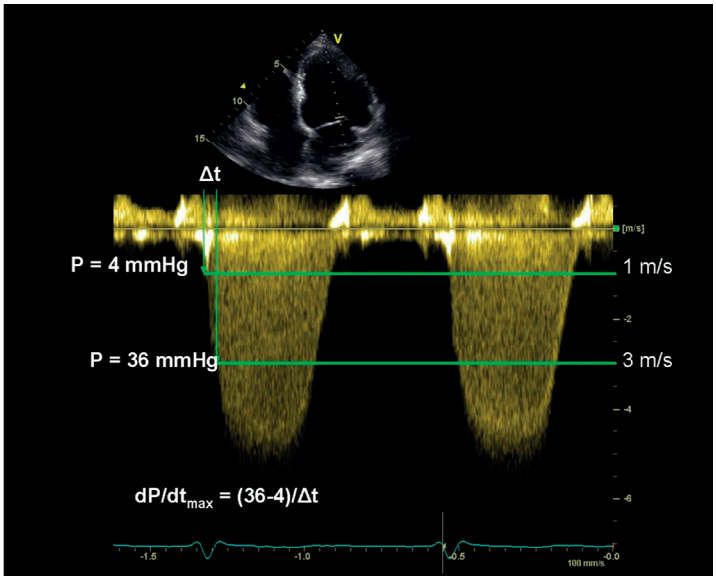


Figure 5. Echocardiographic methods to optimize the AV interval based on LV systolic function. Measurement of LV dP/dt_{max} as indicator of LV performance that permit AV interval optimization.

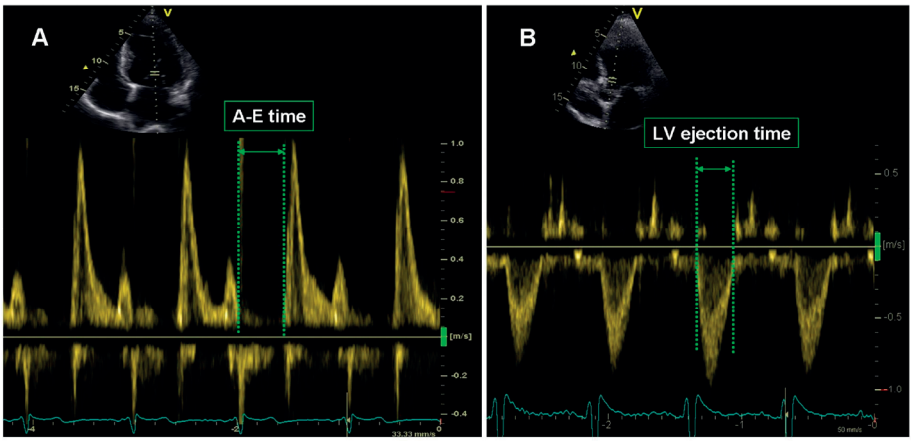


Figure 6. AV interval optimization based on myocardial performance index evaluation. The myocardial performance index is calculated by dividing the sum of the isovolumic relaxation and contraction times by the LV ejection time. The sum of the isovolumic contraction and relaxation times is calculated by measuring the A-E time on pulsed-wave Doppler transmitral inflow recordings (panel A) and the LV ejection time on pulsed-wave Doppler recordings of the LV outflow tract (panel B). Sum of the isovolumic contraction and relaxation times = A-E time – LV ejection time.

difference between two points of the spectral signal is measured (usually between 1 m/s and 3 m/s time points). Then, the pressure gradient between these two points is calculated according to Bernoulli equation. The optimal AV interval corresponds to the highest value of LV dP/dt_{max}. Finally, the measurement of the **myocardial performance index** may be a useful method to optimize the AV interval.[5] The myocardial performance index is a comprehensive measurement of LV function. This index is calculated as the sum of isovolumic contraction and relaxation times divided by the ejection time (Figure 6). The optimal AV interval is defined by the lowest myocardial performance index.

Several non-echocardiographic methods have been proposed to optimize AV interval. The aforementioned measurement of the LV dP/dt_{max} can be performed invasively. During CRT device implantation, this parameter can be measured and the AV interval can be set. However, this invasive approach limits its usability in routine clinical follow-up. **Acoustic cardiography** was proposed as fast and reproducible method to optimize CRT setting.[21] Moreover, **impedance cardiography** optimizes the AV interval by measuring changes in the impedance of an alternating current applied across the thorax of the patient. These changes indicate the cardiac output. With the use of **intracardiac electrograms** the optimal AV interval can be defined by measuring electrical conduction delays (i.e., AV interval and QRS duration) that maximize LV hemodynamics.[22]

3.2 VV interval optmization

VV interval is the time delay between the contraction of the right and LV. In normal subjects, the right and left ventricle are not simultaneously activated.[23] In heart failure patients (particularly in the presence of left bundle branch block) the electrical activation delay between both ventricles is more pronounced with a prolongation of LV pre-ejection time and a shortening of LV ejection time. CRT partially reduces this electrical activation delay, by pacing both the right and left ventricle. However, the first generation of CRT devices could not differentiate the pacing channels and both ventricles were always paced simultaneously. The recent generation of CRT devices allows tailoring the activation delays between right and left ventricle (VV interval), aiming a more physiological activation.[24] The most common methods used to optimize VV interval are based on the assessment of surrogates of stroke volume or cardiac output (LVOT VTI) or on the assessment of mechanical dyssynchrony (Table 2).

The echocardiographic method based on the assessment of LV systolic performance (LVOT VTI) has been discussed in the AV interval optimization section. Similarly, the largest LVOT VTI defines the optimal VV interval (Figure 7).

In contrast to AV interval optimization, **measurement of mechanical dyssynchrony** at different levels (interventricular and intra-LV dyssynchrony) may constitute a further helpful tool to select the optimal VV interval setting. Interventricular dyssynchrony is assessed by the difference between the left and right pre-ejection time measured with pulsed-wave Doppler echocardiography at LVOT and right ventricular outflow tract, respectively. Intra-LV dyssynchrony mainly measured with TDI is also

Table 2. VV interval optimization methods

Echocardiography		Non-echocardiography
Optimization of LV systolic function	Optimization of LV mechanical dyssynchrony	
• LV outflow tract VTI	• Interventricular dyssynchrony (difference between aortic and pulmonary pre-ejection times) • Time to peak systolic velocity at TDI (time difference between 2 or 4 opposing walls, standard deviation of 12 LV segments) • Speckle-tracking echocardiography (radial, longitudinal and circumferential dyssynchrony) • Real time 3D echocardiography (systolic dyssynchrony index)	• Invasive dP/dt_{max} • Radionuclide ventriculography • Finger photo-pletismography • Surface ECG • Impedance cardiography • Acoustic cardiography • Intracardiac electrograms

Abbreviations = LV = left ventricular; TDI = tissue Doppler imaging; VTI = velocity time integral.

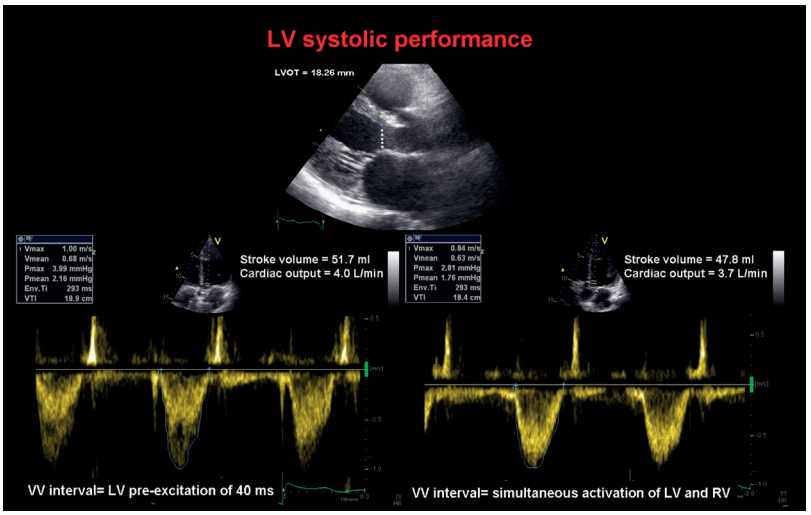


Figure 7. Example of VV interval optimization by measuring stroke volume and cardiac output. Velocity-time integral (VTI) at left ventricular outflow tract (LVOT) is measured with pulsed-wave Doppler echocardiography. Stroke volume can be derived by multiplying the cross sectional area (CSA) with VTI. Cardiac output can be derived by multiplying stroke volume with heart rate (HR). CSA = π/4 X LVOT diameter; Stroke volume = CSA X VTI; Cardiac output = stroke volume X HR.

used as effective means of guiding VV interval optimization.[13, 25] The time difference between peak systolic velocity of 2 or 4 opposing walls or the standard deviation of time to peak systolic velocity of 12 LV segments are the most common methods to measure intra-LV dyssynchrony (Figure 8A). In addition, speckle tracking echocardiography and real time 3-dimensional echocardiography are valuable novel techniques for intra-LV dyssynchrony assessment but so far no studies investigated the role of these techniques for VV interval optimization (Figure 8 B,C).[26]

Several non-echocardiographic methods have been also proposed to optimize VV interval (Table 2). However, the majority of these methods are not routinely used in clinical practice because they require invasive measurements (i.e. invasive LV dP/dt_{max}) or are time-consuming or not widely available (i.e radionuclide ventriculography, acoustic cardiography or finger photo-pletismography).[24,21, 27, 28]

Among the non-echocardiographic methods, **surface ECG derived methods** are the simplest and widely available. Different parameters have been proposed, with measurement of QRS duration at surface ECG in different VV intervals as the easiest method.[29, 30] A substantial agreement was shown between the selection of the optimal VV interval based on the narrowest QRS duration and on LVOT VTI measured with echocardiography among 5 tested VV intervals (LV pre-excitation of 80 and 40 ms, simultaneous pacing, and right ventricle pre-excitation of 40 and 80 ms; Figure 9).[29] This study proposed a combined approach for VV interval optimization

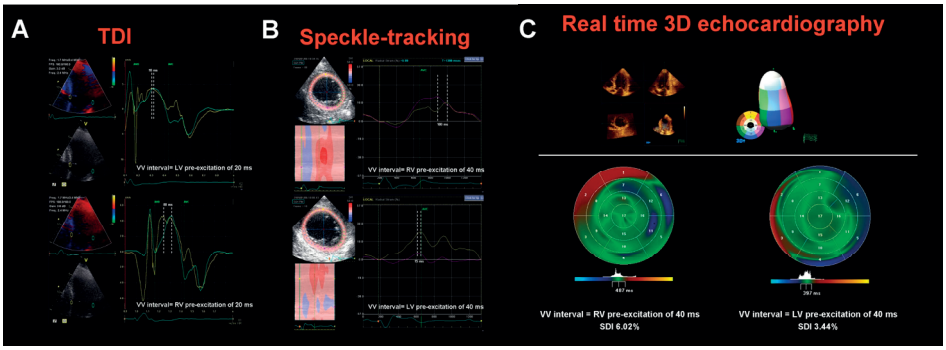


Figure 8. Examples of VV interval optimizations by measuring LV mechanical dyssynchrony. **Panel A.** Tissue Doppler imaging (left) permits the assessment the time difference between peak systolic velocities of 2 opposing walls (septal and lateral wall). **Panel B.** Speckle-tracking echocardiography (middle) permits the assessment of radial dyssynchrony from the parasternal short axis view at papillary muscle level. Radial dyssynchrony is defined as the time difference between the peak systolic radial strain of the antero-septal and posterior wall. **Panel C.** Real time 3D echocardiography (right) permits the assessment of systolic dyssynchrony index (SDI). The LV 3D model is automatically subdivided in 17 standard wedge-shaped (apart from the apex) subvolumes. For each volumetric segment, the time interval to reach the minimum systolic volume is automatically calculated. The standard deviation of these timings for 16 segments (excluding the true apex) is expressed as a percentage of the cardiac cycle, obtaining the SDI.

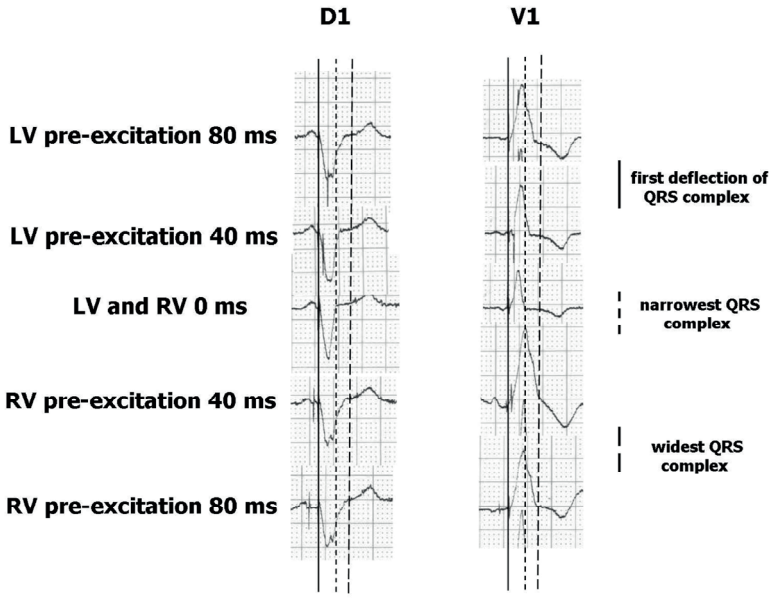


Figure 9. Example of VV interval optimization by measuring QRS duration at surface ECG. The Figure shows QRS complex in D1 and V1 leads for 5 VV intervals. Among these 5 QRS duration measurements, the value corresponding to the narrowest QRS duration was considered as the ECG-optimized VV interval. In this example the ECG-optimized VV interval was simultaneous (LV and RV VV interval = 0 ms). LV: left ventricle; RV: right ventricle

with ECG and echocardiography in 2 steps: first VV interval may be selected by the ECG recording at the 5 VV intervals (LV pre-excitation of 80 and 40 ms, simultaneous pacing, and right ventricle pre-excitation of 40 and 80 ms); next the interval with the greatest QRS duration shortening could be scanned in depth with pulsed-wave Doppler echocardiography (20 ms steps) to determine the optimal VV interval. Such an approach may save time reducing the number of VV intervals that should be tested with echocardiography.[29]

Finally, several methods based on **automated algorithms** typical of different manufacturers have been proposed for VV interval optimization, the majority of them are based on the intracardiac electrograms.[22, 31-33]

3.3 Which method?

At present there are no gold standard methods for AV and VV optimization. Recently, Thomas et al. compared different echocardiographic measurements used for VV interval optimization.[34] The authors showed that among different measurements used for VV interval optimization, LVOT VTI and interventricular dyssynchrony were the most feasible (100% and 93% of feasibility, respectively). Furthermore, LVOT VTI resulted the most reproducible with a coefficient of variation of only 3.0%.[34] Conversely, Zuber et al. found a poor performance of LVOT VTI as method to optimize CRT settings as compared to acoustic cardiography.[21] These controversial results and the absence of a well recognized gold standard method to optimize the setting of the CRT devices claim warrant further larger studies to address this issue.

3.4 Under which conditions?

Preliminary data suggested that AV and VV optimization may improve LV filling and hemodynamic performance. However different physiologic conditions like rest and exercise may markedly change the heart rate and loading conditions of the heart, and therefore some authors hypothesized that in CRT recipients an optimal setting determined at rest may be different during exercise.[35, 36] Particularly, the optimal AV interval was shown to be different between rest and during semisupine bicycle exercise in a considerable proportion of patients and the same group also demonstrated a similar behaviour of optimal VV interval that differed in 57% of the patients between rest and during exercise.[35, 36] These preliminary observations may have important clinical implications since one of the major benefits of CRT is the improvement of exercise capacity. However, no studies investigated the potential long-term clinical benefit of

this strategy. Furthermore, an important field of research may be the development of CRT devices that, similarly to particular dual chamber pacemakers, are able to find the optimal setting automatically (for both AV and also VV interval), and reset it regularly at rest and during exercise.

3.5 Which interval first?

A recurrent question that was never completely addressed in the various studies, is whether AV optimization should be followed by VV optimization or vice versa (or even simultaneously). Indeed, performing this procedure in different order not necessarily produces the same results.[21] The common clinical practice is to optimize the AV interval first, followed by VV optimization; in all studies, AV and VV intervals were optimized separately. It could be possible however that a method that permits simultaneous optimization of the AV and VV intervals may provide additional hemodynamic benefit.

4. WHEN DO WE NEED TO OPTIMIZE THE CRT SETTINGS?

Preliminary evidence showed that the optimal settings obtained immediately after CRT implantation may change during follow-up.[9, 10, 37] Valzania et al. demonstrated in 14 patients who underwent CRT and were followed for 12 months, that optimal AV and VV intervals changed over time. In particular a difference ≥ 40 ms in the optimal VV interval was observed in 57% of the patients at 12 months follow-up.[10] More recently, Zhang et al. underscored the importance of periodic reassessment of the optimal AV delay in CRT recipients; indeed the optimal AV delay had changed (as compared to acutely after CRT implantation) in 56% of the patients at long-term follow-up.[37]

Therefore, the optimal setting of the CRT devices changes during follow up, as loading LV conditions change over time due to LV (reverse) remodeling. Periodic tailoring of CRT devices seems important in order to maintain or improve a positive hemodynamic effect over the long term, and to enhance benefit from CRT. In the daily practice however, systematic optimization and periodic reassessment of AV and VV intervals may not be feasible, but could be restricted to non-responder patients, to potentially improve the effect of CRT. A practical algorithm to decide when this procedure should be performed is proposed in Figure 10.

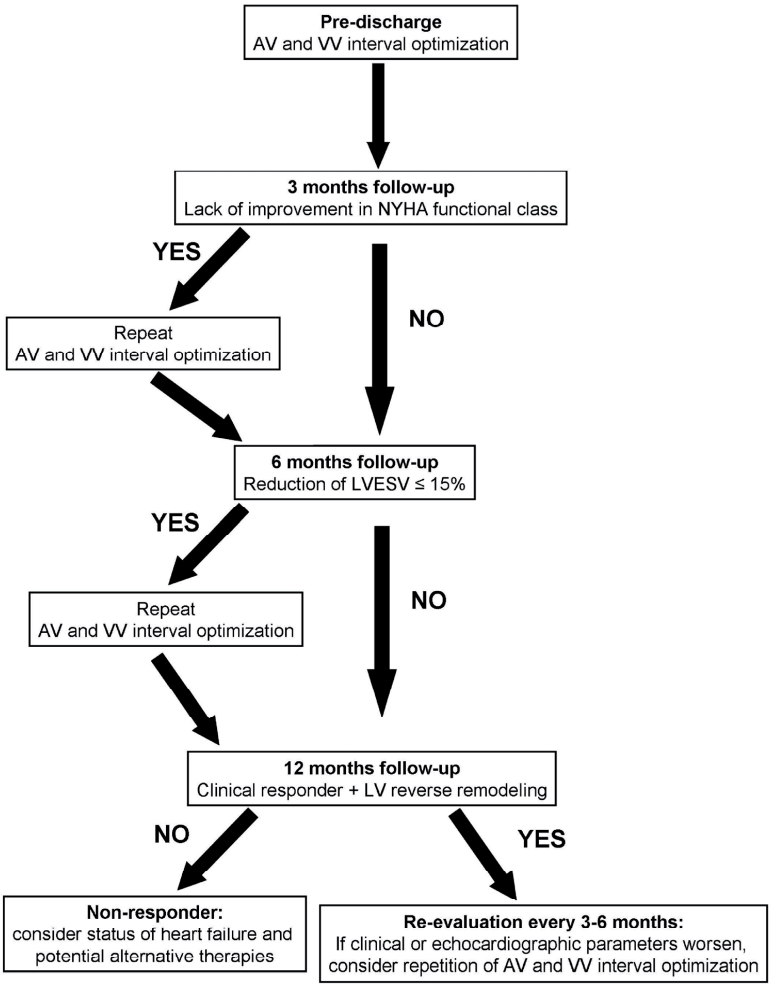


Figure 10: Algorithm to decide when to optimize AV and VV interval during follow-up
LVESV: left ventricular end-systolic volume; NYHA: New York Heart Association

5. CLINICAL EVIDENCE AND TRIALS ON AV AND VV INTERVAL OPTIMIZATION

Several data form single center studies showed that the optimal AV settings further improved hemodynamic benefits of CRT. At present, only one single blind randomized trial investigated the impact of AV delay optimization based on aortic VTI on clinical status 3 months after CRT.[38] The authors showed that 75% of the patients in the arm with optimized AV delay had an improvement by at least 1 New York Heart Association functional class whereas only 40% of the patients in the arm with empiric AV delay had an improvement by at least 1 New York Heart Association functional class ($p < 0.03$).[38]

Similar to AV interval optimization, several data from small single center studies demonstrated that sequential CRT after VV interval optimization, rather than simultaneous CRT, may acutely further improve LV systolic performance (stroke volume, dP/dt_{max}) and LV dyssynchrony.[4, 6, 7] Sogaard et al.[13] showed for the first time the additional benefits on the LV systolic function of the sequential biventricular pacing after VV optimization performed using tissue tracking echocardiography. However, Vidal et al.[25] in single center, nonrandomized clinical study did not show differences in the numbers of CRT non-responders between patients with and without AV and VV intervals optimized.

Finally, 3 multicenter trials investigated the benefits of VV interval optimization on long-term outcomes (InSyncIII, RHYTHM II ICD and DECREASE-HF).[17, 39, 40]

The InSyncIII clinical study[17] evaluated the clinical effect of optimized sequential CRT as compared to the control group (optimal pharmacological medical therapy alone) and to the treatment group (simultaneous biventricular pacing) of the MIRACLE trial. They demonstrated that: 1. optimized sequential CRT significantly improved functional status as compared to the control group; 2. the optimal VV interval showed a relative narrow range between right ventricular pre-excitation of 40 ms and LV pre-excitation of 40 ms, with a higher prevalence of LV pre-excitation; 3. controversial results about the clinical benefits of optimized sequential CRT as compared to simultaneous biventricular pacing (optimized sequential CRT significantly improved only the 6 minute walking distance but not NYHA functional class or quality of life).

In the RHYTHM II ICD study[39] 121 CRT recipients were included randomly assigned in a 1:3 ratio to receive simultaneous biventricular pacing or optimized sequential CRT. After AV interval optimization based on LV filling pattern, optimal VV interval was set at the maximum stroke volume derived by LVOT VTI. The authors evaluated the improvement in clinical end-points, such as NYHA class and 6 minute walking test, after 3 and 6 months follow-up. Similar to InSync III, no additional clinical benefit was demonstrated by the optimized sequential CRT over the simultaneous biventricular pacing.

The DECREASE-HF trial[40] evaluated 306 patients with advanced heart failure and QRS duration ≥150 ms comparing simultaneous biventricular pacing, optimized sequential CRT, and LV pacing alone. Although all 3 pacing modalities led to reduced LV size and improved LV systolic function, there was a trend toward a greater benefit in patients with sequential and simultaneous pacing as compared to LV pacing alone. Furthermore, despite the trial was not designed to specifically compare simultaneous biventricular pacing vs. optimized sequential CRT, no significant differences between these 2 pacing modalities were observed in terms of improvement of LV size and function after 6 months of CRT. Of interest in this trial, the VV interval was

programmed based on intracardiac electrocardiograms at the time of the implantation and was not individually optimized according to the hemodynamic response.

In light of this evidence, AV and VV interval optimization may be beneficial in some groups of heart failure patients treated with CRT, improving the clinical status and LV performance. Non-responder patients and ischemic heart failure patients with extensive myocardial scar tissue may benefit most likely from VV interval optimization. Particularly, in ischemic heart failure patients, the inter- and intraventricular conduction of the electrical pulse is very slow and may require larger LV pre-excitation.[41]

Finally, whether AV and VV interval optimization may result in better long-term outcome awaits further studies.

6. FUTURE PERSPECTIVES AND CONCLUSIONS

Single center studies pointed out the additional hemodynamic benefits provided by the optimized CRT setting. Several echocardiographic and non-echocardiographic techniques have been used to perform this operation but so far there is no accepted gold standard method. In addition, what are the best physiologic conditions (rest or during exercise) to perform the AV and VV optimization and which interval should be optimized first, are issues that still need further study. Furthermore, it has been demonstrated that optimal CRT settings may change during follow-up, but when repeat optimization should be performed is unclear. Thus far, the available multicenter trials did show modest clinical benefits of AV and VV interval optimization at mid- or long-term follow-up. It remains to investigate whether AV and VV interval optimization may improve the long-term survival.

REFERENCES

(1) Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117(20):2608-2616.

(2) Bax JJ, Gorcsan J, III. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol* 2009;53(21):1933-1943.

(3) Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;39(12):2026-2033.

(4) Barold SS, Ilercil A, Herweg B. Echocardiographic optimization of the atrioventricular and interventricular intervals during cardiac resynchronization. *Europace* 2008;10 Suppl 3:iii88-iii95.

(5) Bhan A, Kapetanakis S, Monaghan MJ. Optimization of cardiac resynchronization therapy. *Echocardiography* 2008;25(9):1031-1039.

(6) Stanton T, Hawkins NM, Hogg KJ, Goodfield NE, Petrie MC, McMurray JJ. How should we optimize cardiac resynchronization therapy? *Eur Heart J* 2008;29(20):2458-2472.

(7) Ypenburg C, Van D, V, Westenberg JJ, Bleeker GB, Marsan NA, Henneman MM et al. Noninvasive imaging in cardiac resynchronization therapy--Part 2: Follow-up and optimization of settings. *Pacing Clin Electrophysiol* 2008;31(12):1628-1639.

(8) O'Donnell D, Nadurata V, Hamer A, Kertes P, Mohamed U. Long-term variations in optimal programming of cardiac resynchronization therapy devices. *Pacing Clin Electrophysiol* 2005;28 Suppl 1:S24-S26.

(9) Porciani MC, Dondina C, Macioce R, Demarchi G, Cappelli F, Lilli A et al. Temporal variation in optimal atrioventricular and interventricular delay during cardiac resynchronization therapy. *J Card Fail* 2006;12(9):715-719.

(10) Valzania C, Biffi M, Martignani C, Diemberger I, Bertini M, Ziacchi M et al. Cardiac resynchronization therapy: variations in echo-guided optimized atrioventricular and interventricular delays during follow-up. *Echocardiography* 2007;24(9):933-939.

(11) Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation* 1999;99(23):2993-3001.

(12) Bordachar P, Lafitte S, Reuter S, Sanders P, Jais P, Haissaguerre M et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. *J Am Coll Cardiol* 2004;44(11):2157-2165.

(13) Sogaard P, Egeblad H, Pedersen AK, Kim WY, Kristensen BO, Hansen PS et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. *Circulation* 2002;106(16):2078-2084.

(14) Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352(15):1539-1549.

(15) Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346(24):1845-1853.

(16) Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344(12):873-880.

(17) Leon AR, Abraham WT, Brozena S, Daubert JP, Fisher WG, Gurley JC et al. Cardiac resynchronization with sequential biventricular pacing for the treatment of moderate-to-severe heart failure. *J Am Coll Cardiol* 2005;46(12):2298-2304.

(18) Meluzin J, Novak M, Mullerova J, Krejci J, Hude P, Eisenberger M et al. A fast and simple echocardiographic method of determination of the optimal atrioventricular delay in patients after biventricular stimulation. *Pacing Clin Electrophysiol* 2004;27(1):58-64.

(19) Coats AJ. Doppler ultrasonic measurement of cardiac output: reproducibility and validation. *Eur Heart J* 1990;11 Suppl I:49-61.

(20) Dubin J, Wallerson DC, Cody RJ, Devereux RB. Comparative accuracy of Doppler echocardiographic methods for clinical stroke volume determination. *Am Heart J* 1990;120(1):116-123.

(21) Zuber M, Toggweiler S, Roos M, Kobza R, Jamshidi P, Erne P. Comparison of different approaches for optimization of atrioventricular and interventricular delay in biventricular pacing. *Europace* 2008;10(3):367-373.

(22) Gold MR, Niazi I, Giudici M, Leman RB, Sturdivant JL, Kim MH et al. A prospective comparison of AV delay programming methods for hemodynamic optimization during cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2007;18(5):490-496.

(23) Hirschfeld S, Meyer R, Schwartz DC, Korfhagen J, Kaplan S. Measurement of right and left ventricular systolic time intervals by echocardiography. *Circulation* 1975;51(2):304-309.

(24) Perego GB, Chianca R, Facchini M, Frattola A, Balla E, Zucchi S et al. Simultaneous vs. sequential biventricular pacing in dilated cardiomyopathy: an acute hemodynamic study. *Eur J Heart Fail* 2003;5(3):305-313.

(25) Vidal B, Sitges M, Marigliano A, Delgado V, az-Infante E, Azqueta M et al. Optimizing the programation of cardiac resynchronization therapy devices in patients with heart failure and left bundle branch block. *Am J Cardiol* 2007;100(6):1002-1006.

(26) Conca C, Faletra FF, Miyazaki C, Oh J, Mantovani A, Klersy C et al. Echocardiographic parameters of mechanical synchrony in healthy individuals. *Am J Cardiol* 2009;103(1):136-142.

(27) Burri H, Sunthorn H, Somsen A, Zaza S, Fleury E, Shah D et al. Optimizing sequential biventricular pacing using radionuclide ventriculography. *Heart Rhythm* 2005;2(9):960-965.

(28) Whinnett ZI, Davies JE, Willson K, Manisty CH, Chow AW, Foale RA et al. Haemodynamic effects of changes in atrioventricular and interventricular delay in cardiac resynchronisation therapy show a consistent pattern: analysis of shape, magnitude and relative importance of atrioventricular and interventricular delay. *Heart* 2006;92(11):1628-1634.

(29) Bertini M, Ziacchi M, Biffi M, Martignani C, Saporito D, Valzania C et al. Interventricular delay interval optimization in cardiac resynchronization therapy guided by echocardiography versus guided by electrocardiographic QRS interval width. *Am J Cardiol* 2008;102(10):1373-1377.

(30) Vidal B, Tamborero D, Mont L, Sitges M, Delgado V, Berruezo A et al. Electrocardiographic optimization of interventricular delay in cardiac resynchronization therapy: a simple method to optimize the device. *J Cardiovasc Electrophysiol* 2007;18(12):1252-1257.

(31) Dupuis JM, Kobeissi A, Vitali L, Gaggini G, Merheb M, Rouleau F et al. Programming optimal atrioventricular delay in dual chamber pacing using peak endocardial acceleration: comparison with a standard echocardiographic procedure. *Pacing Clin Electrophysiol* 2003;26(1 Pt 2):210-213.

(32) van Gelder BM, Meijer A, Bracke FA. The optimized V-V interval determined by interventricular conduction times versus invasive measurement by LVdP/dtMAX. *J Cardiovasc Electrophysiol* 2008; 19(9):939-944.

(33) Heinroth KM, Elster M, Nuding S, Schlegel F, Christoph A, Carter J et al. Impedance cardiography: a useful and reliable tool in optimization of cardiac resynchronization devices. *Europace* 2007; 9(9):744-750.

(34) Thomas DE, Yousef ZR, Fraser AG. A critical comparison of echocardiographic measurements used for optimizing cardiac resynchronization therapy: stroke distance is best. *Eur J Heart Fail* 2009;11(8):779-788.

(35) Bordachar P, Lafitte S, Reuter S, Serri K, Garrigue S, Laborderie J et al. Echocardiographic assessment during exercise of heart failure patients with cardiac resynchronization therapy. *Am J Cardiol* 2006;97(11):1622-1625.

(36) Mokrani B, Lafitte S, Deplagne A, Ploux S, Laborderie J, Reant P et al. Echocardiographic study of the optimal atrioventricular delay at rest and during exercise in recipients of cardiac resynchronization therapy systems. *Heart Rhythm* 2009;6(7):972-977.

(37) Zhang Q, Fung JW, Chan YS, Chan HC, Lin H, Chan S et al. The role of repeating optimization of atrioventricular interval during interim and long-term follow-up after cardiac resynchronization therapy. *Int J Cardiol* 2008;124(2):211-217.

(38) Sawhney NS, Waggoner AD, Garhwal S, Chawla MK, Osborn J, Faddis MN. Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. *Heart Rhythm* 2004;1(5):562-567.

(39) Boriani G, Muller CP, Seidl KH, Grove R, Vogt J, Danschel W et al. Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. The Resynchronization for the HemodYnamic Treatment for Heart Failure Management II implantable cardioverter defibrillator (RHYTHM II ICD) study. *Am Heart J* 2006; 151(5):1050-1058.

(40) Rao RK, Kumar UN, Schafer J, Viloria E, De LD, Foster E. Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: a randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. *Circulation* 2007;115(16):2136-2144.

(41) van Gelder BM, Bracke FA, Meijer A, Lakerveld LJ, Pijls NH. Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. *Am J Cardiol* 2004;93(12): 1500-1503.

PART II

Prognostic evaluation

CHAPTER 8

Impact of clinical and echocardiographic response to cardiac resynchronization therapy on long-term survival.

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ABSTRACT

Background. Clinical or echocardiographic mid-term responses to cardiac resynchronization therapy (CRT) may have a different influence on long-term prognosis of heart failure patients treated with CRT. The aim of the study was to establish which definition of response to CRT, clinical or echocardiographic, best predicts long-term prognosis.

Methods and Results. A total of 679 heart failure patients treated with CRT were included. All patients underwent a complete history and physical examination and transthoracic echocardiogram prior to CRT implantation and at 6 months follow-up. The clinical and echocardiographic responses to CRT were defined based on clinical improvement (≥1 NYHA class) and LV reverse remodeling (reduction of LV end-systolic volume≥15%) at 6 months follow-up, respectively. All patients were prospectively followed-up for the occurrence of death. The mean age was 65±11 years and 79% of the patients were male. At 6 months follow-up, 510 (77%) patients showed clinical response to CRT and 412 (62%) patients showed echocardiographic response to CRT. During a mean follow-up of 37±22 months, 140 (21%) patients died. Clinical and echocardiographic responses to CRT were both significantly related to all-cause mortality on univariable analysis. However, on multivariable Cox regression analysis only echocardiographic response to CRT was independently associated with a superior survival (hazard ratio:0.38; 95% CI,0.27-0.50; p<0.001).

Conclusions. In a large population of heart failure patients treated with CRT, the reduction of LV end-systolic volume at mid-term follow-up demonstrated to be a better predictor of long-term survival than improvement in clinical status.

INTRODUCTION

The long-term survival benefits of cardiac resynchronization therapy (CRT) demonstrated in various trials have changed the clinical management of heart failure patients.[1-3] CRT improves left ventricular (LV) performance by partially restoring more physiological and synchronous contraction. As a consequence, significant improvements in clinical status and reduction in LV volumes and mitral regurgitation have been reported. Ultimately, these favorable changes result in improved long-term morbidity and mortality rates.[4, 5] Most of the landmark trials have evaluated the efficacy of CRT by means of improvement in clinical status and/or a reduction of LV end-systolic volume (LVESV) at mid-term follow-up.[6, 7] The value of these surrogate end points relies on their ability to predict long-term survival.[8, 9] Thus far, only few studies have attempted to evaluate the long-term survival implications of mid-term clinical and echocardiographic responses to CRT (commonly assessed at 3-6 months follow-up).[4, 5, 10] In a series of 141 heart failure patients treated with CRT, mid-term LV reverse remodeling had superior accuracy to predict long-term survival than improvement in clinical parameters.[5] A recent subanalysis of the CARE-HF trial showed that LV volumes measured 3 months after CRT implantation predicted long-term survival on univariable analysis with a hazard ratio higher than LV volumes at baseline; however, LV volumes (baseline and after 3 months) were not independent determinants of long-term survival.[10] In view of these results, it remains unclear whether clinical or echocardiographic mid-term responses to CRT have an influence on long-term prognosis of heart failure patients treated with CRT. Accordingly, the present study aimed to establish which definition of CRT response at mid-term follow-up (clinical improvement or LV reverse remodeling) best predicts long-term prognosis.

METHODS

Patient population and protocol

A total of 679 heart failure patients undergoing CRT implantation were included. According to current guidelines, the inclusion criteria were: New York Heart Association (NYHA) functional class III-IV, sinus rhythm, LV ejection fraction ≤35%, and QRS duration ≥120 ms. Etiology of heart failure was considered ischemic in the presence of significant coronary artery disease (>50% stenosis in ≥1 major epicardial coronary artery) on coronary angiography and/or a history of myocardial infarction or revascularization.

All patients underwent a complete history and physical examination, 12-lead surface ECG and transthoracic echocardiogram prior to CRT implantation and at 6 months follow-up. Clinical and ECG variables recorded included NYHA functional class, medication, hemoglobin level, renal dysfunction (estimated glomerular filtration rate ≤60 ml/min/1.73m2),[11, 12] and QRS duration.

In addition, the number of hospitalizations for heart failure within 6 months follow-up was recorded. All clinical data were prospectively entered into the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands) and retrospectively analyzed.

The echocardiographic examination consisted of comprehensive evaluation of LV volumes and function, and severity of mitral regurgitation, if present.

Finally, the clinical and echocardiographic responses to CRT were defined based on clinical improvement and LV reverse remodeling at 6 months follow-up, respectively, as previously described.[6]

All patients were prospectively followed-up for the occurrence of death. To test whether the clinical and echocardiographic mid-term responses to CRT could independently predict mortality, the long-term follow-up started at 6 months after CRT implantation.

Echocardiography

Transthoracic echocardiography was performed with the patients in the left lateral decubitus position using a commercially available ultrasound transducer and equipment (M4S probe, Vivid 7, GE-Vingmed, Horten, Norway). All transthoracic echocardiographic examinations were performed prior to CRT implantation and at 6 months follow-up. All images were digitally stored on hard disks for offline analysis (EchoPAC version 7.0.0 and 108.1.5 GE-Vingmed, Horten, Norway).

A complete 2-dimensional and color Doppler echocardiographic examination was performed. LV end-diastolic (LVEDV) and LVESV were calculated using Simpson's biplane method of discs. LV ejection fraction was calculated and expressed as a percentage.[13] Intra- and inter-observer variability for the assessment of LV volumes and LVEF were previously reported.[14] Severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler data using the 4-chamber apical views according to the ACC/AHA guidelines. Mitral regurgitation was classified as mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20-40%) and severe (jet area/left atrial area >40%).[15]

CRT implantation

All patients received a biventricular pacemaker with cardioverter-defibrillator function (Contak Renewal 4RF, Boston Scientific St. Paul, Minnesota; or InSync Sentry, Medtronic Inc. Minneapolis, Minnesota; Lumax 340 HF-T, Biotronik, Berlin). The right atrial and ventricular leads were positioned conventionally. All LV leads were implanted transvenously, and positioned preferably in a (postero-)lateral vein. A coronary sinus venogram was obtained using a balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to place the LV lead (Easytrak, Boston Scientific, or Attain-SD, Medtronic, or Corox OTW Biotronik) in the coronary sinus.

Definition of CRT response

As previously reported, clinical response to CRT was defined as improvement ≥1 in NYHA functional class at 6 months follow-up and echocardiographic response to CRT was defined by the occurrence of LV reverse remodeling (reduction ≥15% in LVESV at 6 months follow-up).[6]

All clinical and echocardiographic analyses were performed by independent blinded physicians.

Study end points

All patients were followed-up regularly (every 3-6 monthly intervals) and all deaths occurring after 6 months follow-up were recorded as events. All-cause mortality was adjudicated by physicians blinded to the clinical and echocardiographic data.

Statistical analysis

All continuous variables are presented as mean and standard deviation. Categorical variables are presented as frequencies and percentages, and were compared using Chi-square test. Student T test was used to compare unpaired continuous variables. First, the cumulative event rates 6 months after CRT implantation were calculated using the Kaplan-Meier method and dichotomizing the population according to the clinical and echocardiographic response to CRT. The log-rank tests for time-to-event data with respect to all-cause mortality were used for statistical comparison between 2 patient groups. In order to identify independent predictors of all-cause mortality, mul-

tivariable Cox proportional-hazards models were constructed with backward selection (Correct) model. All significant univariable clinical and echocardiographic predictors at baseline, clinical and echocardiographic response to CRT at 6 months follow-up, and hospitalizations for heart failure within 6 months follow-up were entered in the multivariable model as covariates. The Cox proportional-hazards models were then used to estimate hazard ratios and 95% confidence intervals (CI) for those independent variables. To avoid multicollinearity between the univariable predictors, a correlation coefficient of <0.7 (corresponding to a tolerance level of >0.5) was set. Second, the cumulative event rates 6 months after CRT implantation were calculated using the Kaplan-Meier method after dividing the populations in 4 different subgroups based on combined clinical and/or echocardiographic response: patients with both clinical and echocardiographic response, patients with clinical but not echocardiographic response, patients with echocardiographic but not clinical response and patients with neither clinical or echocardiographic response. The log-rank tests for time-to-event data with respect to all-cause mortality were used for statistical comparison between 4 patient subgroups All statistical tests were 2-sided, and a p value <0.05 was considered significant. A statistical software program SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Overall patient population

Of the 679 patients enrolled in the study, 16 (2.4%) patients died before 6 months follow-up and these patients were excluded from further analysis. Therefore, the patient population consisted of 663 heart failure patients.

Baseline clinical, ECG and echocardiographic characteristics are reported in Table 1. The mean age was 65±11 years and 79% of the patients were male. All patients had dilated with depressed LV systolic function.

At 6 months follow-up, 510 (77%) patients showed an improvement ≥1 in NYHA functional class (clinical response to CRT) and 412 (62%) patients showed ≥15% reduction of LVESV (echocardiographic response to CRT). Furthermore, the patient population (n = 663) was divided in 4 subgroups based on combined clinical and/or echocardiographic response to CRT at 6 months follow-up: 348 (52.4%) patients showed both clinical and echocardiographic response, 159 (24%) patients showed clinical but not echocardiographic response, 64 (9.7%) were echocardiographic but not clinical responders, and 92 (13.9%) patients did not show either clinical or echocardiographic response.

Table 1. Baseline characteristics of overall patient population, and survivors versus non-survivors

	Overall population (n=663)	Survivors (n=523)	Non-survivors (n=140)	p value
Demographic characteristics				
Age (yrs)	65±11	65±11	68±10	0.003
Male [n, (%)]	523(79)	405(77)	118(84)	0.078
Body surface area (m2)	1.97±0.22	1.98±0.22	1.94± 0.22	0.041
Body mass index (kg/m2)	26.4±4.3	26.6±4.2	25.6±4.3	0.013
Medical history				
Diabetes [n, (%)]	131(20)	90(17)	41(29)	0.001
Ischemic etiology [n, (%)]	398(60)	300(57)	98(70)	0.007
Systolic blood pressure (mmHg)	121±20	123±20	114±19	<0.001
Diastolic blood pressure (mmHg)	72±12	73±12	69±11	<0.001
Medications [n, (%)]				
ACE inhibitor/Angiotensin receptor blockers	597(90)	477(91)	120(86)	0.054
Beta-blockers	466(70)	381(73)	85(61)	0.005
Diuretics	551(83)	422(81)	129(92)	0.001
Nitrates	161(24)	120(23)	41(25)	0.12
Statins	386(58)	314(60)	72(51)	0.067
Oral anticoagulants/ Aspirin	619(93)	490(94)	129(92)	0.51
Clinical characteristics				
NYHA functional class IV [n, (%)]	40(6.0)	26(5.0)	14(10.0)	0.026
Heart rate (bpm)	72±17	72±17	74±16	0.20
QRS duration (ms)	155± 33	155±33	156±31	0.76
Hemoglobin level (mmol/l)	8.3±0.9	8.4±0.9	8.1±1.0	0.017
Renal dysfunction [(n, (%)]	269 (40.6)	176 (33.7)	93 (66.4)	<0.001
Echocardiographic characteristics				
LV end-diastolic volume (ml)	218±80	215±74	231±96	0.22
LV end-systolic volume (ml)	164±69	160±64	180±84	0.029
LV ejection fraction (%)	25±8	26±8	23±8	<0.001
Severe mitral regurgitation [n, (%)]	113(17)	72(14)	41(29)	<0.001

ACE: angiotensin converting enzyme; LV: left ventricular; NYHA: New York Heart Association.
Renal dysfunction: glomerular filtration rate ≤60 ml/min/1.73m2

Survivors versus non-survivors

During a mean follow-up of 37±22 months, 140 (21%) patients died. Baseline parameters of the survivors versus the non-survivors are reported in Table 2. Of note, the survivors were younger, had less frequently diabetes, ischemic etiology of heart failure, and NYHA functional class IV. Interestingly, the survivors had higher hemoglobin levels and also more preserved renal function. Regarding the echocardiographic data at baseline, the survivors had smaller LVESV, higher LV ejection fraction and less frequently severe mitral regurgitation. There were 7 (1.3%) hospitalizations for heart failure in the survivors and 8 (5.7%) in the non-survivors (p = 0.002) within 6 months follow-up.

The survivors were more frequently clinical responders as compared to the non-survivors (78% versus 70%, p = 0.037). Moreover, the survivors showed higher

Table 2. Cox uni- and multivariable regression analyses for all cause mortality

Dependent variable: All cause mortality	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Independent variables				
Age (yrs)	1.03(1.01-1.05)	0.001	1.03(1.01-1.05)	0.012
Body mass index (Kg/m2)	0.95(0.91-0.99)	0.012	-	-
Diabetes	2.06(1.42-2.97)	<0.001	2.05(1.40-3.01)	<0.001
Ischemic etiology	1.85(1.29-2.67)	0.001	-	-
Systolic blood pressure (mmHg)	0.98(0.97-0.99)	<0.001	0.99 (0.98-0.99)	0.023
Diuretics	2.24(1.21-4.15)	0.010	-	-
Hemoglobin level (mmol/l)	0.75(0.63-0.90)	0.002	-	-
Renal dysfunction	3.05(2.15-4.33)	<0.001	1.93(1.29-2.89)	0.001
LV ejection fraction (%)	0.97(0.95-0.99)	0.003	0.98 (0.96-1.00)	0.088
Severe mitral regurgitation	1.91(1.32-2.75)	0.001	1.47(1.00-2.14)	0.048
Hospitalizations for heart failure within 6 months follow-up	3.93(1.91-8.06)	<0.001	4.03(1.91-8.50)	<0.001
Clinical response	0.59(0.41-0.85)	0.004	-	-
LV reverse remodeling	0.31(0.22-0.43)	<0.001	0.35(0.25-0.50)	<0.001

CI: confidence intervals; HR: hazards ratio; LV: left ventricular
Renal dysfunction: glomerular filtration rate ≤60 ml/min/1.73m2

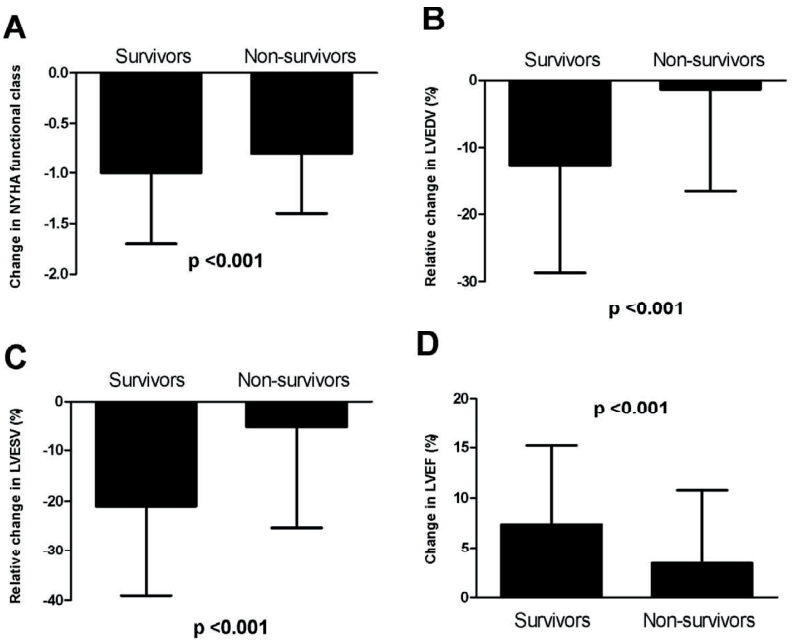

Figure 1. Panel A shows the absolute change between 6 months follow-up and baseline in New York Heart Association (NYHA) functional class. **Panel B and C** show the relative changes in left ventricular end-diastolic (LVEDV) and end-systolic volumes (LVESV). **Panel D** shows the absolute change in left ventricular ejection fraction (LVEF)

echocardiographic response rate as compared to the non-survivors (69% versus 37%, p <0.001). The clinical (change in NYHA functional class at 6 months follow-up) and the echocardiographic (change in LVEDV, LVESV and LV ejection fraction) improvements are illustrated in Figure 1.

Clinical and echocardiographic response to CRT versus long-term mortality

Clinical and echocardiographic responses to CRT were both significantly related to all-cause mortality. When the patient population was dichotomized based on clinical response to CRT, a cumulative 2%, 7% and 12% of the patients with improvement in ≥1 NYHA functional class died by 12, 24 and 36 months follow-up, respectively. In contrast, a respective 7%, 18% and 23% of the patients without improvement in ≥1 NYHA functional class died during the same time period (log-rank p = 0.004: Figure 2A).

When the patient population was dichotomized based on echocardiographic response to CRT, a cumulative 1%, 4% and 8% of the patients with LV reverse remodeling died by 12, 24 and 36 months follow-up, respectively. In contrast, a respective

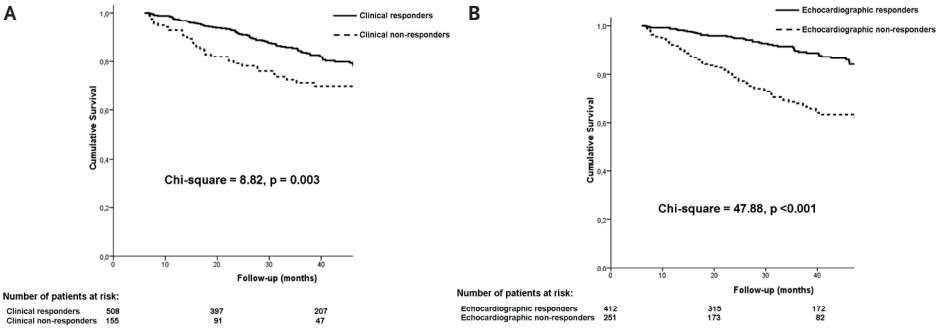

Figure 2. Kaplan Meier curves estimate of all cause mortality. **Panel A** shows the probability of all-cause mortality which differed significantly between the clinical responders and clinical non-responders. **Panel B** shows the probability of all-cause mortality which differed significantly between the echocardiographic responders and echocardiographic non-responders. The orange shadowed bar indicates the 6-month follow-up period after CRT implantation.

8%, 19% and 27% of the patients without LV reverse remodeling died during the same time period (log-rank p <0.001) (Figure 2B).

To identify whether clinical and echocardiographic responses were independent predictors of all-cause mortality during follow-up, significant univariable predictors with a p value <0.05 were entered into the Cox proportional-hazard model as covariates. On multivariable analysis, echocardiographic response (hazard ratio, 0.35; 95% CI, 0.25-0.50; p <0.001) but not clinical response was independently associated with a superior survival.

As expected, the main cause of death was cardiovascular (91[65%] of 140 patients) and specifically related to progression of heart failure (81[89%] of 91 patients). Interestingly, echocardiographic non-responder patients died more frequently for cardiovascular reasons as compared to responder patients (65 [74%] vs. 26[50%] patients, p= 0.004).

Finally, dividing the patient population in 4 subgroups based on combined clinical and/or echocardiographic response, patients with both clinical and echocardiographic response to CRT and patients with echocardiographic but not clinical response had significantly lower mortality (12.9% and 10.9%, respectively) as compared to patients with clinical but not echocardiographic response or patients without any response to CRT (nor clinical or echocardiographic), in whom mortality rates were 32.7% and 39.1%, respectively (chi-square = 48.72, p <0.001). Figure 3 represents the Kaplan-Meier survival curves of these 4 subgroups of patients showing superior survival for patients with both clinical and echocardiographic response to CRT and for patients with echocardiographic but not clinical response to CRT.

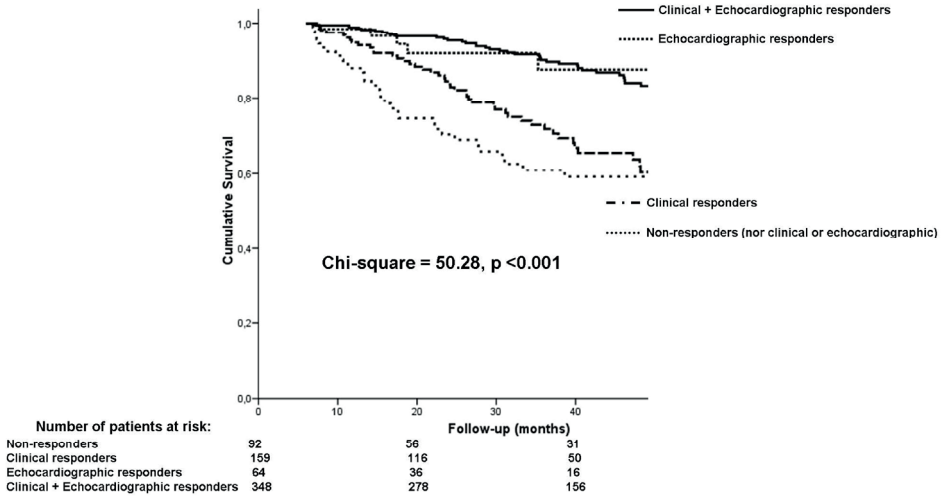

Figure 3. Kaplan Meier curves estimate of all cause mortality in 4 subgroups of patients: clinical + echocardiographic responders, only echocardiographic responders, only clinical responders and non-responders (nor clinical or echocardiographic). The orange shadowed bar indicates the 6-month follow-up period after CRT implantation.

DISCUSSION

The present study demonstrated that reduction of ≥15% LVESV, regardless changes in clinical status, was a predictor of all-cause mortality in heart failure patients treated with CRT. Specifically, LV reverse remodeling was an important and independent predictor of outcome in CRT recipients over other well established predictors of mortality in the general heart failure population.

Clinical and echocardiographic response to CRT

Along the various single- and multi-center trials on CRT, definition of response to CRT has widely varied.[16] Different clinical and echocardiographic parameters have been used to evaluate the efficacy of CRT. In addition, the response to CRT has been evaluated at different time points, most commonly at 3 or 6 months follow-up. However, it has been repeatedly shown that clinical and echocardiographic CRT response may not coincide and, indeed, a significant percentage of patients who showed an improvement in clinical end points did not show any improvement in echocardiographic parameters (≥15% LV reverse remodeling or significant improvement in LV ejection fraction).[6, 16, 17] In the present study, 77% of the patients showed an improvement in NYHA function

class of at least 1-point whereas 62% showed ≥15% reduction in LVESV. This confirms previous findings and suggests the presence of a placebo effect that may overestimate the benefits of CRT when the response is defined according to clinical criteria. However, it may be more interesting to evaluate whether this improvement in clinical status or in echocardiographic parameters at mid-term follow-up conveys or not a superior long-term survival. Indeed, the appropriateness of surrogate end points, such as NYHA functional class or LV reverse remodeling, to evaluate the efficacy of heart failure therapies depends on the strength of the statistical relationship between the change in the surrogate end points over time and the clinical outcome.[8]

Response to CRT versus long-term survival

The present study demonstrated that the occurrence of significant LV reverse remodeling at 6 months follow-up was related with superior long-term survival. In contrast, improvement in NYHA functional class was not associated with improved long-term survival. This was also confirmed dividing the patient population in 4 subgroups based on combined clinical and/or echocardiographic response CRT response. The patients with echocardiographic response to CRT (clinical and echocardiographic or only echocardiographic CRT response) had better survival as compared to the patients without echocardiographic response to CRT (Figure 3). Previously, Yu et al.[5] have shown in 141 heart failure patients that LVESV reduction was independently associated to mid-term outcome after CRT. The authors found a relationship between reduction of LVESV and mid-term clinical outcome. However, the association between improvement in clinical status (defined by ≥1 point in NYHA functional class) and all-cause and cardiovascular mortality was not evaluated. More recently, the results of the REVERSE, MADIT-CRT and RAFT trials have shown that in mildly symptomatic heart failure patients (NYHA functional class I-II), CRT reduced the number of heart failure re-hospitalizations, induced a significant LV reverse remodeling and improved the long-term survival.[18-20] This improvement in long-term survival might be related to improvement in LV performance and LV reverse remodeling rather than improvements in NYHA functional class since the included patients were asymptomatic or mildly symptomatic.

The present study confirms and extends these preliminary results in over 650 heart failure patients treated with CRT. LV reverse remodeling was independently related to all cause mortality (hazard ratio, 0.34; 95% CI, 0.25-0.50; p <0.001) together with age, presence of diabetes, renal dysfunction, and heart failure hospitalizations. These clinical parameters (age, diabetes, systolic blood pressure, renal dysfunction, and heart failure hospitalizations,) are well known strong prognosticators in

patients with advanced heart failure.[21-23] However, thus far, the effects of CRT on LV dimensions and its implications on long-term survival have not been evaluated together with these clinical variables.[4, 5] The fact that LV reverse remodeling at mid-term follow-up was still an independent predictor of long-term outcome after adjusting for these powerful risk factors underlines the relevance of the assessment of CRT response at mid-term follow-up based on LV reverse remodeling.

Study limitations

The study was retrospective and reported the experience of a single center. Data on LV lead position was not included in the present study. The influence of this parameter on CRT response and outcome has been well –described in observational and randomized trials. However, the impact of LV lead position on CRT response and outcome was beyond the scope of the present study which focused on the prognostic implications of clinical and/or echocardiographic response. The percentage of beta-blocker use was relatively low but still higher as compared to previous randomized trials (MIRACLE and COMPANION) and similar to the CARE-HF trial but lower than the recent REVERSE, MADIT-CRT and RAFT trials.[1, 3, 18-20, 24] However all the patients received the maximum tolerated dose of beta-blocker.

CONCLUSIONS

In a large population of heart failure patients treated with CRT, the reduction of LVESV at mid-term follow-up demonstrated to be a better predictor of long-term survival than improvement in clinical status. In addition, LV reverse remodeling was an important and independent predictor of outcome in these patients together with other well established predictors of long-term survival.

REFERENCES

(1) Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.

(2) Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-880.

(3) Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.

(4) Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009;53:483-490.

(5) Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;112:1580-1586.

(6) Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J, III, St John SM, De SJ, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608-2616.

(7) Bax JJ, Gorcsan J, III. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol* 2009;53:1933-1943.

(8) Anand IS, Florea VG, Fisher L. Surrogate end points in heart failure. *J Am Coll Cardiol* 2002;39:1414-1421.

(9) Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol* 2000;35:569-582.

(10) Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am Coll Cardiol* 2008;52:438-445.

(11) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1-266.

(12) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

(13) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.

(14) Bertini M, Marsan NA, Delgado V, van Bommel RJ, Nucifora G, Borleffs CJW, Boriani G, Biffi M, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Effects of cardiac resynchronization therapy on left ventricular twist. *J Am Coll Cardiol* 2009;54:1317-1325.

(15) Bonow RO, Carabello BA, Kanu C, de LA, Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:e84-231.

(16) Fornwalt BK, Sprague WW, BeDell P, Suever JD, Gerritse B, Merlino JD, Fyfe DA, Leon AR, Oshinski JN. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. *Circulation* 2010;121:1985-1991.

(17) Auger D, van Bommel RJ, Bertini M, Delgado V, Ng AC, Ewe SH, Shanks M, Marsan NA, Mooyaart EAQ, Witkowski T, Poldermans D, Schalij MJ, Bax JJ. Prevalence and characteristics of patients with clinical improvement but not significant left ventricular reverse remodeling after cardiac resynchronization therapy. *Am Heart J* 2010;160:737-743.

(18) Linde C, Abraham WT, Gold MR, St John SM, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;52: 1834-1843.

(19) Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-1338.

(20) Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363:2385-2395.

(21) Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;38:955-962.

(22) Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de ZD, Pocock S, van Veldhuisen DJ. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;113:671-678.

(23) McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004;109: 1004-1009.

(24) Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De MT, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.

CHAPTER 9

Longitudinal mechanics of the periinfarct zone and ventricular tachycardia inducibility in patients with chronic ischemic cardiomyopathy.

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ABSTRACT

Background. Quantification of segmental left ventricular (LV) strain by speckle-tracking echocardiography can identify transmural infarcts in patients with chronic ischemic cardiomyopathy. The aim of the study was to explore the relationship between the LV longitudinal peak systolic strain (LPSS) of the infarct, peri-infarct and remote zones and monomorphic ventricular tachycardia (VT) inducibility on electrophysiological (EP) study.

Methods. A total of 134 patients with chronic ischemic cardiomyopathy scheduled for EP study were included. The protocol consisted of clinical, ECG and echocardiographic evaluation, including LV longitudinal strain analysis using speckle-tracking echocardiography, immediately before EP study. An infarct segment was defined as a longitudinal strain value of >-5%, and a peri-infarct segment was defined as immediately adjacent to an infarct segment.

Results. The infarct zone had the most impaired longitudinal strain (-0.5±3.0%), whereas the peri-infarct and remote zones had more preserved longitudinal strain (-10.8±1.9% and -14.5±3.0%, respectively; ANOVA p<0.001). Seventy-two (54%) patients had inducible monomorphic VT on EP study. There was no significant difference in LVEF (31±9% vs. 32±11%, p=0.29) between inducible and non-inducible patients. LPSS of the peri-infarct zone was more impaired in inducible patients (-9.8±1.5% vs. -11.0±2.1%, p=0.001), but no differences in LPSS of the infarct (-0.5±3.2% vs. -0.4±2.7%, p=0.75) and remote (-14.6±2.8% vs. -14.5±3.4%, p=0.92) zones were observed. Only LPSS of the peri-infarct zone (OR 1.43, 95% CI 1.15-1.78, p=0.001) was independently related to monomorphic VT inducibility on multiple logistic regression.

Conclusions. Longitudinal strain analysis may be a useful imaging tool to risk-stratify ischemic patients for malignant ventricular arrhythmia.

INTRODUCTION

Coronary artery disease, provoking lethal ventricular arrhythmias, is one of the most common causes of sudden cardiac death.[1] Usually, the electrical sequence is due to the initial development of monomorphic ventricular tachycardia (VT) that subsequently degenerate into ventricular fibrillation.[2] The classical anatomical substrate for monomorphic VT is the peri-infarct zone with re-entry pathways that abounds the infarcted myocardial scar tissue.[3] These scar areas represented by the infarct zone are normally highly fibrosed, whereas the peri-infarct zone constitutes a highly heterogeneous area with intermediate degrees of non-transmural fibrosis.[4] The tissue heterogeneity of the peri-infarct zone may be electrically unstable and constitute the substrate for re-entrant VT.[4-6]

Recently cardiac magnetic resonance imaging (CMR) permits identification of myocardial scar tissue and can also characterize the peri-infarct zone.[7, 8] Specifically, the extent of peri-infarct zone can be quantified with contrast-enhanced CMR, whereas the mechanical properties of the peri-infarct zone can be assessed by tagged CMR.[7, 8] These studies demonstrated a strong relationship between the peri-infarct zone heterogeneity and monomorphic VT inducibility.[7, 8]

Novel speckle-tracking echocardiography with quantifications of regional left ventricular (LV) longitudinal strain has been shown to have good sensitivity and specificity in identifying transmural scar tissue by contrast-enhanced CMR.[9] Therefore, regional speckle-tracking analysis of LV longitudinal peak systolic strain (LPSS) permits the differentiation of the infarct, peri-infarct and remote zones by characterizing the different tissue mechanical properties. Thus, the aim of the present study was to explore the relationship between the LPSS of the peri-infarct zone detected with speckle-tracking echocardiography and monomorphic VT inducibility in patients with chronic ischemic cardiomyopathy.

METHODS

Patient population and protocol

A total of 141 consecutive patients scheduled for cardiac electrophysiological (EP) study were included. Inclusion criteria were previous history of myocardial infarction (>40 days ago), referral for a clinically indicated EP study because of syncope or non-sustained ventricular tachycardia at ECG-Holter monitoring, and sinus rhythm during the echocardiographic examination.

The protocol consisted of an extensive clinical, electrocardiographic (ECG), and echocardiographic evaluation, including LPSS analysis. Afterwards (maximum 24 hours later), all patients underwent a clinically indicated EP study to induce monomorphic VT. All echocardiographic analyses were performed by an independent observer blinded to the EP study results. The echocardiographic analyses included assessments of LV volumes, LV ejection fraction (LVEF) and wall motion scoring. Speckle-tracking analysis using automated function imaging was applied to determine global LPSS. In addition, the LPSS of the infarct, peri-infarct and remote zones were determined based on segmental strain values.[9] Finally, the clinical, ECG, and echocardiographic variables were tested by uni- and multivariable logistic regression analysis to investigate the association with inducibility of monomorphic VT at EP study.

Standard echocardiography

All patients were imaged in left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwakee, Wisconsin, USA). Standard 2-dimensional images were obtained using a 3.5-MHz transducer and digitally stored in cine-loop format; the analysis was performed offline using EchoPAC version 108.1.5 (General Electric-Vingmed).

LV end-diastolic volume (LVEDV), end-systolic volume (LVESV) and LVEF were calculated using Simpson's biplane method of discs as recommended by the American Society of Echocardiography guidelines.[10]

Segmental wall motions were evaluated and scored as 1: normal; 2: hypokinesia; 3: akinesia; 4: dyskinesia. Global wall motion score index was calculated using the sum of the segmental scores divided by the number of segments analyzed, as previously described.[10]

Speckle-tracking analysis

The speckle-tracking software tracks frame-to-frame movements of natural myocardial acoustic markers, or speckles, on standard gray scale images. Each region of the myocardium has a characteristic speckle-pattern; therefore it can be followed during the cardiac cycle. Furthermore, speckle-tracking analysis is an angle independent technique that allows the evaluation of myocardial contraction/relaxation in the circumferential, longitudinal and radial directions.[11, 12]

Longitudinal strain analysis: global, infarct, peri-infarct and remote LPSS

Myocardial strain can be assessed from temporal differences in the mutual distance of neighboring speckles. The change in length/initial length of the speckle-pattern over the cardiac cycle can be used to calculate longitudinal strain, with myocardial shortening represented as negative strain, and myocardial lengthening as positive strain. During the systole the myocardium shortens in the longitudinal direction and, conventionally, is presented as negative values. Therefore, more negative values indicate larger and more preserved longitudinal strain. LV longitudinal strain was determined from the apical long-axis, 4- and 2-chamber views with optimal 2D gray scale image frame rates ranging from 50 to 100 frame/s. After defining the mitral annulus and the LV apex with 3 index points at the end-systolic frame in each apical view, the automated function imaging software automatically traces the endocardial border while allowing the user to manually adjust the region of interest width to include the entire myocardial wall. Further manual adjustments of the endocardial border were performed to ensure adequate tracking throughout the cardiac cycle. The LV was automatically divided in 6 segments in each apical view and tracking quality was validated for each segment. Finally, the automated algorithm provides the LPSS value for each LV segment in a 17-segment model polar plot, with the average value of LPSS for each apical view and the averaged global LPSS value for the entire LV.

According to previous evidence, a segmental longitudinal strain value >-5% was consistent with transmural scar on delayed enhancement cardiac magnetic resonance imaging, and was classified as infarcted segment.[9] Thus, all segments adjacent to the infarcted segments were classified as peri-infarct segments and all remaining segments were classified as remote segments (Figure 1). Finally, LPSS of the infarct, peri-infarct and remote zones were calculated as the means of the LPSS of the infarct, peri-infarct and remote segments respectively.

The intra- and inter-observer variabilities for longitudinal strain analysis as assessed with Bland-Altman analysis were previously reported and were -0.3 ± 0.6% and -0.2 ± 2.6%, respectively.[13]

Cardiac electrophysiological testing

The cardiac EP study was performed within 24 hours after echocardiographic evaluations. Studies were performed in the post absorptive, non-sedated state. Antiarrhythmic drugs were discontinued for 5 half-lives, with the exception of amiodarone which was continued in 13 patients.

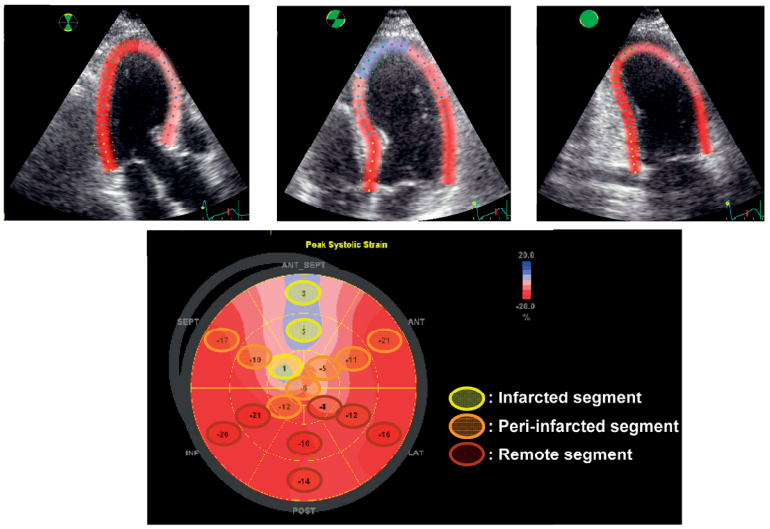

Figure 1. Example of assessment of longitudinal strain from the 3 apical views (upper panel from left to the right: 3-chamber, 4-chamber and 2-chamber views). From the polar plot model (lower panel), all segments with segmental strain value >-5% were classified as infarct segments. All segments adjacent to infarcted segments were classified as peri-infarct segments, and the remaining segments were classified as remote segments. Infarct zone strain (the average of the strain of the infarcted segments) was 2.7%. Peri-infarct zone strain (the average of the strain of the peri-infarcted segments) was -11.7%. Remote zone strain (the average of the strain of the remote segments) was -16.1%.

The EP study consisted of a programmed extrastimulation protocol using 3 drive cycle lengths (600, 500, 400 ms) and 1, 2 and 3 extrastimuli while pacing at 2 right ventricular sites (right ventricular apex and right ventricular outflow tract). The initial S2 coupling interval in each stimulation sequence was at least 300 ms and stimulation was not performed at a coupling interval of <200 ms. Inducibility at EP study was defined as the induction of a monomorphic VT lasting for more than 30 seconds or monomorphic VT requiring termination because of hemodynamic compromise.

Statistical analysis

All continuous variables are presented as mean ± SD. Categorical data are presented as numbers and percentages. Differences in LPSS and number of segments between the different zones (infarct, peri-infarct and remote) in the overall population were assessed by one-way analysis of variance (ANOVA), and post-hoc analyses were performed with Bonferroni correction. Unpaired Student's t-test and Chi-square test were used to compare continuous and categorical variables respectively for inducible

vs. non-inducible patients. In order to identify variables related to a positive response to EP study, uni- and multivariable logistic regression analyses were performed and included clinical (age, gender, etiology, cardiovascular risk factors, time since last myocardial infarction, New York Heart Association [NYHA] functional class, heart rate, and medications), ECG (PR, QRS duration and corrected QT interval duration), and echocardiographic (LV volumes, LVEF, wall motion score index, global LPSS, infarct LPSS, peri-infarct LPSS, remote LPSS) variables. Only univariable predictors with a p value ≤0.10 were entered as covariates in multivariable logistic regression model using an enter method. Odds ratio and 95% confidence intervals were calculated. All statistical tests were 2-sided, and a p value <0.05 was considered significant. A statistical software program SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

RESULTS

Overall population

Reliable speckle-tracking was obtained in 134 (95%) patients and constituted the final study population. Tables 1 and 2 show the demographic and clinical characteristics of the overall patient population. In particular, the mean age of the overall patient population was 67 ± 10 years and 119 (89%) patients were men. Both the QRS duration and the corrected QT interval were slightly prolonged (122 ± 28 ms and 444 ± 35 ms respectively). Beta-blockers and angiotensin-converting enzyme inhibitor or angiotensin receptor blockers treatments were present in 67% and 92% of the patients, respectively; whereas 10% and 16% of the patients were treated with amiodarone or sotalol, respectively.

All the patients had dilated LV volumes (LVEDV and LVESV were 171 ± 57 ml and 120 ± 50 ml respectively) and reduced LVEF (31 ± 10%). The mean global LPSS was -9.1 ± 3.8%. A progressive increment in LPSS from the infarct to peri-infarct and remote zones (ANOVA p <0.001; Figure 2) was observed. The infarct zone showed the most impaired LPSS values (-0.5 ± 3.0%), whereas the peri-infarct and remote zones showed more preserved values of LPSS (-10.8 ± 1.9% and -14.5 ± 3.0%, respectively; Figure 2).

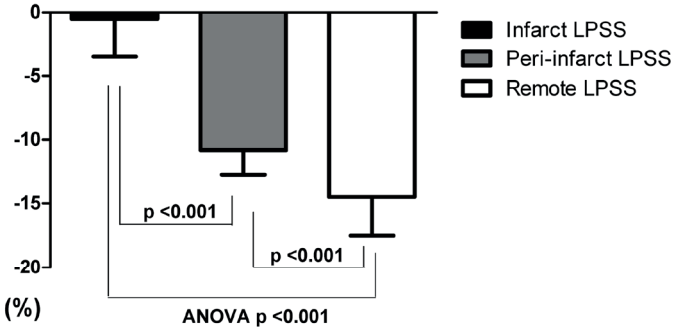

Figure 2. Differences in longitudinal peak systolic strain (LPSS) among infarct, peri-infarct and remote zones.

Inducible vs. non-inducible patients

The EP study was conducted in all the patients without major complications. After EP study, 72 (54%) patients were classified as inducible and 62 (46%) as non-inducible. Table 1 shows the demographic and clinical characteristics of inducible and non-

Table 1. Demographic and clinical characteristics of overall population, and inducible vs. non-inducible patients.

	Overall population (n=134)	Inducible monomorphic VT (n=72)	Non-inducible monomorphic VT (n=62)	p value
Age (yrs)	67±10	67±10	67±10	0.84
Male (%)	119 (89)	67 (87)	52 (90)	0.093
Hypertension (%)	58 (43)	31 (43)	27 (44)	0.95
Diabetes (%)	35 (26)	17 (24)	18 (29)	0.47
Family history of cardiac disease (%)	46 (34)	29 (40)	17 (27)	0.12
Current smoker (%)	21 (16)	11 (15)	10 (16)	0.89
Time since last myocardial infarction (months)	88±90	100±94	74±83	0.090
NYHA functional class III-IV (%)	47 (35)	24 (33)	23 (37)	0.65
Heart rate (bpm)	67±10	66±11	68±10	0.13
PR interval (ms)	182±32	185±32	178±33	0.21
QRS duration (ms)	122±28	126±27	117±28	0.044
Corrected QT interval duration (ms)	444±35	446±33	441±36	0.45

MVT: monomorphic ventricular tachycardia; NYHA: New York Heart Association

inducible patients. There were no significant differences in age, gender, cardiac risk factors, NYHA functional class and heart rate. Inducible patients tended to have longer time since last myocardial infarction (100 ± 94 months vs. 74 ± 83 months, p = 0.090). In addition, QRS duration was significantly longer in inducible patients (126 ± 27 ms vs. 117 ± 28 ms, respectively, p = 0.044). Table 2 showed no significant differences in the use of cardiac medication between inducible and non-inducible patients.

In regards to the echocardiographic variables, there was a trend towards a more dilated LV in inducible patients (178 ± 60 ml vs. 161 ± 53 ml, p = 0.094) but there were no significant differences in LVEF (31 ± 9% vs. 32 ± 11%, p = 0.29). However, LPSS of the peri-infarct zone was more impaired in inducible patients (-9.8 ± 1.5% vs. -11.0 ± 2.1%, respectively, p = 0.001), but there were no significant differences in LPSS of the infarct (-0.5 ± 3.2% vs. -0.4 ± 2.7%, p = 0.75) and remote (-14.6 ± 2.8% vs. -14.5 ± 3.4%, p = 0.92) zones (Table 3). Figure 3 shows examples of patients with and without inducible monomorphic VT. The patient with inducible monomorphic VT had a more reduced LPSS of the peri-infarct zone. Furthermore, in this subgroup of patients mean VT cycle length was 288 ± 65 ms and this was modestly but significantly related to global LPSS (r = 0.52, p <0.001; Figure 4). Conversely, VT cycle length was not correlated to LPSS of the peri-infarct zone.

Table 2. Medications use of overall population, and inducible vs. non-inducible patients.

	Overall population (n=134)	Inducible monomorphic VT (n=72)	Non-inducible monomorphic VT (n=62)	p value
Beta-blockers (%)	90 (67)	46 (64)	44 (71)	0.38
ACE inhibitor/Angiotensin receptor blockers (%)	124 (92)	64 (89)	60 (97)	0.083
Ca-antagonists (%)	12 (9)	9 (12)	3 (5)	0.12
Sotalol (%)	21 (16)	12 (17)	9 (15)	0.73
Amiodarone (%)	13 (10)	6 (8)	7 (11)	0.56
Diuretics (%)	90 (67)	49 (68)	41 (66)	0.81
Nitrates (%)	22 (16)	14 (19)	8 (13)	0.31
Statins (%)	106 (79)	56 (78)	50 (81)	0.68
Acetil salicylic acid/anticoagulants (%)	126 (94)	68 (94)	58 (94)	0.83

ACE: angiotensin-converting enzyme; MVT: monomorphic ventricular tachycardia

Table 3. Echocardiographic characteristics of overall population, and inducible vs. non-inducible patients.

	Overall population (n=134)	Inducible monomorphic VT (n=72)	Non-inducible monomorphic VT (n=62)	p value
LVEDV (ml)	171±57	178±60	161±53	0.094
LVESV (ml)	120±50	126±52	113±47	0.13
LVEF (%)	31±10	31±9	32±11	0.29
WMSI	1.7±0.4	1.8±0.4	1.7±0.4	0.45
Global LPSS (%)	-9.1±3.8	-9.1±3.4	-9.0±4.2	0.81
LPSS of the infarct zone (%)	-0.5±3.0	-0.5±3.2	-0.4±2.7	0.75
LPSS of the peri-infarct zone (%)	-10.8±1.9	-9.8±1.5	-11.0±2.1	0.001
LPSS of the remote zone (%)	-14.5±3.0	-14.6±2.8	-14.5±3.4	0.92

LPSS: longitudinal peak systolic strain; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; MVT: monomorphic ventricular tachycardia; WMSI: wall motion score index.

Predictors of inducibility

After analyzing all clinical, ECG and echocardiographic variables, male gender, time since last myocardial infarction, QRS duration, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers usage, LVEDV and LPSS of the peri-infarct zone had a p value ≤0.10 on univariable logistic regression analysis and were entered in the multivariable model (Table 4). Only LPSS of the peri-infarct zone (odds ratio 1.43, 95% confidence intervals 1.15-1.78, p = 0.001) was independently related to monomorphic VT inducibility on EP study.

DISCUSSION

The current study showed that in patients with chronic ischemic cardiomyopathy, LPSS of the peri-infarct zone was strongly associated to monomorphic VT inducibility. In particular, after correction for clinical, ECG and echocardiographic variables, LPSS of the peri-infarct zone was the only independent factor related to monomorphic VT inducibility.

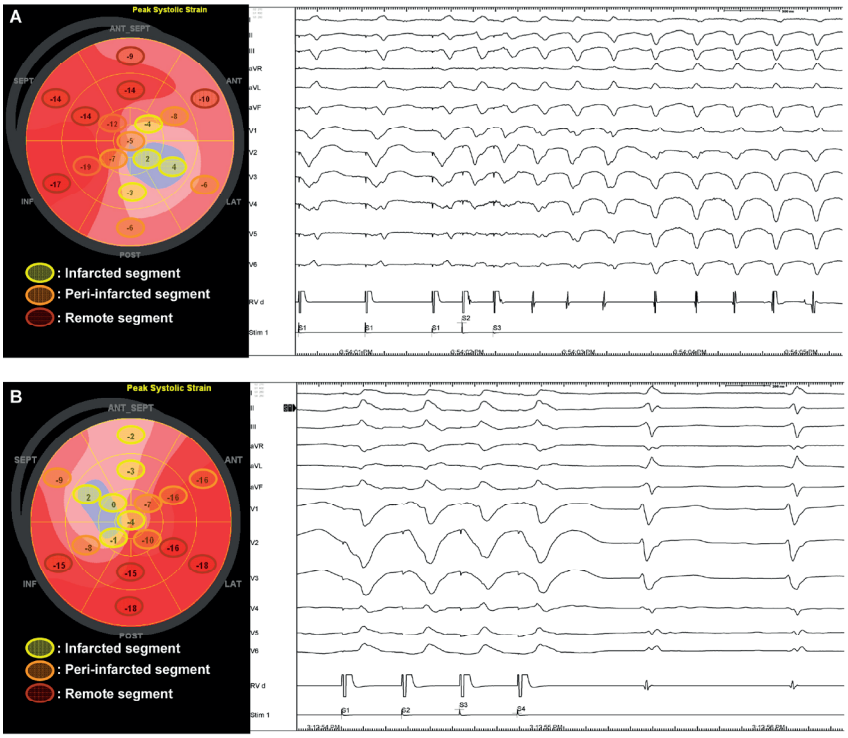

Figure 3. Example of 2 patients with and without inducible monomorphic ventricular tachycardia (VT). The panels show the polar plot model illustrating the values of the longitudinal peak systolic strain for every segment (left) and the electrocardiogram at 100 mm/sec obtained during the electrophysiological test for inducibility (right). **Panel A.** Patient with postero-lateral scar with inducible monomorphic VT. LPSS of the peri-infarct zone was -9.0%. **Panel B.** Patient with septal and apical scar without inducible monomorphic VT. LPSS of the peri-infarct zone was more preserved (-11.0%) as compared to the inducible patient.

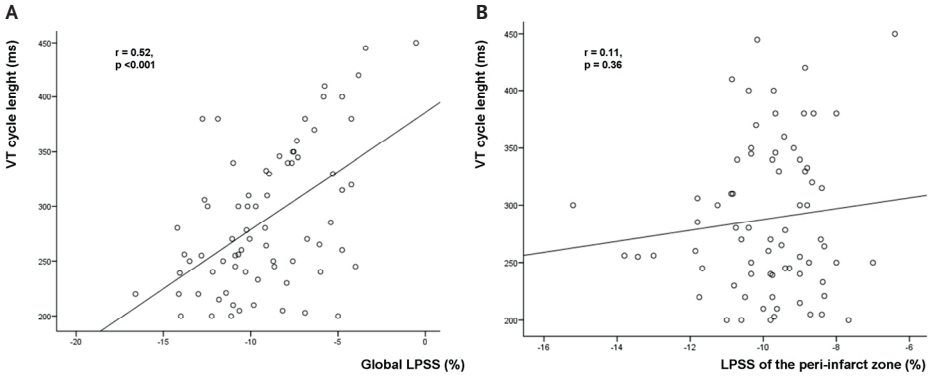

Figure 4. Panel A: Correlation between ventricular tachycardia (VT) cycle length and global longitudinal peak systolic strain (LPSS). **Panel B:** Correlation between ventricular tachycardia (VT) cycle length and LPSS of the peri-infarct zone.

Table 4. Uni- and multivariate logistic regression analysis to identify predictors of monomorphic ventricular tachycardia inducibility

Dependent variable: Inducibility of monomorphic VT	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Independent variables				
Male	2.58 (0.83-8.00)	0.10	1.89 (0.53-6.72)	0.33
Time since last myocardial infarction (months)	1.00 (1.00-1.01)	0.093	1.00 (0.99-1.01)	0.16
QRS duration (ms)	1.01 (1.00-1.03)	0.047	1.01 (0.99-1.02)	0.44
ACE inhibitor/Angiotensin receptor blockers (%)	0.27 (0.05-1.31)	0.10	0.32 (0.06-1.69)	0.18
LVEDV (ml)	1.01 (1.00-1.01)	0.097	1.00 (0.99-1.01)	0.35
LPSS of the peri-infarct zone (%)	1.44 (1.16-1.80)	0.001	1.43 (1.15-1.78)	0.001

CI: confidence intervals; LPSS: longitudinal peak systolic strain; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MVT: monomorphic ventricular tachycardia; OR: odds ratio.

Peri-infarct zone and monomorphic VT

In the chronic phase of myocardial infarction, monomorphic VT is caused by re-entrant pathways around the borders of infarcted scar area.[3, 5] Therefore, the peri-infarct zone is the anatomical substrate for these malignant ventricular arrhythmias.[3, 5, 14]

Previous animal studies demonstrated that 2 months after induction of myocardial infarction, the myofibers of the peri-infarct zone were highly disorganized with replacement by connective tissue.[14] In particular, peri-infarct zone was characterized by non-uniform anisotropic areas with isles of viable myocardium and fibrosis, resulting in slow electrical conduction of the cardiac pulse.[14] This tissue heterogeneity with altered mechanical properties results in electrical instability and may predispose to ventricular arrhythmias.

The tissue heterogeneity of the peri-infarct zone has been investigated with different techniques trying to characterize the electrical, anatomical and mechanical properties.

The electrical characterization of the peri-infarct zone has been studied with bipolar electrograms derived from electro-anatomic mapping techniques.[4, 6, 15, 16] The infarct areas had the lowest voltage amplitudes whereas the remote areas had the highest voltages amplitudes.[15, 16] The peri-infarct zone had intermediate voltage amplitudes and subsequently, several clinical studies have demonstrated that these areas were the target of successful monomorphic VT ablation.[4, 6] Recently, contrast-enhanced

CMR has been shown to be a useful imaging technique to anatomically characterize the peri-infarct zone.[8, 17, 18] Whereas the infarct zone shows high-intensity contrast signal, the peri-infarct zone shows an intermediate-intensity contrast signal that can be quantified with dedicated algorithms.[8, 17, 18] The extent of the peri-infarct zone has been related to an increased mortality after myocardial infarction, and increased inducibility for monomorphic VT on EP testing.[8, 18] Indeed, Yan et al.[18] demonstrated that the extent of peri-infarct zone predicted an increased mortality in patients with previous myocardial infarction. Subsequently, Schmidt et al.[8] found that that larger extent of peri-infarct zone was independently related with an increased inducibility for sustained monomorphic VT. More recently, Roes et al.[17] corroborated these previous observations by reporting the association between the peri-infarct zone extent and the occurrence of spontaneous ventricular arrhythmia detected as appropriate therapies of implantable cardioverter-defibrillator (ICD) in 91 patients with previous myocardial infarction and who underwent ICD implantation.

Finally, the mechanical properties of the peri-infarct zone have been recently studied by Fernandes et al.[7] using tagged CMR. The authors evaluated the circumferential strain and time to peak circumferential strain at the peri-infarct zone. An enhanced peak circumferential strain and earlier time to peak circumferential strain at the peri-infarct zone were positively related with monomorphic VT inducibility.

In the present study 2-dimensional speckle-tracking analyses of the standard grey-scale echocardiographic images was used. This imaging technique provides valuable information on the mechanical properties of the peri-infarct zone. Particularly, in the current study the longitudinal mechanics of the peri-infarct zone was investigated. Inducible patients had larger impairment of LPSS in the peri-infarct zone (-9.8 ± 1.5% vs. -11.0 ± 2.1%, p = 0.001). Furthermore, after correcting for clinical, ECG and echocardiographic variables, LPSS of the peri-infarct zone was the only independent determinant of monomorphic VT inducibility (adjusted odds ratio 1.39, 95% confidence interval 1.11-1.78, p = 0.005). Therefore, this observation confirmed the independent relationship between the mechanical properties of the peri-infarct zone, particularly the longitudinal mechanics, and monomorphic VT inducibility.

Importantly, in contrast to global LPSS, peri-infarct peak longitudinal strain was not related to VT cycle length. This finding underscores that the LPSS values of peri-infarct zone did not reflect the extension of the scar but only the longitudinal function of the tissue adjacent to the infarcted segments. Conversely, global LPSS may reflect the total scar burden,[19] and more impaired global LPSS are associated to longer VT cycle length.

Clinical implications

The present study underscores the independent relationship between reduced peri-infarct zone longitudinal strain and VT inducibility in patients with chronic ischemic cardiomyopathy. Regional LV longitudinal strain analysis by speckle-tracking echocardiography may be helpful in identifying patients with increased risk of malignant ventricular arrhythmias. Furthermore, quantifications of LPSS of the peri-infarct zone may be a potentially useful tool for selecting patients who might benefit from ICD therapy.

CONCLUSIONS

In patients with chronic ischemic cardiomyopathy, LPSS of the peri-infarct zone was independently associated to monomorphic VT inducibility. Thus, speckle-tracking analysis may be a useful imaging tool to risk-stratify patients with chronic ischemic cardiomyopathy who might benefit from ICD.

REFERENCES

(1) Holmes DR, Jr., Davis KB, Mock MB, Fisher LD, Gersh BJ, Killip T, III, Pettinger M. The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study. *Circulation* 1986;73:1254-1263.

(2) Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation* 1998;98:2334-2351.

(3) Eckardt L, Haverkamp W, Johna R, Bocker D, Deng MC, Breithardt G, Borggrefe M. Arrhythmias in heart failure: current concepts of mechanisms and therapy. *J Cardiovasc Electrophysiol* 2000;11: 106-117.

(4) Deneke T, Muller KM, Lemke B, Lawo T, Calcum B, Helwing M, Mugge A, Grewe PH. Human histopathology of electroanatomic mapping after cooled-tip radiofrequency ablation to treat ventricular tachycardia in remote myocardial infarction. *J Cardiovasc Electrophysiol* 2005;16:1246-1251.

(5) de Bakker JM, van Capelle FJ, Janse MJ, Wilde AA, Coronel R, Becker AE, Dingemans KP, van Hemel NM, Hauer RN. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. *Circulation* 1988;77:589-606.

(6) Verma A, Marrouche NF, Schweikert RA, Saliba W, Wazni O, Cummings J, bdul-Karim A, Bhargava M, Burkhardt JD, Kilicaslan F, Martin DO, Natale A. Relationship between successful ablation sites and the scar border zone defined by substrate mapping for ventricular tachycardia post-myocardial infarction. *J Cardiovasc Electrophysiol* 2005;16:465-471.

(7) Fernandes VR, Wu KC, Rosen BD, Schmidt A, Lardo AC, Osman N, Halperin HR, Tomaselli G, Berger R, Bluemke DA, Marban E, Lima JA. Enhanced infarct border zone function and altered mechanical activation predict inducibility of monomorphic ventricular tachycardia in patients with ischemic cardiomyopathy. *Radiology* 2007;245:712-719.

(8) Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, Gerstenblith G, Weiss RG, Marban E, Tomaselli GF, Lima JA, Wu KC. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation* 2007;115:2006-2014.

(9) Roes SD, Mollema SA, Lamb HJ, van der Wall EE, de Roos A, Bax JJ. Validation of echocardiographic two-dimensional speckle tracking longitudinal strain imaging for viability assessment in patients with chronic ischemic left ventricular dysfunction and comparison with contrast-enhanced magnetic resonance imaging. *Am J Cardiol* 2009;104:312-317.

(10) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.

(11) Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-1029.

(12) Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004;17:630-633.

(13) Delgado V, Mollema SA, Ypenburg C, Tops LF, van der Wall EE, Schalij MJ, Bax JJ. Relation between global left ventricular longitudinal strain assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. *J Am Soc Echocardiogr* 2008;21:1244-1250.

(14) Ursell PC, Gardner PI, Albala A, Fenoglio JJ, Jr., Wit AL. Structural and electrophysiological changes in the epicardial border zone of canine myocardial infarcts during infarct healing. *Circ Res* 1985;56:436-451.

(15) Callans DJ, Ren JF, Michele J, Marchlinski FE, Dillon SM. Electroanatomic left ventricular mapping in the porcine model of healed anterior myocardial infarction. Correlation with intracardiac echocardiography and pathological analysis. *Circulation* 1999;100:1744-1750.

(16) Soejima K, Stevenson WG, Maisel WH, Sapp JL, Epstein LM. Electrically unexcitable scar mapping based on pacing threshold for identification of the reentry circuit isthmus: feasibility for guiding ventricular tachycardia ablation. *Circulation* 2002;106:1678-1683.

(17) Roes SD, Borleffs JW, van der Geest RJ, Westenberg JJM, Ajmone Marsan N, Kaandorp TAM, Reiber JHC, Zeppenfeld K, Lamb HJ, de Roos A, Schalij MJ, Bax JJ. Infarct tissue heterogeneity assessed with contrast-enhanced magnetic resonance imaging predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. *Circ Cardiovasc Imaging* 2009;2:183-190.

(18) Yan AT, Shayne AJ, Brown KA, Gupta SN, Chan CW, Luu TM, Di Carli MF, Reynolds HG, Stevenson WG, Kwong RY. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation* 2006;114:32-39.

(19) D'Andrea A, Caso P, Scarafile R, Riegler L, Salerno G, Castaldo F, Gravino R, Cocchia R, Del VL, Limongelli G, Di SG, Ascione L, Iengo R, Cuomo S, Santangelo L, Calabro R. Effects of global longitudinal strain and total scar burden on response to cardiac resynchronization therapy in patients with ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2009;11:58-67.

CHAPTER 10

Global longitudinal strain predicts long-term survival in patients with chornic ischemic cardiomyopathy.

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Circ Cardiovasc Imaging. 2012; 5(3):383-91

ABSTRACT

Background. Left ventricular (LV) global longitudinal strain (GLS) is a measure of the active shortening of the LV in the longitudinal direction which can be assessed with speckle tracking echocardiography. The aims of this evaluation were to validate the prognostic value of GLS as new index of LV systolic function in a large cohort of patients with chronic ischemic cardiomyopathy and determine the incremental value of GLS to predict long-term outcome over other strong and well established prognostic factors.

Methods and Results. A total of 1060 patients underwent baseline clinical evaluation and transthoracic echocardiography. Median age was 66.9 years [interquartile range (IQR) 58.4, 74.2 years], 739 (70%) men. The median follow-up duration for the entire patient population was 31 months. During the follow-up, 270 patients died and 309 patients reached the combined end point (all-cause mortality and heart failure hospitalization). Compared to survivors, patients who died (270, [25%]) had larger LV volumes ($p<0.05$), lower LV ejection fraction ($p=0.004$), higher wall motion score index ($p=0.001$) and greater impairment of LV GLS ($p<0.001$). After dichotomizing the population based on the median value of LV GLS (-11.5%), patients with a LV GLS ≤-11.5% had superior outcome compared with patients with a LV GLS >-11.5% (log rank chi squared 13.86 and 14.16 for all-cause mortality and combined end point respectively, $p<0.001$ for both). On multivariate analysis, GLS was independently related to all-cause mortality (hazard ratio per 5% increase, 1.69, 95% CI 1.33-2.15; $p<0.001$) and combined end point (1.64, 95% CI 1.32-2.04; $p<0.001$).

Conclusions. The assessment of LV GLS with speckle tracking echocardiography is significantly related to long-term outcome in patients with chronic ischemic cardiomyopathy.

INTRODUCTION

Several studies have shown that various clinical, electrocardiographic (ECG), and echocardiographic parameters predict long-term outcome in patients with chronic ischemic cardiomyopathy.[1, 2] In patients with chronic ischemic cardiomyopathy, left ventricular (LV) ejection fraction (EF) and wall motion score index (WMSI) are well established predictors of long-term outcome.[3-7] However, both LVEF and WMSI have some limitations related to reproducibility, geometric assumption and expertise.

Recently new parameters derived from two-dimensional (2D) speckle tracking echocardiography permit the assessment of active myocardial deformation in multiple directions (radial, circumferential and longitudinal).[8-10] Particularly, the measurement of LV global longitudinal strain (GLS), which is a measure of the active shortening of the LV in the longitudinal direction, is more reproducible than LVEF and WMSI and does not rely on geometrical assumptions.[11-13]

Thus far, preliminary data suggest that LV GLS may be superior to LVEF and WMSI for the prediction of long-term outcome in different populations.[14] However, whether LV GLS is related to long-term outcome in patients with chronic ischemic heart disease is not established yet. Accordingly, the aims of this evaluation were to validate the prognostic value of LV GLS as new index of LV systolic function in a large cohort of patients with chronic ischemic cardiomyopathy, and determine the incremental value of LV GLS to predict long-term outcome over other strong and well established clinical, ECG and echocardiographic prognostic factors.

METHODS

Patient population and evaluation

The present evaluation consisted of retrospective analysis of clinical and echocardiographic data from patients with chronic ischemic heart disease. Patients with known coronary artery disease and prior myocardial infarction (>90 days prior to the index echocardiography) who underwent echocardiography between 1999 and 2009 were included in the present evaluation. This patient cohort formed part of ongoing institutional registries.[15, 16] Clinical and echocardiographic data were prospectively entered into the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center) and the echocardiography database, respectively. All patients received optimal medical treatment and coronary revascularization according to the current guidelines.[17, 18] In the present evaluation, atrial fibrillation, recent

myocardial infarction (< 90 days) and poor acoustic window resulting in inadequate speckle tracking analysis were exclusion criteria.

All patients underwent an extensive baseline clinical history and physical examination, 12-lead ECG and transthoracic echocardiography. Baseline clinical variables included New York Heart Association (NYHA) functional class, cardiovascular risk factors, medical treatment, and glomerular filtration rates (GFR) calculated by the Modification of Diet in Renal Disease formula as recommended by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative Guidelines.[19] Baseline echocardiographic variables included LV volumes, LVEF, WMSI, and LV GLS. All patients were prospectively followed up for the occurrence of death for any cause. From the various clinical, ECG and echocardiographic variables recorded, independent determinants of all-cause mortality were identified.

Echocardiography

Transthoracic echocardiography was performed with the patients at rest in the left lateral decubitus position with commercially available ultrasound equipment (M4S probe, Vivid 7, GE-Vingmed, Horten, Norway). All images were digitally stored on hard disks for offline analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway).

LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using Simpson's biplane method of discs. LVEF was calculated and expressed as a percentage. To calculate the WMSI, the LV was divided into 16 segments. A semiquantitative scoring system (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia) was used to analyze each study. Global WMSI was calculated by the standard formula: sum of the segment scores divided by the number of segments scored.[20]

Speckle tracking longitudinal strain analysis

In the present evaluation, global systolic LV myocardial function was determined with 2D speckle tracking strain analysis.[12, 21, 22] The speckle tracking software tracks the frame-to-frame movement of natural myocardial acoustic markers, or speckles, on standard gray scale images. Speckle tracking analysis is angle independent and allows accurate evaluation of myocardial deformation in all the LV segments.[8, 10] The change in length/initial length of the speckle pattern over the cardiac cycle is used to calculate longitudinal strain, with myocardial lengthening or stretching represented as positive strain, and myocardial shortening as negative strain.

To quantify LV GLS, 2D speckle tracking analyses were performed on standard routine grey scale images of the apical 2-, 4-chamber and long-axis views. During analysis, the endocardial border was manually traced at an end-systolic frame and the software traced automatically a region of interest that includes the entire myocardium. The width of the region of interest could be manually adjusted to ensure proper tracking of the myocardial wall. The software then automatically tracked natural myocardial acoustic markers and accepted segments of good tracking quality and rejected poorly tracked segments, while allowing the observer to manually override its decisions based on visual assessments of tracking quality. Results of the LV longitudinal strain analysis were automatically displayed as a 17-segment polar map model with 17 segmental/regional strain values and a mean global strain value for the entire LV (Figure 1).[12, 22, 23]

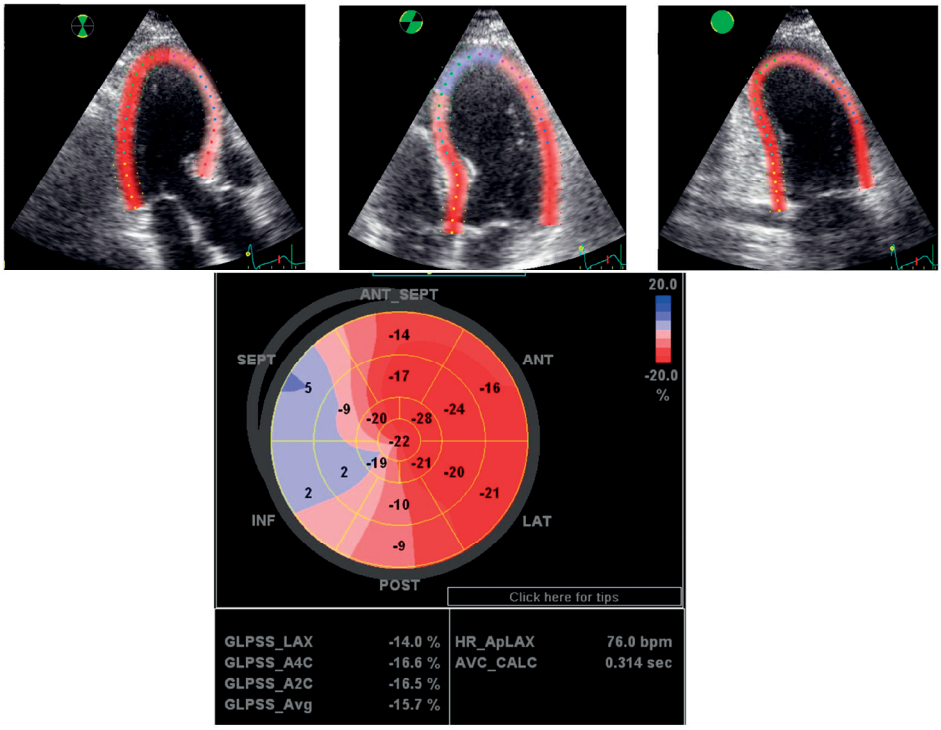

Figure 1. Example of assessment of global longitudinal myocardial strain (GLS) as provided by the EchoPAC software: apical long-axis view where the closure of aortic valve is defined (left upper panel), 4- (right upper panel) and 2-chamber (left lower panel) views. In the lower panel, the "bull's eye" plot, using a 17-segment model, provides the value of longitudinal strain for each segment of the left ventricle and the values of longitudinal strain of apical long-axis (GLPSS-LAX), 4-chamber (GLPSS_A4C), 2 chamber (GLPSS_A2C) and the value of GLS (GLPSS_Avg)

Previously reported intra- and inter-observer variabilities for LV GLS analysis expressed as mean absolute difference ± 1 standard deviation were 1.2 ± 0.5% and 0.9 ± 1.0% respectively.[22]

Follow-up and end points

Patients were followed up at 6- 12 monthly intervals according to protocol.[15, 16] Data on the occurrence of adverse events at follow-up were collected by reviewing medical records, retrieval of survival status through the municipal civil registries and telephone interviews. In the present evaluation, all-cause mortality and heart failure hospitalizations were recorded as event. Patients without data on the last 6 months were considered as lost to clinical follow-up. Data of these patients were included up to the last date of follow-up. From the various clinical, ECG and echocardiographic variables recorded, independent determinants of all-cause mortality were identified.

Statistical analysis

For uniformity reasons, continuous variables were presented as median and interquartile range (IQR). Categorical variables were presented as frequencies and percentages, and were compared using Chi-square test with Yates' correction. Mann-Whitney U test was used to compare unpaired continuous variables. Cumulative event rates from the time of inclusion were calculated using the Kaplan-Meier method for each independent predictor of all-cause mortality. The log-rank tests for time-to-event data with respect to the primary outcome were used for statistical comparison between 2 patient groups.

Multivariate Cox proportional-hazards models were constructed to identify independent clinical, ECG and echocardiographic determinants of all-cause mortality and combined end point. Univariate variables with a p-value <0.10 were entered as covariates using the stepwise backward likelihood ratio selection method. In all the analyses, the Cox proportional-hazards models were used to estimate hazard ratios and 95% confidence intervals for those independent variables. To avoid multicolinearity between the univariate predictors, a correlation coefficient of <0.7 (corresponding to a tolerance of >0.5) was set. The correlation coefficients between LV GLS and LVEF and WMSI were 0.87 and 0.85, respectively (both p<0.001) whereas the correlation coefficient between LVEF and WMSI was 0.88 (p<0.001). Accordingly, the independent predictive value of echocardiographic variables such as WMSI, LVEF and GLS was evaluated in different multivariate models. Finally, the incremental value of LV GLS to predict long-term outcome over WMSI and LVEF

was assessed by calculating the increment in Harrell's C concordance statistic.[24] A two-sided p value of < 0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 15 and STATA software (version 10.1, StataCorp, Texas).

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

RESULTS

Patient population

Of the 1125 patients included, adequate echocardiographic analyses were feasible in 1060 (94%) patients (median age 66.9 years [IQR 58.4, 74.2 years], 739 [70%] men) and constituted the final patient population. The general characteristics of the overall patient population are reported in Table 1.

Hypertension, dyslipidemia and diabetes were present in 459 (43%), 440 (41%) and 298 (28%) patients, respectively. Most patients were treated with antiplatelets and/or oral anticoagulants (92%), beta-blockers (69%) and angiotensin converting enzyme inhibitors or angiotensin-receptor blockers (84%). In addition, 606 (57%) patients received an implantable cardioverter-defibrillator device. Furthermore, 32% underwent prior coronary-aorto bypass grafting whereas 25% underwent percutaneous coronary intervention. The remaining 43% of patients received optimal medical treatment. Table 2 summarizes the echocardiographic characteristics of the patient population. The median LVEDV, LVESV and LVEF were 140 ml (IQR 91-199 ml), 87 ml (IQR 39-150 ml), and 34% (IQR 25-58%), respectively. The median WMSI was 1.5 (IQR 1.0-2.0), and the median LV GLS was -11.5% (IQR -17.0 - -7.6%).

Survivors versus non survivors

The median follow-up duration for the entire patient population was 31.0 months (IQR 15.5, 52.7 months). A total of 270 (25%) patients died during the study duration and the median time to death was 25.9 months (IQR 13.0, 44.5 months). Differences in baseline clinical, ECG and echocardiographic variables between patients who died and patients who survived are outlined in Tables 1 and 2. Patients who died were more likely to be older (p <0.001) and diabetic (p <0.001), and to be in NYHA functional class III-IV (p <0.001). Interestingly, patients who died had lower hemoglobin (p =

Table 1. Clinical characteristics of overall population, and survivors versus non-survivors

	Overall population (n=1060)	Survivors (n=790)	Non-survivors (n=270)	p value
Demographic characteristics				
Age – years, median (IQR)	66.9 (58.4-74.2)	65.4 (56.8-72.6)	71.7 (64.0-76.7)	<0.001
Male gender – (%)	739 (70)	556 (70)	183 (68)	0.42
Body surface area – m^2, median (IQR)	1.97 (1.83-2.10)	1.97 (1.84-2.11)	1.95 (1.83-2.08)	0.24
Medical history				
NYHA functional class III-IV– (%)	420 (40)	282 (36)	138 (51)	<0.001
Hypertension – (%)	459 (43)	343 (43)	116 (43)	0.89
Dyslipidemia – (%)	440 (41)	338 (43)	102 (38)	0.15
Diabetes – (%)	298 (28)	199 (25)	99 (37)	<0.001
Current smoker – (%)	253 (24)	174 (22)	79 (29)	0.016
Family history ischemic heart disease – (%)	339 (32)	239 (30)	100 (37)	0.039
Systolic blood pressure - mmHg, median (IQR)	130 (112-150)	130 (115-150)	125 (110-148)	0.075
Diastolic blood pressure – mmHg, median (IQR)	77 (70-84)	77 (70-85)	75 (65-81)	0.030
Device therapy- (%)				
Implantable cardioverter-defibrillator	606 (57)	438 (55)	168 (62)	0.052
Cardiac resynchronization therapy	429 (40)	296 (37)	133 (49)	0.001
Revascularization- (%)				0.028
Percutaneous coronary intervention	269 (25%)	216	53	
Coronary-aorto bypass grafting	336 (32%)	243	93	
Medication at baseline – (%)				
Antiplatelets	627 (59)	477 (60)	150 (56)	0.16
Anticoagulants	446 (42)	314 (40)	132 (49)	0.009
Beta-blocker	740 (69)	545 (69)	195 (72)	0.32
ACE inhibitor or angiotensin-receptor blocker	896 (84)	671 (85)	225 (83)	0.53

Table 1. Clinical characteristics of overall population, and survivors versus non-survivors (continued)

	Overall population (n=1060)	Survivors (n=790)	Non-survivors (n=270)	p value
Calcium channel blocker	199 (19)	142 (18)	57 (21)	0.25
Diuretic	662 (62)	472 (60)	190 (70)	0.002
Nitrate	208 (20)	136 (17)	72 (27)	0.001
Statin	774 (73)	583 (74)	191 (71)	0.33
Laboratory measure at baseline				
Hemoglobin – g/dL, median (IQR)	13.9 (12.6-14.8)	14.0 (12.7-14.8)	13.7 (11.9-14.5)	0.004
Estimated GFR – mL/min/1.73m^2, median (IQR)	66.8 (51.3-82.8)	71.8 (57.0-85.2)	53.7 (39.7-67.0)	<0.001
Electrocardiogram at baseline				
Heart rate – beats/min, median (IQR)	70 (61-80)	70 (61-80)	73 (63-82)	0.005
QRS duration – ms, median (IQR)	100 (100-146)	100 (100-142)	116 (100-154)	0.001

ACE: angiotensin converting enzyme; IQR: interquartile range; NYHA: New York Heart Association;

0.004) and GFR (p <0.001). In addition, they had a higher heart rate (p = 0.005) and wider QRS complex (p = 0.001). Regarding echocardiographic parameters, patients who died had larger LVEDV (p = 0.012) and LVESV (p = 0.005) and lower LVEF (p = 0.004). Finally, patients who died had higher WMSI (p = 0.001) and a greater impairment of LV GLS (p <0.001).

Table 2. Echocardiographic characteristics of overall population, and survivors versus non-survivors

	Overall population (n=1060)	Survivors (n=790)	Non-survivors (n=270)	p value
Echocardiography at baseline				
Wall motion score index, median (IQR)	1.5 (1.0-2.0)	1.5 (1.0-1.9)	1.6 (1.0-2.1)	0.001
LVEF – %, median (IQR)	34 (25-58)	35 (26-59)	33 (22-56)	0.004
LVEDV – ml, median (IQR)	140 (91-199)	136 (90-195)	153 (94-225)	0.012
LVESV – ml, median (IQR)	87 (39-150)	84 (36-142)	100 (42-170)	0.005
GLS – %, median (IQR)	-11.5 (-17.0- -7.6)	-12.3 (-17.5- -8.5)	-9.8 (-15.3- -6.5)	<0.001

GLS: global longitudinal left ventricular strain; IQR: interquartile range; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume.

Follow-up

Kaplan-Meier curves for LV GLS of all-cause mortality in ischemic cardiomyopathy patients are reported in Figure 2A. Particularly, when the patient population was dichotomized based on the median LV GLS (-11.5%), a cumulative 4%, 10% and 17% of patients with a LV GLS ≤-11.5% (less impaired LV shortening) died by 1, 2 and 3 years follow-up respectively. In contrast, a respective 7%, 17% and 27% of patients with a LV GLS >-11.5% (more impaired LV shortening) died during the same time period (log rank chi squared = 13.86, p <0.001; Figure 2A).

In addition, the combined end point (heart failure hospitalization and all-cause mortality) was reached by 309 patients during the follow-up. Kaplan-Meier estimates of the time to the combined end point for patients with an LV GLS ≤-11.5% and patients with an LV GLS >-11.5% are indicated in Figure 2B. After 3 years of follow-up, the cumulative free survival rates of combined end point in the group of patients with an LV GLS ≤-11.5% were 6%, 13% and 20% at 1, 2 and 3 years follow-up, respectively. In contrast, the group of patients with an LV GLS >-11.5% showed cumulative free survival rates of combined end point of 10%, 20% and 29% at 1, 2 and 3 years follow-up, respectively (log rank chi squared = 14.16, p<0.001; Figure 2B).

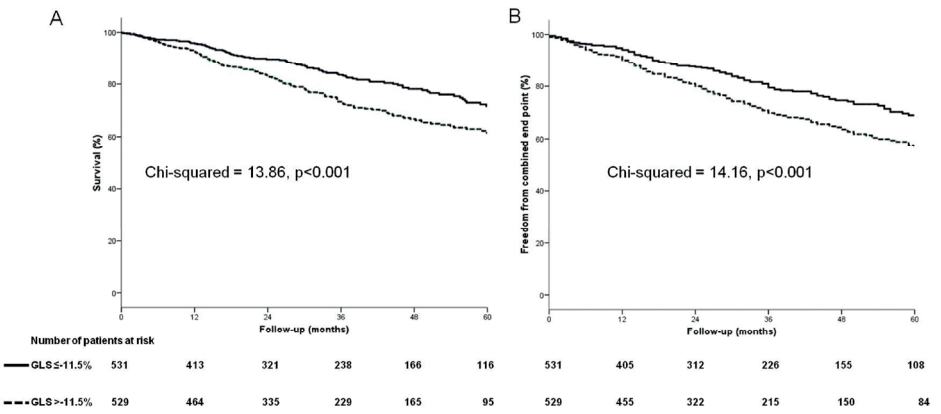

Figure 2: Kaplan Meier estimates of all-cause mortality (panel A) and combined end point (panel B). The cumulative survival rates were compared between patients with left ventricular GLS ≤-11.5% (solid line) and patients with GLS >-11.5% (dotted line).

Predictors of all-cause mortality and combined end point

To identify predictors of all-cause mortality, univariate Cox analyses were performed. First, among various clinical and ECG variables, the independent determinants were

identified (Table 3). Age, diabetes mellitus, hemoglobin and renal function (measured with GFR) were independent determinants of all-cause mortality. Next, several echocardiographic variables of LV function were introduced in different multivariate models to evaluate their prognostic value (Table 4). WMSI (HR 1.43, 95% CI 1.14-1.79; p=0.002), LVEF (HR 1.04, 95% CI 1.00-1.08; p=0.026) and LV GLS (HR 1.69, 95% CI 1.33-2.15; p<0.001) were significantly associated with all-cause mortality. However, the model including LV GLS had the best relative fit and LV GLS provided the highest Harrell's C concordance statistics (Table 5).

In addition, the clinical and ECG variables that were independently associated with the combined end point (heart failure hospitalization and all-cause mortality) were age, diabetes mellitus and renal function. The predictive value of WMSI, LVEF and LV GLS was evaluated in different multivariate Cox regression analyses to avoid multicolinearity. WMSI (HR 1.44, 95% CI 1.16-1.78; p=0.001), LVEF (HR 1.04, 95% CI 1.00-1.08; p=0.009) and LV GLS (HR 1.64, 95% CI 1.32-2.04; p<0.001) were independent predictors of the combined end point (Table 4). In addition, the model including LV GLS had the highest Harrell's C statistic (Table 5).

Table 3. Cox uni- and multivariable regression analysis to identify clinical predictors of all-cause mortality and combined end point during follow-up

Dependent variable: Death from any cause	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Independent variables				
Age – years	1.05 (1.03-1.06)	<0.001	**1.04 (1.03-1.06)**	**<0.001**
NYHA functional class III-IV	1.79 (1.41-2.28)	<0.001	1.23 (0.92-1.66)	0.164
Diabetes	1.60 (1.25-2.05)	<0.001	**1.49 (1.15-1.92)**	**0.002**
Diastolic blood pressure, per 10 mmHg increase	0.98 (0.97-0.99)	<0.001	0.94 (0.84-1.04)	0.227
Cardiac resynchronization therapy	1.73 (1.38-2.16)	0.002	1.32 (0.88-1.98)	0.177
Anticoagulants	1.33 (1.04-1.68)	0.021	1.13 (0.87-1.47)	0.350
Diuretics	1.55 (1.19-2.02)	0.001	0.96 (0.71-1.31)	0.815
Nitrates	1.45 (1.11-1.90)	0.009	1.23 (0.93-1.62)	0.144
Hemoglobin, per 1 g/dl decrease	1.36 (1.06-1.22)	<0.001	**1.08 (1.01-1.16)**	**0.043**
GFR, per 10 ml/min/1.73m^2 decrease	1.02 (1.02-1.03)	<0.001	**1.15 (1.09-1.22)**	**<0.001**
Heart rate, per 5 beats/min increase	1.05 (1.00-1.09)	0.030	...	...
QRS duration, per 20 ms increase	1.03 (0.99-1.07)	0.060	...	...

Table 3 (continued)

Dependent variable: Combined end point	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Independent variables				
Age – years	1.04 (1.02-1.05)	<0.001	**1.03 (1.01-1.04)**	**<0.001**
NYHA functional class III-IV	1.63 (1.33-2.03)	<0.001	...	...
Diabetes	1.37 (1.08-1.74)	0.009	**1.30 (1.02-1.66)**	**0.034**
Diastolic blood pressure, per 10 mmHg increase	0.88 (0.80-0.96)	0.007	...	...
Cardiac resynchronization therapy	1.45 (1.15-1.81)	0.001	...	...
Anticoagulants	1.26 (1.01-1.58)	0.043	...	...
Diuretics	1.40 (1.10-1.78)	0.006	...	...
Nitrates	1.34 (1.04-1.73)	0.025	...	...
Hemoglobin, per 1 g/dl decrease	1.12 (1.04-1.20)	0.001	...	...
GFR, per 10 ml/min/1.73m^2 decrease	1.20 (1.14-1.26)	<0.001	**1.15 (1.09-1.22)**	**<0.001**
Heart rate, per 5 beats/min increase	1.04 (0.99-1.08)	0.072	...	...
QRS duration, per 20 ms increase	1.03 (1.00-1.07)	0.041	...	...

CI: confidence intervals; GFR: glomerular filtration rate; HR: hazard ratio; NYHA: New York Heart Association

Table 4. Cox uni- and multivariable regression analysis to identify echocardiographic predictors of all-cause mortality during follow-up

Dependent variable: All-cause mortality	Multivariable analysis		-2 log Likelihood
	HR (95% CI)	p value	
Independent variables: clinical + WMSI			**3226.8**
Age – years	**1.04 (1.03-1.06)**	**<0.001**	
Diabetes	**1.55 (1.21-1.99)**	**<0.001**	
Hemoglobin, per 1 g/dl decrease	**1.08 (0.99 -1.16)**	**0.059**	
GFR, per 10 ml/min/1.73m^2 decrease	**1.17 (1.05-1.24)**	**<0.001**	
WMSI	**1.43 (1.14-1.79)**	**0.002**	
Independent variables: clinical + LVEF			**3231.6**
Age – years	**1.04 (1.03-1.06)**	**<0.001**	
Diabetes	**1.59 (1.23-2.04)**	**<0.001**	

Table 4 (continued)

Dependent variable: All-cause mortality	**Multivariable analysis**		**-2 log Likelihood**
	HR (95% CI)	**p value**	
Hemoglobin, per 1 g/dl decrease	**1.08 (0.99-1.16)**	**0.048**	
GFR, per 10 ml/min/1.73m^2 decrease	**1.16 (1.10-1.24)**	**<0.001**	
LVEF, per 5% decrease	**1.04 (1.00-1.08)**	**0.026**	
Independent variables: clinical + GLS			**3215.9**
Age – years	**1.04 (1.03-1.06)**	**<0.001**	
Diabetes	**1.60 (1.24-2.05)**	**<0.001**	
Hemoglobin, per 1 g/dl decrease	**1.08 (1.00-1.16)**	**0.043**	
GFR, per 10 ml/min/1.73m^2 decrease	**1.15 (1.09-1.22)**	**<0.001**	
GLS, per 5% increment	**1.69 (1.33-2.15)**	**<0.001**	
Dependent variable: Combined end point	**Multivariable analysis**		
	HR (95% CI)	**p value**	**-2 log Likelihood**
Independent variables: clinical + WMSI			**3733.3**
Age – years	1.03 (1.02-1.04)	<0.001	
Diabetes	1.37 (1.08-1.74)	0.010	
GFR, per 10 ml/min/1.73m^2 decrease	1.15 (1.09-1.21)	<0.001	
WMSI	1.44 (1.16-1.78)	0.001	
Independent variables: clinical + LVEF			**3737.3**
Age – years	1.03 (1.02-1.04)	<0.001	
Diabetes	1.34 (1.06-1.70)	0.016	
GFR, per 10 ml/min/1.73m^2 decrease	1.16 (1.10-1.22)	<0.001	
LVEF, per 5% decrease	1.04 (1.01-1.08)	0.009	
Independent variables: clinical + GLS			**3724.2**
Age – years	1.03 (1.02-1.04)	<0.001	
Diabetes	1.37 (1.08-1.74)	0.010	
GFR, per 10 ml/min/1.73m^2 decrease	1.14 (1.08-1.21)	<0.001	
GLS, per 5% increment	1.64 (1.32-2.04)	<0.001	

CI: confidence intervals; GFR: glomerular filtration rate; GLS: global longitudinal left ventricular strain; HR: hazard ratio; LVEF: left ventricular ejection fraction; WMSI: wall motion score index.

Table 5. Incremental prognostic value of LV GLS: discrimination indices analysis.

Model	All-cause mortality	Harrell's C-concordance statistic index
1	Clinical parameters + WMSI	0.689
2	Clinical parameters + LVEF	0.686
3	Clinical parameters + GLS	0.700
Model	Combined end point	Harrell's C-concordance statistic index
1	Clinical parameters + WMSI	0.653
2	Clinical parameters + LVEF	0.648
3	Clinical parameters + GLS	0.659

GLS: global longitudinal left ventricular strain; HR: hazard ratio; LVEF: left ventricular ejection fraction; WMSI: wall motion score index.

DISCUSSION

The main findings of the present study were as follows: 1) LV GLS was significantly related to long-term outcome; 2) the predictive model including LV GLS provided the best relative fit and, finally, 3) LV GLS was independently related to all-cause mortality and combined end point and had prognostic incremental value over other well established clinical and ECG predictors.

Global longitudinal strain vs. left ventricular ejection fraction and wall motion score index

As previously described, LVEF and WMSI are important echocardiographic prognosticators, especially in patients with coronary artery disease.[3-7] However, the assessment of LVEF and WMSI has several limitations. The measurement of LVEF with 2D echocardiography is based on geometrical assumptions used to calculate LV volumes. Although biplane Simpson's method is the most accurate 2D measurement to calculate LVEF, the presence of wall motion abnormalities or distorted LV geometry, may reduce the accuracy of this method to estimate LV systolic function and increase the intra- and inter-observer variability. Moreover, the assessment of WMSI is based on visual assessment and requires high expertise.

At present, speckle tracking echocardiography is emerging as novel technique to allow the assessment of LV mechanics through the quantification of active myocardial deformation.[8-10] Cumulative data show that, unlike LVEF and WMSI, the

assessment of LV mechanics with 2D speckle tracking strain imaging is feasible and reproducible, does not rely on geometric assumptions and is independent of LV geometry.[8-10] In particular, the assessment of LV GLS with 2D speckle tracking echocardiography has shown to be an accurate marker of LV function.[22, 25]

Stanton et al.[13] reported in a retrospective analysis of 546 unselected patients that LV GLS assessed with 2D speckle tracking echocardiography had incremental value over LVEF and WMSI for the prediction of outcome. Furthermore, the authors showed that LV GLS assessment was more reproducible as compared to LVEF assessment.[13] These findings were also confirmed in subsequent series of heart failure patients.[14, 26]

Thus far, the largest series reporting the prognostic value of GLS included 603 patients with acute myocardial infarction,[27] 697 patients with ST-segment elevation acute myocardial infarction treated with primary coronary intervention[11] and 546 unselected patients clinically referred for echocardiography (34% had prior myocardial infarction and 17% had prior coronary revascularization.[13] The present patient population is unique as it includes a homogeneous population with chronic ischemic heart disease and far larger (n=1060) compared with previous series. Furthermore, the current study provides further insight into the prognostic value of LV GLS in patients with chronic ischemic heart disease. In this group of patients, assessment of LV systolic function may be challenged by the presence of wall motion abnormalities and highly abnormal LV geometry. Therefore, LV GLS may be a more appropriate measure of LV systolic function by direct evaluation of the myocardial contractile properties. Particularly, this study investigated the prognostic value of LV GLS in 1060 patients extending previous results. LV GLS similarly to LVEF and WMSI was more preserved in survivor patients. However, among echocardiographic parameters, GLS was independently related to all-cause mortality (hazard ratio per 5% increase, 1.69, 95% CI 1.33-2.15; p<0.001) and combined end point (all-cause mortality and heart failure hospitalization) (1.64, 95% CI 1.32-2.04; p<0.001).

Global longitudinal strain and long-term outcome

Prognosis of patients with coronary artery disease is influenced by several clinical parameters.[2, 17] Similarly to previous series, the present study showed that age, diabetes, hemoglobin levels and renal function (assessed as GFR) were significantly and independently related to all-cause mortality in patients with chronic ischemic cardiomyopathy.[2, 17] More importantly, the present study demonstrated the superior prognostic value of LV GLS over these clinical well established predictors of mortality. Furthermore, LV GLS provided significant incremental value over the clinical inde-

pendent predictors of long-term outcome. Particularly, in the present evaluation the patient population was dichotomized based on the median value of LV GLS (-11.5%) showing a significantly better long-term survival for patients with less impaired LV GLS.

This finding underscores that LV GLS assessed with 2D speckle tracking echocardiography may be used as novel index of LV longitudinal function and also as strong predictor of all-cause mortality in patients with chronic ischemic cardiomyopathy.[22, 25]

Study limitations

Although the present evaluation was retrospective in design, this is the largest population cohort in which LV GLS was analyzed. An additional limitation to the present study is that radial and circumferential strains were not explored. However, it has recently been proven that longitudinal deformation may be a more sensitive marker of cardiac function which better exploring the endocardial function as compared to radial or circumferential strain.[28, 29] This issue is particularly relevant in chronic ischemic patients.[29]

The multivariate models presented are non-nested models and therefore, the comparison between the likelihoods may not be appropriate. Therefore, we could not demonstrate that GLS provided superior incremental prognostic value over LVEF and WMSI. However, the models including GLS had the lowest -2log likelihood and the highest Harrell's C statistic suggesting that GLS may be a valuable method to risk stratifiy patients with chronic ischemic heart disease. Other echocardiographic parameters related to long-term outcome of patients with chronic ischemic heart disease such as left atrial volume, mitral regurgitation and diastolic function were not evaluated.

CONCLUSION

The assessment of LV GLS with speckle tracking echocardiography is significantly related to long-term outcome in patients with chronic ischemic cardiomyopathy. Particularly, LV GLS was independently related to all-cause mortality and provided incremental prognostic value over other well established clinical and ECG predictors.

Clinical perspective

In patients with chronic ischemic cardiomyopathy, left ventricular (LV) ejection fraction (EF) and wall motion score index (WMSI) are well established predictors of long-term outcome. However, both LVEF and WMSI have some limitations related to reproducibility, geometric assumption and expertise. Recently, two-dimensional (2D) speckle tracking echocardiography permit the assessment of active myocardial deformation in radial, circumferential and longitudinal directions. The measurement of LV global longitudinal strain (GLS), which is a measure of the active shortening of the LV in the longitudinal direction, is more reproducible than LVEF and WMSI and does not rely on geometrical assumptions. The present study showed that the assessment of LV GLS with 2D speckle tracking echocardiography is significantly related to long-term outcome in patients with chronic ischemic cardiomyopathy. Moreover, LV GLS was independently related to all-cause mortality and provided incremental prognostic valve over other well established clinical and ECG predictors. Therefore, these findings underscore that LV GLS assessed with 2D speckle tracking echocardiography may be used as novel index of LV longitudinal function and also as predictor of all-cause mortality in patients with chronic ischemic cardiomyopathy.

REFERENCES

(1) Lewis EF, Moye LA, Rouleau JL, Sacks FM, Arnold JM, Warnica JW, Flaker GC, Braunwald E, Pfeffer MA. Predictors of late development of heart failure in stable survivors of myocardial infarction: the CARE study. *J Am Coll Cardiol* 2003;42:1446-1453.

(2) Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Levy S, Linde C, Lopez-Sendon JL, Nieminen MS, Pierard L, Remme WJ. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:1115-1140.

(3) Galasko GI, Basu S, Lahiri A, Senior R. A prospective comparison of echocardiographic wall motion score index and radionuclide ejection fraction in predicting outcome following acute myocardial infarction. *Heart* 2001;86:271-276.

(4) Kearney MT, Fox KA, Lee AJ, Prescott RJ, Shah AM, Batin PD, Baig W, Lindsay S, Callahan TS, Shell WE, Eckberg DL, Zaman AG, Williams S, Neilson JM, Nolan J. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol* 2002;40: 1801-1808.

(5) Mollema SA, Nucifora G, Bax JJ. Prognostic value of echocardiography after acute myocardial infarction. *Heart* 2009;95:1732-1745.

(6) Peteiro J, Bouzas-Mosquera A, Pazos P, Broullon FJ, Castro-Beiras A. Prognostic value of exercise echocardiography in patients with left ventricular systolic dysfunction and known or suspected coronary artery disease. *Am Heart J* 2010;160:301-307.

(7) Solomon SD, Anavekar N, Skali H, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Wang D, Pocock S, Pfeffer MA. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005;112:3738-3744.

(8) Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, Kaluski E, Krakover R, Vered Z. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-1029.

(9) Ng AC, Tran dT, Newman M, Allman C, Vidaic J, Kadappu KK, Boyd A, Thomas L, Leung DY. Comparison of myocardial tissue velocities measured by two-dimensional speckle tracking and tissue Doppler imaging. *Am J Cardiol* 2008;102:784-789.

(10) Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004;17:630-633.

(11) Antoni ML, Mollema SA, Delgado V, Atary JZ, Borleffs CJ, Boersma E, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Prognostic importance of strain and strain rate after acute myocardial infarction. *Eur Heart J* 2010;31:1640-1647.

(12) Mollema SA, Delgado V, Bertini M, Antoni ML, Boersma E, Holman ER, Stokkel MP, van der Wall EE, Schalij MJ, Bax JJ. Viability assessment with global left ventricular longitudinal strain predicts recovery of left ventricular function after acute myocardial infarction. *Circ Cardiovasc Imaging* 2010;3:15-23.

(13) Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. *Circ Cardiovasc Imaging* 2009; 2:356-364.

(14) Mignot A, Donal E, Zaroui A, Reant P, Salem A, Hamon C, Monzy S, Roudaut R, Habib G, Lafitte S. Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: a multicenter study. *J Am Soc Echocardiogr* 2010;23:1019-1024.

(15) Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, Viergever EP, van RC, Padmos I, Sedney MI, van Exel HJ, Verwey HF, Atsma DE, van d, V, Jukema JW, van der Wall EE, Schalij MJ. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. *Am Heart J* 2007;153:14-11.

(16) van Bommel RJ, Borleffs CJ, Ypenburg C, Marsan NA, Delgado V, Bertini M, van der Wall EE, Schalij MJ, Bax JJ. Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: influence of pre-implantation characteristics on long-term outcome. *Eur Heart J* 2010;31:2783-2790.

(17) Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, de BG, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. *Eur Heart J* 2006;27:1341-1381.

(18) Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009;53:e1-e90.

(19) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1-266.

(20) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.

(21) Bertini M, Mollema SA, Delgado V, Antoni ML, Ng AC, Holman ER, Boriani G, Schalij MJ, Bax JJ. Impact of time to reperfusion after acute myocardial infarction on myocardial damage assessed by left ventricular longitudinal strain. *Am J Cardiol* 2009;104:480-485.

(22) Delgado V, Mollema SA, Ypenburg C, Tops LF, van der Wall EE, Schalij MJ, Bax JJ. Relation between global left ventricular longitudinal strain assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. *J Am Soc Echocardiogr* 2008;21:1244-1250.

(23) Bertini M, Ng AC, Borleffs CJ, Delgado V, Wijnmaalen AP, Nucifora G, Ewe SH, Shanks M, Thijssen J, Zeppenfeld K, Biffi M, Leung DY, Schalij MJ, Bax JJ. Longitudinal mechanics of the periinfarct zone and ventricular tachycardia inducibility in patients with chronic ischemic cardiomyopathy. *Am Heart J* 2010;160:729-736.

(24) Harrell FE, Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA* 1982;247:2543-2546.

(25) Belghitia H, Brette S, Lafitte S, Reant P, Picard F, Serri K, Lafitte M, Courregelongue M, Dos SP, Douard H, Roudaut R, DeMaria A. Automated function imaging: a new operator-independent strain method for assessing left ventricular function. *Arch Cardiovasc Dis* 2008;101:163-169.

(26) Nahum J, Bensaid A, Dussault C, Macron L, Clemence D, Bouhemad B, Monin JL, Rande JL, Gueret P, Lim P. Impact of longitudinal myocardial deformation on the prognosis of chronic heart failure patients. *Circ Cardiovasc Imaging* 2010;3:249-256.

(27) Hung CL, Verma A, Uno H, Shin SH, Bourgoun M, Hassanein AH, McMurray JJ, Velazquez EJ, Kober L, Pfeffer MA, Solomon SD. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. *J Am Coll Cardiol* 2010;56:1812-1822.

(28) Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH. Differentiation of subendocardial and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-axis myocardial function. *J Am Coll Cardiol* 2006;48:2026-2033.

(29) Sengupta PP, Narula J. Reclassifying heart failure: predominantly subendocardial, subepicardial, and transmural. *Heart Fail Clin* 2008;4:379-382.

CHAPTER 11

Prediction of atrial fibrillation in patients with an implantable cardioverter-defibrillator and heart failure.

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ABSTRACT

Aims. Heart failure and atrial fibrillation (AF) frequently coexist and AF worsens heart failure prognosis. Device-based diagnostics derived from implantable cardioverter-defibrillator (ICD) interrogation provide an accurate method for detecting AF episodes. This study sought to determine clinical and echocardiographic predictors of AF occurrence, including an index of total atrial conduction time derived by tissue Doppler imaging (PA-TDI duration), in patients with heart failure. Moreover, the role of PA-TDI duration on the prediction of AF occurrence in subgroups of patients with and without history of AF was explored.

Methods and Results. A cohort of 495 heart failure patients who underwent ICD implantation was studied. Baseline echocardiographic parameters of systolic and diastolic function were evaluated together with clinical parameters. Furthermore, PA-TDI duration was measured. All patients were prospectively followed up after ICD implantation for AF occurrence detected by ICD interrogation. A total of 142 (29%) patients experienced AF over a follow-up period of 16.4±11.2 months. PA-TDI duration was longer in patients with AF occurrence as compared to patients without AF occurrence (154±27ms vs. 135±24ms, $p<0.001$). On Cox-multivariable analysis, female gender (hazard ratio=1.60; 95% confidence intervals=1.09-2.35; $p=0.017$), history of AF (hazard ratio=2.22; 95% confidence intervals=1.51-3.27; $p<0.001$), and PA-TDI duration (hazard ratio=1.27; 95% confidence intervals=1.13-1.42; $p<0.001$) were independent predictors of AF occurrence. In the subgroups of patients with and without history of AF, PA-TDI duration remained an independent predictor of AF occurrence.

Conclusions. PA-TDI duration may be useful to risk-stratify for AF occurrence in heart failure patients with and without a history of AF.

INTRODUCTION

Atrial fibrillation (AF) is a frequent arrhythmia associated with increased cardiovascular morbidity and mortality.[1, 2] In particular, AF is well known to result in a substantially increased risk for stroke.[3] Heart failure is a serious condition frequently associated with AF.[4] In particular, AF may further worsen the long-term prognosis of heart failure by increasing the risk of cardiac thromboembolism.[4-6] Thus, the identification of predictors of AF occurrence in heart failure patients is crucial for the initiation of prophylactic oral anticoagulant therapy in order to reduce the risk of cardiogenic stroke.

Recently, a novel non-invasive echocardiographic index derived by tissue Doppler imaging was demonstrated to predict AF occurrence in a heterogeneous patient population.[7] Merckx et al. showed that the time-interval from the beginning of the electrocardiogram P wave and the peak of $A'_{LATERAL}$ wave on tissue Doppler images (PA-TDI duration) provided a good estimation of the total atrial conduction time.[8] In addition, de Vos et al. demonstrated the independent association between PA-TDI duration and AF occurrence in patients without history of AF.[7] However, the capability of this index (PA-TDI duration) to predict AF in heart failure patients with and without history of AF still remains unknown. Furthermore, it should be emphasized that clinical follow-up based on history of AF related symptoms fails to identify asymptomatic AF episodes. These asymptomatic episodes have been shown to be present in almost 20% of patients with paroxysmal AF and they have important prognostic clinical implications.[9, 10] Device-based diagnostics derived from pacemaker or implantable cardioverter-defibrillator (ICD) interrogation provide an accurate method for detecting asymptomatic AF episodes.[9, 10] Accordingly, in order to detect all AF episodes including the asymptomatic AF episodes, a cohort of heart failure patients who had undergone ICD implantation was studied, and AF episodes were identified by ICD interrogation.

The aims of the present study were two-fold. Firstly, to identify clinical, and/or echocardiographic predictors of AF occurrence, including left atrial (LA) volumes, LA function and PA-TDI duration, in patients with heart failure. Secondly, the role of PA-TDI duration on the prediction of AF occurrence was explored in the subgroups of patients with and without history of AF.

METHODS

Patient population and protocol

A total of 627 consecutive patients with mild to severe heart failure scheduled for ICD implantation for primary or secondary prevention according to the current AHA/ACC/ESC guidelines were included.[11] Exclusion criteria were: 1) absence of normal sinus rhythm during echocardiographic examination; 2) acoustic window with poor image quality.

All patients underwent a complete baseline history taking and physical examination, 12-lead electrocardiogram and transthoracic echocardiogram prior to ICD implantation. History of AF, defined as documented AF on surface ECG or ECG-Holter monitoring was collected. In addition, history of AF was divided into persistent and paroxysmal AF. Specifically, history of persistent AF was defined based on the requirement for pharmaceutical or electrical cardioversion. Conversely, paroxysmal AF did not require pharmaceutical or electrical cardioversion.[5] Patients with permanent AF were excluded from the study because of the absence of normal sinus rhythm during the echocardiographic examination.

Baseline clinical variables recorded included New York Heart Association (NYHA) functional class, cardiac risk factors and consequent $CHADS_2$ score[5], and medication. Baseline electrocardiographic variables recorded included heart rate, PR interval, QRS duration, and corrected QT interval calculated by Bazett's formula (corrected $QT=QT/\sqrt{RRinterval}$). Baseline echocardiographic parameters of systolic and diastolic function were included. Furthermore, the total atrial conduction time was estimated with tissue Doppler imaging (PA-TDI duration), as previously described[8]. All baseline clinical, electrocardiographic and echocardiographic analyses were performed by independent blinded observers.

All patients were prospectively followed up after ICD implantation for AF occurrence recorded by ICD. AF occurrence after ICD implantation was defined as atrial high-rate episodes (>180 bpm) lasting at least 10 minutes in patients with cardiac resynchronization therapy and dual-chamber devices. In patients with single-chamber devices, AF occurrence was defined based on ICD interrogation with device-based diagnostics.[12, 13]

From the various clinical, electrocardiographic and echocardiographic variables recorded, independent predictors of AF occurrence were identified. The patients were subsequently divided in 2 subgroups based on the history of AF (present or absent) and independent predictors of AF occurrence were identified in each subgroup.

Echocardiography

All patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwakee, Wisconsin, USA). Standard 2-dimensional images were obtained using a 3.5-MHz transducer and, digitally stored in cine-loop format; the analysis was performed offline using EchoPAC version 108.1.5 (General Electric-Vingmed). From the standard apical views (4- and 2-chamber) left ventricular volumes and left ventricular ejection fraction were calculated according to the American Society of Echocardiography guidelines.[14]

Severity of mitral regurgitation was graded semi-quantitatively from colour-flow Doppler data using the 4-chamber apical views according to the ACC/AHA guidelines.[15] Mitral regurgitation was classified as mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20-40%) and severe (jet area/left atrial area >40%).

Left atrial volumes (LAVs) were calculated from the 4- and 2-chamber apical views as recommended by the American Society of Echocardiography guidelines.[14] LAVs were measured at 3 time points during the cardiac cycle: 1) maximum LAV (LAVmax) at end-systole, just before mitral valve opening; 2) minimum LAV (LAVmin) at end-diastole, just before mitral valve closure; 3) LAV before atrial active contraction (LAVpreA) obtained from the last frame before mitral valve reopening or at the time of the P wave on the electrocardiogram. Left atrial function was derived from the LAV and expressed with the following formulas: 1) Total left atrial (LA) emptying fraction = [(LAV max – LAVmin)/LAVmax] × 100; 2) left atrial expansion index: LA reservoir function = [(LAVmax – LAVmin)/LAVmin] × 100; 3) passive LA emptying fraction: LA conduit function = [(LAVmax – LAVpreA)/LAVmax] × 100; and 4) active LA emptying fraction: LA booster function = [(LAVpreA – LAVmin)/LAVpreA] × 100, which is considered an index of LA active contraction.[16, 17]

Spectral Doppler velocities were measured from the apical 4-chamber view using a 2 mm sample volume positioned at the mitral leaflet tips. Peak transmitral early (E wave) and atrial (A wave) mitral velocities, and the E wave deceleration time were obtained. Doppler tracings were obtained in accordance to the recommendations of the American Society of Echocardiography.[14]

Colour-coded tissue Doppler images of the left ventricle obtained in the apical 4-chamber view were acquired at high frame rates (at least 150 frames/s) during end-expiration. Early diastolic myocardial velocities (E') were determined at the septal and lateral sides of the mitral annulus (E'_{SEPTAL}, $E'_{LATERAL}$). E'_{MEAN} was calculated as $(E'_{SEPTAL}+E'_{LATERAL})/2$.[18]

Total atrial conduction time was estimated with colour-coded tissue Doppler images by first placing the sample size on the LA lateral wall just above the mitral

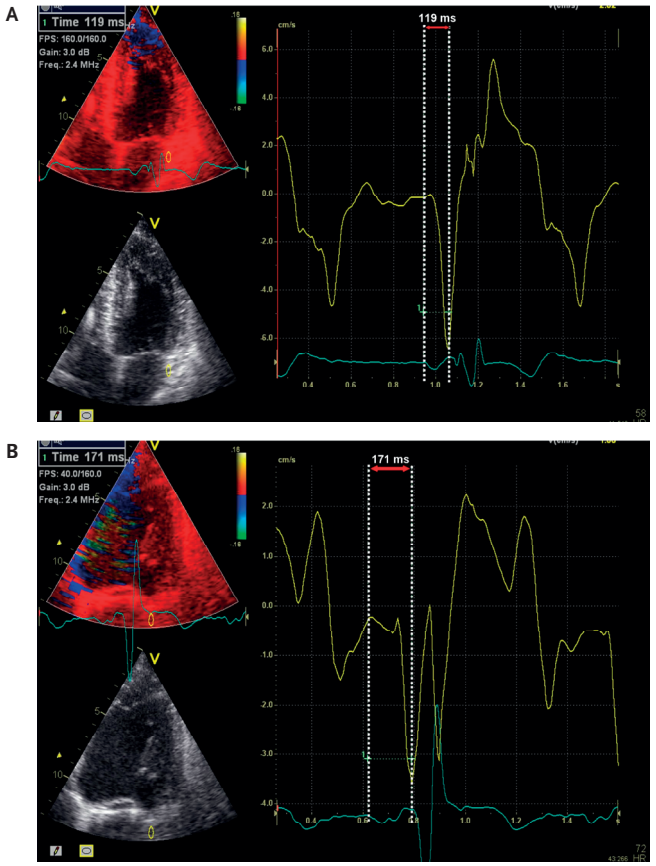


Figure 1. The time-interval from the beginning of the electrocardiogram P wave and the peak of $A'_{LATERAL}$ wave (PA-TDI duration) was obtained with tissue Doppler images by placing the sample size on the LA lateral wall just above the mitral annulus; next the PA-TDI duration was measured. **Panel A**. Patient without atrial fibrillation (AF) occurrence. PA-TDI duration was 119 ms. **Panel B.** Example of patient with AF occurrence and longer PA-TDI (171 ms).

annulus. Next, the time-interval from the onset of the P-wave on lead II of the electrocardiogram (on echocardiographic images) to the peak of $A'_{LATERAL}$ wave (PA-TDI duration) was measured (Figure 1).[8]

Bland-Altman analysis demonstrated a good intra-observer and inter-observer agreements with a non-significant bias for PA-TDI duration measurement. Mean differences ± 2 standard deviations for PA-TDI duration were 1.8 ± 10 ms for intra-observer agreement and 1.7 ± 10 ms for inter-observer agreement.

Statistical analysis

Continuous data are presented as mean ± SD and categorical data are presented as frequencies and percentages. All continuous variables were evaluated for normal distribution with Kolmogorov-Smirnov tests. Unpaired T test and Mann-Whitney U-test were used to compare continuous variables between patients with vs. without AF occurrence and between patients with vs. without history of AF, as appropriate. Chi-square test was used to compare categorical variables between patients with vs. without AF occurrence and between patients with vs. without history of AF. Univariable and multivariable Cox proportional hazards regression analyses were performed to identify clinical and echocardiographic predictors of AF occurrence. Only significant ($p < 0.05$) univariable predictors were entered as covariates in the multivariable analysis, which was performed using the enter model. Hazard ratios and 95% confidence intervals (CI) were calculated. Time to first episode of atrial fibrillation in relation to PA-TDI duration was analyzed with the Kaplan-Meier method and compared with the log-rank test. Therefore, PA-TDI was dichotomized based on the median (139 ms). Similarly to the overall patient population, univariable and multivariable Cox proportional hazards regression analyses were used to identify predictors of AF occurrence in the subgroups of patients with and without history of AF. For all the multivariable Cox proportional hazards regression analyses a correlation coefficient of <0.7 (corresponding to a tolerance of >0.5) was set to avoid multicollinearity between the univariable predictors. To increase clinical utility, the hazard ratios and 95% CI of LAVmin PA-TDI duration were reported as per 10 ml/m^2 increase and per 20 ms increase, respectively. A 2-tailed p value of <0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 16.

RESULTS

In total 495 patients were included in the analysis: 94 patients were excluded due to the absence of normal sinus rhythm during the echocardiographic examination and 38 patients were excluded because of suboptimal image quality. Primary prevention of sudden cardiac death was the reason for implantation in 434 (88%) of the patients, whereas 61 (12%) patients were implanted for secondary prevention of sudden cardiac death. Overall, 481 (97%) patients were implanted with cardiac resynchronization therapy or dual-chamber ICD devices; whereas only 14 (3%) patients got a single-chamber ICD device.

The general characteristics of the patient population are reported in Tables 1-3. The mean age of the overall population was 62±12 years, and 21% of the patients were women. A history of AF was present in 102 (21%) patients and, the majority of the patients had high thromboembolic risk according to the $CHADS_2$ score (2.2±1.1). The mean QRS duration was 128±32 ms, and 61% of the patients received a cardiac resynchronization therapy device. Most of the patients were treated with angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and diuretics (84%, 69%, and 73%, respectively). All of the patients had dilated left ventricles (left ventricular end-diastolic volume = 95±35 ml/m²) with depressed left ventricular ejection fraction (29±6%). Similarly, the LA was significantly dilated (LAVmax = 31±13 ml/m²) and LA function was reduced (total LA emptying fraction = 43±15%). Finally, the total atrial activation time expressed as PA-TDI duration was 141±26 ms.

Table 1. Demographic and clinical characteristics of overall population, and patients with vs. without AF occurrence during follow-up

	Overall population (n=495)	Patients with AF occurrence (n=142)	Patients without AF occurrence (n=353)	p value
Age (yrs)	62.2 ± 11.7	61.9 ± 11.7	62.3 ± 11.8	0.65
Female (%)	105 (21)	42 (30)	63 (18)	0.004
Hypertension (%)	164 (33)	50 (35)	114 (32)	0.53
Diabetes (%)	104 (21)	32 (23)	72 (20)	0.60
History of AF (%)	102 (21)	58 (41)	44 (13%)	<0.001
Previous PCI/CABG	259 (52)	69 (49)	190 (54)	0.29
NYHA functional class	2.2±0.8	2.4±0.8	2.2±0.8	0.025
$CHADS_2$ score	2.2±1.1	2.2±1.1	2.2±1.1	0.88
Heart rate (bpm)	70±13	72±14	70±13	0.16
PR interval (ms)	174±34	173±33	174±35	0.73
QRS duration (ms)	128±32	131±31	127±32	0.15
Corrected QT interval duration (ms)	444.8 ± 31.4	444.6 ± 31.3	444.9 ± 31.4	0.95
Cardiac resynchronization therapy (%)	304 (61)	99 (70)	205 (58)	0.016

AF: atrial fibrillation; CABG: coronary artery bypass; NYHA: New York Heart Association; PCI: percutaneous coronary intervention.

Patients with vs. patients without AF occurrence

There were no differences in age between patients with and patients without AF occurrence. The percentage of women was higher in the group with AF occurrence as compared to the group without AF occurrence (30% vs. 18%, p = 0.004) as was the history of AF (41% vs. 13%, p <0.001). NYHA functional class was higher in patients with AF occurrence as compared to the patients without AF occurrence (2.4±0.8 vs. 2.2±0.8, p = 0.023). In addition, 70% of the patients with AF occurrence received a cardiac resynchronization therapy device, whereas only 58% of the patients without AF occurrence received a cardiac resynchronization therapy device (p = 0.016; Table 1).

The use of medications was different for beta-blockers (lower in patients with AF occurrence, p = 0.006), diuretics/aldosterone antagonists (higher for the patients with AF occurrence, p = 0.046), and for statins (lower for the patients with AF occurrence, p = 0.018; Table 2).

Regarding the echocardiographic characteristics, patients with AF occurrence as compared to the patients without AF occurrence had larger LAVmax (34±16 ml/m2 vs. 30±12 ml/m2, p = 0.003), LAVmin (21±13 ml/m2 vs. 17±10 ml/m2, p = 0.001), LAVpre-A (24±14 ml/m2 vs. 21±10 ml/m2, p = 0.010). In addition, LA booster function was more depressed in patients with AF occurrence (18±11% vs. 21±12%, p = 0.007). Finally, PA-TDI duration was longer in patients with AF occurrence as

Table 2. Medication use of overall population, and patients with vs. without AF occurrence during follow-up.

	Overall population (n=495)	Patients with AF occurrence (n=142)	Patients without AF occurrence (n=353)	p value
ACE inhibitors/Angiotensin receptor blockers (%)	417 (84)	117 (82)	300 (85)	0.47
Beta-blockers (%)	341 (69)	85 (60)	246 (73)	0.006
Ca-antagonists (%)	30 (6)	7 (5)	23 (7)	0.50
Antiarrhythmics class III (%)	100 (20)	33 (23)	67 (19)	0.29
Diuretics/aldosterone antagonists (%)	363 (73)	113 (80)	257 (73)	0.046
Nitrates (%)	89 (18)	21 (15)	68 (19)	0.24
Statins (%)	345 (70)	88 (62)	257 (73)	0.018
Oral anticoagulants (%)	263 (53)	77 (54)	183 (53)	0.80
Aspirin (%)	210 (42)	54 (38)	156 (44)	0.21

ACE: angiotensin-converting enzyme

Table 3. Echocardiographic characteristics of overall population, and patients with vs. without AF occurrence during follow-up.

	Overall population (n=495)	Patients with AF occurrence (n=142)	Patients without AF occurrence (n=353)	p value
LVEDV indexed (ml/m2)	95±35	92±34	97±35	0.22
LVESV indexed (ml/m2)	69±31	67±30	70±32	0.31
LVEF (%)	29±10	29±10	29±10	0.93
Severe mitral regurgitation (%)	28 (6)	9 (6)	19 (5)	0.68
E/A ratio	1.3±0.9	1.4±0.9	1.3±0.9	0.041
Deceleration time (ms)	176±72	181±81	174±68	0.65
E/E' ratio	22±25	22±20	22±27	0.53
LAVmax indexed (ml/m2)	31±13	34±16	30±12	0.012
LAVmin indexed(ml/m2)	18±11	21±13	17±10	0.004
LAVpre-A indexed (ml/m2)	22±11	25±14	21±10	0.013
LA emptying fraction (%)	43±15	41±16	44±14	0.052
LA reservoir function (%)	92±60	86±61	94±60	0.10
LA conduit function (%)	29±13	29±14	30±13	0.67
LA booster function (%)	20±12	18±11	21±12	0.002
PA-TDI duration (ms)	141±26	154±27	135±24	<0.001

LA: left atrial; LAVmax: maximum left atrial volume; LAVmin: maximum left atrial volume; LAVpre-A: left atrial volume before atrial active contraction; LVEDV indexed: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; PA-TDI duration: time-interval from the beginning of the electrocardiogram P wave and the peak of $A'_{LATERAL}$ wave at tissue Doppler images

compared to patients without AF occurrence (154±27 ms vs. 135±24 ms, p <0.001; Figure 1).

Predictors of AF occurrence in the overall patient population

A total ofOverall 142 of the 495 (29%) patients experienced a first AF episode during a mean follow-up of 16.4±11.2 months.

To identify independent predictors of AF during follow-up, univariable predictors with a p-value <0.05 were entered into the Cox proportional-hazard model as covariates.

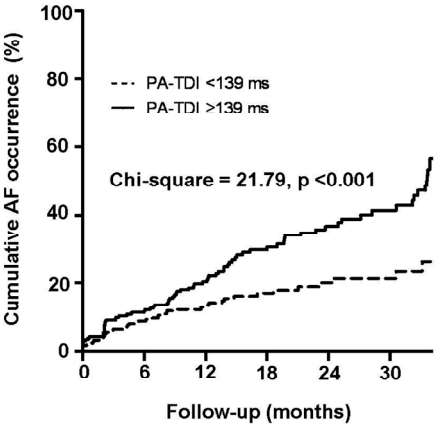
On multivariable analysis, female gender (hazard ratio, 1.60; 95% CI, 1.09-2.35; p = 0.017), history of AF (hazard ratio, 2.22; 95% CI, 1.51-3.27; p <0.001), and PA-TDI duration (hazard ratio per 20 ms increase, 1.27; 95% CI, 1.13-1.42; p <0.001), were independently associated with AF occurrence during follow-up (Table 4).

When the patient population was dichotomized based on the median PA-TDI duration (139 ms), the Kaplan-Meier curve demonstrated that patients with longer PA-TDI duration experienced significantly higher AF occurrence as compared to patients with shorter PA-TDI duration (log rank p <0.001; Figure 2). In particular, a cumulative 18%, 30%, and 44% of patients with longer PA-TDI experienced AF occurrence at 6, 12 and 18 months follow-up, respectively. In contrast, a respective 10%, 13%, and 18% of patients with shorter PA-TDI duration experienced AF occurrence during the same time period. Figures 3A and 3B show the Kaplan-Meier curves for the other 2 variables independently related to AF occurrence during follow-up: female gender and history of AF.

Table 4. Cox uni- and multivariable regression analysis to identify predictors of AF occurrence during follow-up

Dependent variable: AF occurrence during follow-up	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Independent variables				
Female	1.73 (1.21-2.48)	0.003	**1.60 (1.09-2.35)**	**0.017**
History of AF	3.42 (2.44-4.78)	<0.001	**2.22 (1.51-3.27)**	**<0.001**
NYHA functional class	1.32 (1.01-1.63)	0.011	1.09 (0.83-1.43)	0.55
Cardiac resynchronization therapy	1.69 (1.18-2.41)	0.004	1.29 (0.85-1.96)	0.24
Beta-blockers	0.59 (0.42-0.83)	0.002	0.81 (0.56-1.16)	0.24
Diuretics/aldosterone antagonists	1.59 (1.01-2.39)	0.026	1.04 (0.65-1.65)	0.89
Statins	0.66 (0.47-0.93)	0.016	0.95 (0.66-1.36)	0.78
LAVmin indexed (per 10ml/m2)	1.29 (1.13-1.48)	<0.001	1.09 (0.92-1.29)	0.31
LA booster function (per 1%)	0.09 (0.02-0.40)	0.002	0.47 (0.08-2.72)	0.40
PA-TDI duration (per 20ms)	1.44 (1.30-1.60)	<0.001	**1.27 (1.13-1.42)**	**<0.001**

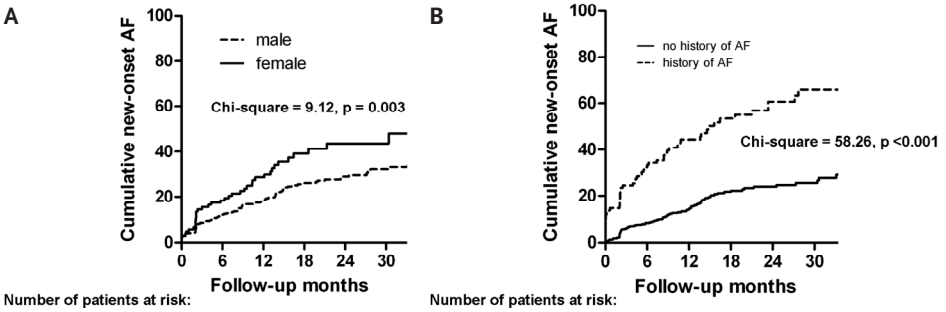
AF: atrial fibrillation; CI: confidence intervals; HR: hazard ratio; LA: left atrial; LAVmin: maximum left atrial volume; NYHA: New York Heart Association; PA-TDI duration: time-interval from the beginning of the electrocardiogram P wave and the peak of $A'_{LATERAL}$ wave at tissue Doppler images.



Number of patients at risk:

PA-TDI duration <139 ms	253	226	140	94	66	38
PA-TDI duration ≥139 ms	242	193	133	83	64	43

Figure 2. Kaplan-Meier estimates of occurrence of atrial fibrillation (AF). The probability of AF occurrence differed significantly between the 2 groups dichotomized based on the median total atrial conduction time estimated with tissue Doppler imaging (PA-TDI duration) of 139 ms.



Number of patients at risk:

male	390	336	217	145	110	67
female	105	82	54	29	18	12

Number of patients at risk:

No history of AF	393	350	230	147	108	68
History of AF	102	68	41	27	18	11

Figure 3. Kaplan-Meier estimates of occurrence of atrial fibrillation (AF) in male and female (**Panel A**), and in patients with and without history of AF (**Panel B**).

Patients with vs. patients without history of AF

From According to the baseline clinical history, a total of 102 (21%) patients had a history of AF. Of the 102 patients with history of AF, 56 (55%) had history of paroxysmal AF and 46 (45%) of persistent AF. Specifically, AF occurrence during follow-up was higher in patients with history of persistent AF as compared to paroxysmal AF (70% vs. 46%, p = 0.019). There were no differences in the clinical characteristics between

patients with and without history of AF except for age, patients with history of AF were older than the patients without history of AF (65±10 vs. 61±12 years, p = 0.005). In addition, patients with history of AF were most often treated with antiarrhythmic drugs and oral anticoagulants (43% vs. 14%, p <0.001 and 64% vs. 51%, p <0.001, respectively), whereas the use of aspirin was larger in patients without history of AF (45% vs. 32%, p = 0.021).

Regarding the echocardiographic characteristics, as compared to the patients without history of AF, the patients with history of AF had larger LAV (37±18 ml/m² vs. 30±12 ml/m², p <0.001 for LAVmax, 24±14 ml/m² vs. 17±9 ml/m², p <0.001 for LAVmin, 28±15 ml/m² vs. 21±10 ml/m², p <0.001 for LAVpre-A) and poorer LA functions (38±15% vs. 45±14%, p <0.001 for total LA empting function, 72±50% vs. 97±62%, p <0.001, for LA reservoir function, 27±13% vs. 30±13%, p = 0.028, for LA conduit function, 15±10% vs. 22±12%, p <0.001, for LA booster function). In addition, PA-TDI duration was significantly longer in patients with history of AF as compared to the patients without history of AF (159±32 ms vs. 136±22 ms, p <0.001).

Predictors of AF occurrence in patients without history of AF

To identify independent predictors of AF during follow-up in patients without history of AF, significant univariable predictors were entered into the Cox proportional-hazard model as covariates. On multivariable analysis, female gender (hazard ratio, 1.95; 95% CI, 1.22-3.10; p = 0.005), and PA-TDI duration (hazard ratio per 20 ms increase, 1.34; 95% CI, 1.13 to 1.58; p = 0.001), were independently associated with AF occurrence during follow-up (Table 5). Figure 4A shows the Kaplan-Meier curves for the PA-TDI duration in patients without history of AF.

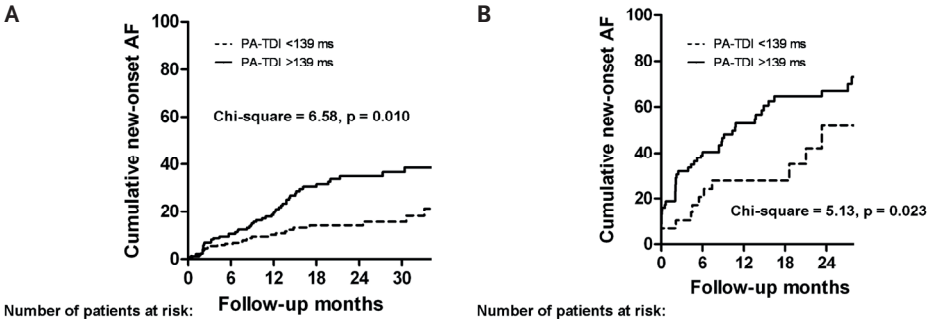


Figure 4. Kaplan-Meier estimates of occurrence of atrial fibrillation (AF) in patients without history of AF (**Panel A**) and with history of AF (**Panel B**).

Table 5. Cox uni- and multivariable regression analysis to identify predictors of AF occurrence during follow-up in the subgroup of patients without history of AF

Dependent variable: AF occurrence during follow-up	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Independent variables				
Female	1.98 (1.25-3.14)	0.003	**1.95 (1.22-3.10)**	**0.005**
NYHA functional class	1.31 (0.99-1.72)	0.051	...	...
Cardiac resynchronization therapy	1.24 (0.80-1.94)	0.34	...	...
Beta-blockers	0.71 (0.45-1.13)	0.15	...	...
Diuretics/aldosterone antagonists	1.33 (0.81-2.18)	0.26	...	...
Statins	0.56 (0.36-0.87)	0.010	0.65 (0.42-1.02)	0.060
LAVmin indexed (per 10ml/m2)	1.14 (0.92-1.42)	0.23	...	...
LA booster function (per 1%)	0.29 (0.05-1.76)	0.16	...	...
PA-TDI duration (per 20ms)	1.34 (1.13-1.58)	0.001	**1.34 (1.13-1.58)**	**0.001**

AF: atrial fibrillation; CI: confidence intervals; HR: hazard ratio; LA: left atrial; LAVmin: maximum left atrial volume; NYHA: New York Heart Association; PA-TDI duration: time-interval from the beginning of the electrocardiogram P wave and the peak of $A'_{LATERAL}$ wave at tissue Doppler images.

Predictors of AF occurrence during follow-up in patients with history of AF

To identify independent predictors of AF during follow-up in patients with history of AF, significant univariable predictors were entered into the Cox proportional-hazard model as covariates. On multivariable analysis, cardiac resynchronization device therapy (hazard ratio, 2.67; 95% CI, 1.39-5.10; p = 0.003), and PA-TDI duration (hazard ratio per 20 ms increase, 1.19; 95% CI, 1.03 to 1.38; p = 0.022), were independently associated with AF occurrence during follow-up (Table 6). Figure 4B shows Kaplan-Meier curves for the PA-TDI duration in patients with history of AF.

DISCUSSION

The main findings of the present study are: 1) the independent predictors of AF occurrence in advanced heart failure patients were female gender, history of AF and PA-TDI

Table 6. Cox uni- and multivariable regression analysis to identify predictors of AF occurrence during follow-up in the subgroup of patients with history of AF

Dependent variable: AF occurrence during follow-up	**Univariable analysis**		**Multivariable analysis**	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Independent variables				
Female	1.39 (0.77-2.51)	0.27	...	...
NYHA functional class	1.30 (0.91-1.86)	0.14	...	...
Cardiac resynchronization therapy	2.99 (1.58-5.65)	0.001	**2.67 (1.39-5.10)**	**0.003**
Beta-blockers	0.84 (0.50-1.40)	0.50	...	...
Diuretics/aldosterone antagonists	1.72 (0.82-3.64)	0.15	...	...
Statins	1.09 (0.64-1.86)	0.76	...	...
LAVmin indexed (per 10ml/m2)	1.15 (0.96-1.38)	0.12	...	...
LA booster function (per 1%)	0.12 (0.01-2.05)	0.14	...	...
PA-TDI duration (per 20ms)	1.25 (1.08-1.45)	0.003	**1.19 (1.03-1.38)**	**0.022**

AF: atrial fibrillation; CI: confidence intervals; HR: hazard ratio; LA: left atrial; LAVmin: maximum left atrial volume; NYHA: New York Heart Association; PA-TDI duration: time-interval from the beginning of the electrocardiogram P wave and the peak of $A'_{LATERAL}$ wave at tissue Doppler images.

duration; 2) in the subgroups of patients with and without history of AF, PA-TDI duration remained an independent predictor of AF occurrence during follow-up.

Heart failure and AF

Heart failure and AF are two disorders that frequently coexist. Indeed, many clinical conditions such as age, hypertension, diabetes and coronary artery disease are common risk factors for both AF and heart failure.[19] Moreover, in heart failure patients conditions such as atrial enlargement or poor atrial function related to the remodelling processes may predispose to AF occurrence.[6] In addition, previous studies have shown that heart failure patients who develop AF have a worse prognosis than heart failure patients free from AF.[1, 20-23] Therefore, the identification of heart failure patients at higher risk for AF occurrence may be useful in order to initiate early prophylactic therapies and improve the long-term outcome of these patients.

process is the ability to identify all of the AF episodes in these patients. In particular, asymptomatic AF episodes may be misclassified during clinical follow-up and it has been shown that these asymptomatic AF episodes may have relevant

AF-related complications similar to overt, symptomatic AF episodes.[24, 25] Interrogation of newer more sophisticated pacemaker or ICD devices allows the detection of asymptomatic AF episodes.[9, 26] A study by Glotzer et al.[9] demonstrated that in patients with a pacemaker for sinus node dysfunction the atrial high rate events detected by pacemaker interrogation were significantly related to the risk of death or stroke. However, the interrogation of the device to classify AF episodes can be applied only in patients with a pacemaker or ICD. Therefore, in the current study, heart failure patients selected for ICD implantation were recruited in order to detect all the AF episodes, including the asymptomatic episodes, through the ICD interrogation.

Predictors of AF occurrence in the overall heart failure patient population

In the present study, clinical and echocardiographic predictors of AF occurrence in heart failure patients were explored. In particular, among the clinical predictors, female gender and history of AF were confirmed to be independently associated with AF occurrence.[5] Among the echocardiographic variables, LA volumes and booster function together with PA-TDI duration were associated with AF occurrence at univariable analysis. However, at multivariable analysis only PA-TDI duration was an independent echocardiographic predictor of AF occurrence (adjusted hazard ratio = 1.27, 95% CI 1.13-1.42, p <0.001). This finding underlines that a surrogate of the total atrial conduction time like PA-TDI was a stronger predictor of AF occurrence as compared to LA volumes and LA function. A possible explanation may be that the LA remodelling present in heart failure patients is associated with an increased risk of the development of AF. The remodelling process causes an increase in LA volumes, with a deterioration in LA function and an increase in LA fibrosis. Both LA enlargement and LA fibrosis may promote the occurrence of AF in these patients.[27] The total atrial conduction time (PA-TDI duration) may be influenced not only by LA enlargement but also by LA fibrosis which may further slow down the electrical atrial conduction. Therefore, PA-TDI duration may be more strongly related to AF occurrence than measurement of LA volumes or function.

PA-TDI duration as a predictor of AF occurrence in the subgroup without history of AF

Previous studies have explored the role of total atrial conduction time detected with tissue Doppler imaging for the prediction of AF occurrence in patients without history of AF.[7, 28] In particular, de Vos et al. used the PA-TDI duration to predict AF occurrence in 249 patients with preserved ejection fraction (60±10%) referred for a standard

echocardiographic examination. The authors demonstrated that PA-TDI duration was independently related to AF occurrence during follow-up. In the present study, 393 of the heart failure patients had no previous history of AF and the mean ejection fraction in this subgroup of patients was 29±10%. PA-TDI was still an independent predictor of AF occurrence during follow-up. Therefore, the current study highlights that PA-TDI is also an important predictor of AF occurrence in heart failure patients with depressed left ventricular ejection fraction, extending previous results in different patient populations.[7, 28]

PA-TDI duration as a predictor of AF occurrence in the subgroup with history of AF

In the present study a total of 102 heart failure patients had a history of AF. The analysis of this subset of patients underlined that PA-TDI duration was still an independent predictor of AF occurrence together with implantation of a cardiac resynchronization therapy device. Patients selected for cardiac resynchronization therapy were characterized by more advanced heart failure, a condition shown to be an important predictor of AF occurrence.[4, 5] In addition, the relevance of measuring PA-TDI duration in these patients is stressed by previous findings.[29] Specifically, Buck et al. reported that an estimation of total atrial conduction time with PA-TDI may have great relevance for the selection of advanced heart failure patients who will be amenable to cardiac resynchronization therapy.[29]

The finding that PA-TDI duration was again independently associated with AF occurrence during follow-up shows for the first time the relevance of this index even in patients with history of AF. Therefore, PA-TDI duration may be useful for the risk-stratification of heart failure patients with or without history of AF.

Clinical implications

Early risk stratification for AF occurrence is very important, especially in heart failure patients who have increased risk of thromboembolic complications during AF. The present study has demonstrated that PA-TDI duration can predict AF occurrence in heart failure patients. However, future large randomized trials are needed to clarify the potential relation between PA-TDI duration and thromboembolic complications during AF in heart failure patients.

CONCLUSIONS

PA-TDI duration was independently associated with AF occurrence in heart failure patients with or without history of AF. This parameter may be useful to risk-stratify heart failure patients for AF occurrence.

REFERENCES

(1) Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009;11: 676-683.

(2) Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946-952.

(3) Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-988.

(4) Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003;91:2D-8D.

(5) Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). *Eur Heart J* 2006;27:1979-2030.

(6) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008;10:933-989.

(7) de Vos CB, Weijs B, Crijns HJ, Cheriex EC, Palmans A, Habets J, Prins MH, Pisters R, Nieuwlaat R, Tieleman RG. Atrial tissue Doppler imaging for prediction of new-onset atrial fibrillation. *Heart* 2009;95:835-840.

(8) Merckx KL, de Vos CB, Palmans A, Habets J, Cheriex EC, Crijns HJ, Tieleman RG. Atrial activation time determined by transthoracic Doppler tissue imaging can be used as an estimate of the total duration of atrial electrical activation. *J Am Soc Echocardiogr* 2005;18:940-944.

(9) Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation* 2003;107:1614-1619.

(10) Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation* 1994;89:224-227.

(11) Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias

and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;8:746-837.

(12) Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland JG, Freemantle N, Erdmann E. Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. *Circulation* 2006;114:18-25.

(13) Theuns DA, Klootwijk AP, Goedhart DM, Jordaens LJ. Prevention of inappropriate therapy in implantable cardioverter-defibrillators: results of a prospective, randomized study of tachyarrhythmia detection algorithms. *J Am Coll Cardiol* 2004;44:2362-2367.

(14) Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463.

(15) Bonow RO, Carabello BA, Kanu C, de LA, Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation* 2006;114:e84-231.

(16) Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J* 2008;156:1056-1064.

(17) Marsan NA, Bleeker GB, Ypenburg C, Van Bommel RJ, Ghio S, Van d, V, Delgado V, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Real-time three-dimensional echocardiography as a novel approach to assess left ventricular and left atrium reverse remodeling and to predict response to cardiac resynchronization therapy. *Heart Rhythm* 2008;5:1257-1264.

(18) Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107-133.

(19) Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation* 1994;89:724-730.

(20) Aronow WS, Ahn C, Kronzon I. Prognosis of congestive heart failure after prior myocardial infarction in older persons with atrial fibrillation versus sinus rhythm. *Am J Cardiol* 2001;87:224-229.

(21) Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 1998;32:695-703.

(22) Mathew J, Hunsberger S, Fleg J, Mc SF, Williford W, Yusuf S. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest* 2000;118:914-922.

(23) Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. *Circulation* 1991;84:40-48.

(24) Kirchhof P, Bax J, Blomstrom-Lundquist C, Calkins H, Camm AJ, Cappato R, Cosio F, Crijns H, Diener HC, Goette A, Israel CW, Kuck KH, Lip GY, Nattel S, Page RL, Ravens U, Schotten U, Steinbeck G, Vardas P, Waldo A, Wegscheider K, Willems S, Breithardt G. Early and comprehensive management of atrial fibrillation: executive summary of the proceedings from the 2nd AFNET-EHRA consensus conference 'research perspectives in AF'. *Eur Heart J* 2009;30:2969-77c.

(25) Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation: executive summary. *Eur Heart J* 2007;28:2803-2817.

(26) Borleffs CJ, Ypenburg C, Van Bommel RJ, Delgado V, van EL, Schalij MJ, Bax JJ. Clinical importance of new-onset atrial fibrillation after cardiac resynchronization therapy. *Heart Rhythm* 2009;6:305-310.

(27) Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230-246.

(28) Roshanali F, Mandegar MH, Yousefnia MA, Rayatzadeh H, Alaeddini F, Amouzadeh F. Prediction of atrial fibrillation via atrial electromechanical interval after coronary artery bypass grafting. *Circulation* 2007;116:2012-2017.

(29) Buck S, Rienstra M, Maass AH, Nieuwland W, van Veldhuisen DJ, Van G, I. Cardiac resynchronization therapy in patients with heart failure and atrial fibrillation: importance of new-onset atrial fibrillation and total atrial conduction time. *Europace* 2008;10:558-565.

CHAPTER 12

Conclusions

SUMMARY AND CONCLUSIONS

The general introduction of the thesis outlines the role of cardiac mechanics assessment in the evaluation and risk stratification of HF patients.

Part I

This part of the thesis summarizes current imaging techniques to assess various aspects of LV mechanics in HF patients (**Chapter 2**), differentiating between ischemic and non-ischemic HF (**Chapter 3**) and investigating its role in the selection of HF patients who are candidates to CRT (**Chapters 4-6**). Furthermore, the role of imaging techniques to optimize the results of CRT is summarized in **Chapter 7**.

Part II

The final part focuses on long-term prognosis of advanced HF patients. Novel echocardiographic techniques provide several parameters that have incremental prognostic value over well-recognized echocardiographic and clinical parameters (**Chapters 8-11**).

CONCLUSIONS

The study of cardiac mechanics is crucial in advanced HF patients. Particularly, using imagine techniques as speckle-tracking echocardiography, important information on the effects of CRT in heart failure patients may be derived. Moreover, studying LV mechanics may be helpful for understanding the differences in pathophysiological mechanisms of different HF aetiologies. Finally, the role of non-invasive imaging techniques for the study of LV mechanics may be paramount for the definition of long-term prognosis in advanced HF patients.

SAMENVATTING EN CONCLUSIES

De algemene introductie van deze scriptie geeft kort weer wat de rol is van de analyse van cardiale dynamiek bij de evaluatie en risico inschatting van hartfalen patienten.

Deel 1

Dit onderdeel is een samenvatting van de huidige beeldvomings technieken voor het beoordelen van de LV dynamiek in hartfalen patienten (Hoofdstuk 2), de differentiatie tussen ischemische en non-ischemische hartfalen (Hoofdstuk 3) en de rol hiervan in de selectie van CRT kandidaten.

Deel 2

Het laatste gedeelte richt zich op de lange termijn prognose van patienten met eindstadium hartfalen. Nieuwe echocardiografische technieken en metingen hebben steeds meer toenemende waarde naast de bekende, conventionele echocardiografische en klinische parameters (Hoofdstuk 8-11).

Onderzoek naar cardiale dynamiek is van cruciaal belang bij patienten met eindstadium hartfalen. Met beeldvorming zoals speckle-tracking echocardiografie kan belangrijke informatie worden verkregen over de effecten van CRT bij deze populatie. Bovendien kan analyse van LV dynamiek helpen bij het onderkennen van verschillende pathofysiologische processen bij verscheidene vormen van hartfalen. De rol van non-invasieve beeldvorming zou van essentieel belang kunnen zijn bij het vaststellen van lange termijn prognose bij patienten met eindstadium hartfalen.

LIST OF PUBLICATIONS

1. **Bertini M**, Marcantoni L, Toselli T, Ferrari R. Remote monitoring of implantable devices: should we continue to ignore it? *Int J Cardiol 2015 in Press*
2. Ng AC, Kong WK, Kamperidis V, **Bertini M**, Antoni ML, Leung DY, Marsan NA, Delgado V, Bax JJ. Anaemia in patients with aortic stenosis: influence on long-term prognosis. *Eur J Heart Fail. 2015. In Press.*
3. Sassone B. **Bertini M**. Reply: To PMID 25465934. *Am J Cardiol 2015; 115(12):1781-2.*
4. Sassone B, Gambetti S, **Bertini M**, Beltrami M, Mascioli G, Bressan S, Fuca' G, Pacchioni F, Pedaci M, Michelotti F, Bacchi Reggiani L, Padeletti L. Relation of QRS Duration to Response to Cardiac Resynchronization Therapy. *Am J Cardiol 2015;115:214-19*
5. Ziacchi M, Diemberger I, Biffi M, Martignani C, **Bertini M**, Rocchi G, Biagini E, Graziosi M, Mazzotti A, Rapezzi C, Boriani G. Predictors of nonsimultaneous interventricular delay at cardiac resynchronization therapy optimization. *J Cardiovasc Med 2014 in Press*
6. Santoro A, Alvino F, Antonelli G, Cameli M, **Bertini M**, Molle R, Mondillo S. Left Ventricular Strain Modifications after Maximal Exercise in Athletes: A Speckle Tracking Study. *Echocardiography 2014 in Press*
7. Marcantoni L, Toselli T, Urso G, Pratola C, Ceconi C, **Bertini M**. Impact of Remote Monitoring on the Management of Arrhythmias in patients with Implantable Cardioverter-Defibrillator. *J Cardiovasc Med 2014 in Press*
8. Abate E, Hoogslag GE, Leong DP, **Bertini M**, Antoni ML, Nucifora G, Joyce E, Holman ER, Siebelink HM, Schalij MJ, Bax JJ, Delgado V, Ajmone Marsan N. Association between Multilayer Left Ventricular Rotational Mechanics and the Development of Left Ventricular Remodeling after Acute Myocardial Infarction. *J Am Soc Echocardiogr. 2014; 27(3):239-48*
9. Auger D, Hoke U, Ajmone Marsan N, Tops L, Leong D, **Bertini M**, Schalij M, Bax J, Delgado V. Effect of induced LV dyssynchrony by right ventricular apical pacing on all-cause mortality and heart failure hospitalization rates at long-term follow-up. *J Cardiovasc Electrophysiol 2014; 6:631-7*
10. Biffi M, **Bertini M,** Ziacchi M, Diemberger I, Martignani C, Boriani G. Left ventricular lead stabilization to retain cardiac resynchronization therapy at long term: when is it advisable? *Europace 2014;16(4): 533-40*
11. Malagù M, Marcantoni L, Scalone A, Toselli T, Pratola P, **Bertini M**. A migrant left ventricular lead. *J Cardiovasc Med 2014. In Press.*
12. **Bertini M**, Hoke U, van Bommel RJ, Ng ACT, Shanks M, Nucifora G, Auger D, Borleffs CJW, van Rijnsoever EPM, van Erven L, Schalij MJ, Ajmone Marsan N, Bax JJ, Delgado V. Impact of clinical and echocardiographic response to cardiac

resynchronization therapy on long-term survival. *Eur Heart J Cardiovasc Imaging. 2013; 14(8): 774-81*

13. **Bertini M**, Toselli T, Pratola C. Correspondence "Left ventricular pacing rate lower than expected during manual pacing threshold test in a biventricular defibrillator". *Europace 2013; 15(4): 613.*
14. **Bertini M**, Schalij MJ, Bax JJ, Delgado V. Emerging role of multimodality imaging to evaluate patients at risk for sudden cardiac death. *Circ Cardiovasc Imaging. 2012;5(4):525-35*
15. Nucifora G, **Bertini M**, Ajmone Marsan N, Scholte AJ, Siebelink HM, Holman ER, Schalij MJ, van der Wall EE, Bax JJ, Delgado V. Temporal evolution of left ventricular dyssynchrony after myocardial infarction: relation with changes in left ventricular systolic function. *Eur Heart J Cardiovasc Imaging. 2012;13(12):1041-6.*
16. **Bertini M**, Ng AC, Antoni ML, Nucifora G, Ewe SH, Auger D, Ajmone Marsan N, Schalij MJ, Bax JJ, Delgado V. Global Longitudinal Strain Predicts Long-Term Survival in Patients with Chronic Ischemic Cardiomyopathy. *Circ Cardiovasc Imaging. 2012; 5(3):383-91*
17. Auger D, Bleeker GB, **Bertini M**, Ewe SH, van Bommel RJ, Witkowski TG, Ng AC, van Erven L, Schalij MJ, Bax JJ, Delgado V. Effect of cardiac resynchronization therapy in patients without left intraventricular dyssynchrony. *Eur Heart J 2012; 33(7):913-20.*
18. Ng AC, Auger D, Delgado V, van Elderen SG, **Bertini M**, Siebelink HM, van der Geest RJ, Bonetti C, van der Velde ET, de Roos A, Smit JW, Leung DY, Bax JJ, Lamb HJ. Association Between Diffuse Myocardial Fibrosis by Cardiac Magnetic Resonance Contrast-Enhanced T1 Mapping and Subclinical Myocardial Dysfunction in Diabetic Patients: A Pilot Study. *Circ Cardiovasc Imaging. 2012;5(1):51-9*
19. Shanks M, Antoni ML, Hoke U, **Bertini M**, Ng AC, Auger D, Marsan NA, van Erven L, Holman ER, Schalij MJ, Bax JJ, Delgado V. The effect of cardiac resynchronization therapy on left ventricular diastolic function assessed with speckle-tracking echocardiography. *Eur J Heart Fail. 2011;13(10):1133-9.*
20. Ng AC, Yiu KH, Ewe SH, van der Kley F, **Bertini M**, de Weger A, de Roos A, Leung DY, Schuijf JD, Schalij MJ, Bax JJ, Delgado V. Influence of left ventricular geometry and function on aortic annular dimensions as assessed with multi-detector row computed tomography:implications for transcatheter aortic valve implantation. *Eur Heart J. 2011 32(22):2806-13.*
21. Biffi M, Ziacchi M, **Bertini M**, Gardini B, Mazzotti A, Massaro G, Martignani C, Diemberger I, Boriani G, Corsini D. How to truly value implantable cardioverter-defibrillators technology: Up-front cost or daily cost? *Int J Technol Assess Health Care. 2011 Jul;27(3):201-6.*

22. Auger D, **Bertini M**, Marsan NA, Hoke U, Ewe SH, Thijssen J, Witkowski TG, Yiu KH, Ng AC, van der Wall EE, Schalij MJ, Bax JJ, Delgado V. Prediction of Response to Cardiac Resynchronization Therapy Combining Two Different Three-Dimensional Analyses of Left Ventricular Dyssynchrony. *Am J Cardiol. 2011; 108(5):711-7.*
23. Biffi M, **Bertini M**, Ziacchi M, Gardini B, Mazzotti A, Massaro G, Diemberger I, Martignani C, Valzania C, Boriani G. Management of Phrenic Stimulation in CRT Patients over the Long Term: Still an Unmet Need ? *Pacing Clin Electrophysiol. 2011;34:1201-1208.*
24. van Bommel RJ, Ypenburg C, Mollema SA, Borleffs CJ, Delgado V, **Bertini M**, Marsan NA, van der Wall EE, Schalij MJ, Bax JJ. Site of latest activation in patients eligible for cardiac resynchronization therapy: Patterns of dyssynchrony among different QRS configurations and impact of heart failure etiology. *Am Heart J. 2011 Jun;161(6):1060-6*
25. den Uijl DW, Delgado V, **Bertini M**, Tops LF, Trines SA, Van de Veire NRL, Zeppenfeld K, Schalij MJ, Bax JJ. Impact of left atrial fibrosis on the outcome of catheter ablation for atrial fibrillation. *Heart 2011; 97(22):1847-51.*
26. Ng AC, Delgado V, **Bertini M**, Antoni ML, van Bommel RJ, van Rijnsoever EP, van der Kley F, Ewe SH, Witkowski T, Auger D, Nucifora G, Schuijf JD, Poldermans D, Leung DY, Schalij MJ, Bax JJ. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: a two-dimensional speckle tracking analysis. *Eur Heart J. 2011; 32(12):1542-50.*
27. **Bertini M**, Ng AC, Delgado V, Bax JJ. Reply to the letter by Lin et al "Longitudinal mechanics of the periinfarct zone and ventricular tachycardia inducibility in patients with chronic ischemic cardiomyopathy". *Am Heart J. 2011 Apr;161(4):e19*
28. Shanks M , Delgado V, Ng ACT, Auger D, Mooyart EAQ, **Bertini M**, Ajmone Marsan N, van Bommel RJ, Holman ER, Poldermans D, Schalij MJ, Bax JJ. Clinical and echocardiographic predictors of nonresponse to cardiac resynchronization therapy. *Am Heart J 2011; 161(3):552-7.*
29. **Bertini M**, Ziacchi M, Biffi M, Biagini E, Rocchi G, Martignani C, Ferlito M, Pasquale F, Cervi E, Branzi A, Rapezzi C, Boriani G. Effects of cardiac resynchronization therapy on dilated cardiomyopathy with isolated ventricular non-compaction. *Heart 2011;97(4):295-300*
30. Ng AC, Delgado V, Djaberi R, Schuijf JD, Boogers MJ, Auger D, **Bertini M**, de Roos A, van der Meer RW, Lamb HJ, Bax JJ. Multimodality imaging in diabetic heart disease. *Curr Probl Cardiol. 2011 Jan;36(1):9-47.*
31. Witkowski TG, ten Brinke EA, Delgado V, Ng ACT, **Bertini M**, Ajmone Marsan N, Ewe SH, Auger D, Yiu KH, Braun J, Klein P, Steendijk P, Versteegh MIM, Klautz RJ,

Bax JJ. Surgical Ventricular Restoration for Patients with Ischemic Heart Failure: Determinants of Two-year Survival**.** *Ann Thorac Surg. 2011;91(2):491-8*

32. Biffi M, **Bertini M**, Mazzotti A, Gardini B, Mantovani V, Ziacchi M, Valzania C, Martignani C, Diemberger I, Boriani G. Long-Term RV Threshold Behavior by Automated Measurements: Safety is the Standpoint of Pacemaker Longevity! *Pacing and Clin Electrophysiol 2011; 34: 89-95*
33. Brandts A, **Bertini M**, van Dijk EJ, Delgado V, Ajmone Marsan N, Siebelink HM, de Roos A, Bax JJ, Westenberg JJM. Left ventricular diastolic function assessment from three-dimensional three-directional velocity-encoded MRI with retrospective valve tracking. *J Magn Reson Imaging. 2011 Feb;33(2):312-9*
34. Delgado V, van Bommel RJ, **Bertini M**, Borleffs CJW, Ajmone Marsan N, Nucifora G, van de Veire NRL, Ypenburg C, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Relative merits of left ventricular dyssynchrony, left ventricular lead position and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. *Circulation 2011; 123: 70-78*
35. Ziacchi M, **Bertini M**, Biffi M, Martignani C, Diemberger I, Cervi E, Valzania C, Mazzotti A, Gardini B, Massaro G, Moschini C, Mantovani V, Marziali A, Boriani G. L'ottimizzazione degli intervalli AV e VV nei pazienti con device biventricolare: revisione della letteratura e contributo sperimentale. *Giac 2010; 13: 208-16.*
36. Ng ACT, Delgado V, **Bertini M**, van der Meer RW, Rijzewijk LJ, Ewe SH, Siebelink HM, Smit JWA, Diamant M, Romijn JA, de Roos A, Leung DY, Lamb HJ, Bax JJ. Myocardial Steatosis and Biventricular Strain and Strain Rate Imaging in Patients with Type 2 Diabetes Mellitus. *Circulation 2010; 122(24):2538-44.*
37. van Bommel RJ, Tanaka H, Delgado V, **Bertini M**, Borleffs CJ, Ajmone Marsan N, Holzmeister J, Ruschitzka F, Schalij MJ, Bax JJ, Gorcsan J 3rd. Association of intraventricular mechanical dyssynchrony with response to cardiac resynchronization therapy in heart failure patients with a narrow QRS complex. *Eur Heart J. 2010; 31(24):3054-62.*
38. **Bertini M**, Ng ACT, Borleffs CJW, Delgado V, Boersma E, Piers SRD, Thijssen J, Nucifora G, Shanks M, Ewe SH, Biffi M, Van de Veire NRL, Leung DY, Schalij MJ, Bax JJ. Predictors of Death and Occurrence of Appropriate Implantable Defibrillator Therapies in Patients With Chronic Ischemic Cardiomyopathy. *Am J Cardiol 2010; 106(11): 1566-73.*
39. **Bertini M**, Delgado V, Nucifora G, Ajmone Marsan N, Ng ACT, Shanks M, Antoni ML, van de Veire NRL, van Bommel RJ, Rapezzi C, Schalij MJ, Bax JJ. Left ventricular rotational mechanics in patients with coronary artery disease: differences in subendo- and subepicardial layers. *Heart 2010; 96(21): 1737-43.*
40. Auger D, van Bommel RJ, **Bertini M,** Delgado V, Ng ACT, Ewe SH, Shanks M, Ajmone Marsan N, Mooyaart EAQ, Witkoski T, Poldermans D, Schalij MJ, Bax

JJ. Prevalence and characteristics of patients with clinical improvement but not significant left ventricular reverse remodeling after cardiac resynchronization therapy. *Am Heart J 2010;160 (4): 737-43*

41. Nucifora G, Delgado V, **Bertini M**, Ajmone Marsan N, Van de Veire NRL, Ng ACT, Siebelink HM, Schalij MJ, Holman ER, Sengupta PP, Bax JJ. Left Ventricular Muscle and Fluid Mechanics in Acute Myocardial Infarction. *Am J Cardiol 2010;106:1404-09*
42. van Bommel RJ, Ajmone Marsan N, Koppen H, Delgado V, Borleffs CJW, Ypenburg C, **Bertini M**, Schalij MJ, Bax JJ. Effect of Cardiac Resynchronization Therapy on Cerebral Blood Flow. *Am J Cardiol 2010;106(1):73-7*
43. Boriani G, Diemberger I, Valzania C, Biffi M, Martignani C, Raschi E, Mantovani V, Ziacchi M, **Bertini M**, De Ponti F, Branzi A. Role of drugs and devices in patients at risk of sudden cardiac death. *Fundam Clin Pharmacol. 2010; 24(5):575-94*
44. van Bommel RJ, van Rijnsoever EP, Borleffs CJW, Delgado V, Ajmone Marsan N, **Bertini M**, Schalij MJ, Bax JJ. Effects of Cardiac Resynchronization Therapy in Patients with New York Heart Association Functional Class IV Heart Failure. *Am J Cardiol 2010;106: 1146-51*
45. Abdulrahman RM, Delgado V, Ng A, Ewe SH, **Bertini M**, Holman ER, Hovens GC, Pereira AM, Romijn JA, Bax JJ, Smit JW. Abnormal cardiac contractility in long term exogenous subclinical hyperthyroid patients as demonstrated by two-dimensional echocardiography speckle tracking imaging. *Eur J Endocrinol. 2010; 163(3):435-41.*
46. Shanks M, Delgado V, Ng ACT, van der Kley F, Schuijf JD, Boersma E, van de Veire NRL, Nucifora G, Bertini M, de Roos A, Kroft L, Schalij MJ, Bax JJ. Mitral Valve Morphology Assessment: Three-dimensional Transesophageal Echocardiography versus Computed Tomography. *Ann Thorac Surg. 2010; 90(6):1922-9.*
47. **Bertini M**, Ng ACT, Borleffs CJW, Delgado V, Wijnmaalen AP, Nucifora G, Ewe SH, Shanks M, Thijsssen J, Zeppenfield K, Biffi M, Leung DY, Schalij MJ, Bax JJ. Longitudinal Mechanics of the Peri-infarct Zone and Ventricular Tachycardia Inducibility in Patients with Chronic Ischemic Cardiomyopathy. *Am Heart J 2010; 160 (4): 729-36*
48. van Bommel RJ, Mollema SA, Borleffs CJW, **Bertini M**, Ypenburg C, Ajmone Marsan N, Delgado V, van der Wall EE, Schalij MJ, Bax JJ. Impaired Renal Function is Associated with Echocardiographic Non-response and Poor Prognosis after Cardiac Resynchronization Therapy *J Am Coll Cardiol 2011 Feb 1;57(5):549-55*
49. van Bommel RJ, Borleffs CJW, Ypenburg C, Ajmone Marsan N, Delgado V, **Bertini M**, van der Wall EE, Schalij MJ, Bax JJ. Morbidity and mortality in heart failure patients treated with cardiac resynchronization therapy: influence of pre-implantation characteristics on long-term outcome. *Eur Heart J 2010; 31(22):2783-90.*

50. Tops LF, Delgado V, **Bertini M**, Ajmone Marsan N, den Uijl DW, Trines SAIP, Zeppenfeld K, Holman ER, Schalij MJ, Bax JJ. Left Atrial Strain Predicts Reverse Remodeling after Catheter Ablation for Atrial Fibrillation. *J Am Coll Cardiol 2011 18;57(3):324-31*
51. Biffi M, **Bertini M**, Boriani G. Cardiac resynchronization therapy: is systole all that matters? *Europace 2010; 12(9):1209-10.*
52. Nucifora G, Ajmone Marsan N, **Bertini M**, DelgadoV, Siebelink H-M J, van Werkhoven JM, Scholte AJ, Schalij MJ, van der Wall EE, Holman, ER, Bax JJ. Reduced Left Ventricular Torsion Early After Myocardial Infarction is Related to Left Ventricular Remodeling. *Circ Cardiovasc Imaging 2010; 3(4): 433-42.*
53. **Bertini M**, Borleffs JW, Delgado V, Ng ACT, Piers SRD, Shanks M, Antoni ML, Biffi M, Boriani G, Schalij MJ, Bax JJ, Van de Veire NRL. Prediction of atrial fibrillation in patients with implantable cardioverter-defibrillator and heart failure. *Eur J Heart Fail 2010; 12(10):1101-10.*
54. Delgado V, Mooyart E AQ, Ng ACT, Auger D, **Bertini M**, van Bommel RJ, Yiu K-H, Ewe SH, Witkoski TG, Ajmone Marsan N, Schuijf JD, van der Wall EE, Schalij MJ, Bax JJ. Echocardiography and non invasive imaging in cardiac resynchronization therapy. *Minerva Cardioangiol 2010; 58 (3): 313-32.*
55. Domenichini G, Diemberger I, Biffi M, Martignani C, Valzania, C, **Bertini M**, Saporito D, Ziacchi M, Branzi, A, Boriani G. Long-Term Follow-Up of Patients with Syncope Evaluated by Head-Up Tilt Test. *Annals of Noninvasive Electrocardiology 2010; 15(2):101-6.*
56. **Bertini M**, Delgado V, Nucifora G, Marsan NA, Ng ACT, Shanks M, van Bommel RJ, Borleffs CJW, Ewe SH, Boriani G, Biffi M, Schalij MJ, Bax JJ. Effect of Cardiac Resynchronization Therapy on Subendo- and Subepicardial Left Ventricular Twist Mechanics and Relation to Favorable Outcome. *Am J Cardiol 2010;106(5): 682-7.*
57. Shanks M , **Bertini M**, Delgado V, Ng ACT, Nucifora G, van Bommel RJ, Borleffs CJW, Holman ER, Van de Veire NRL, Schalij MJ, Bax JJ. Effect of Biventricular Pacing on Diastolic Dyssynchrony. *J Am Coll Cardiol 2010; 56: 1567-1575.*
58. Valzania C, Fallani F, Gavaruzzi G, Biffi M, Martignani C, Diemberger I, **Bertini M**, Domenichini G, Ziacchi M, Gadler F, Eriksson MJ, Braunschweig F, Franchi R, Branzi A, Rapezzi C, Boriani G. Radionuclide Angiographic Determination of Regional Left Ventricular Systolic Function during Rest and Exercise in Patients with Non-Ischemic Cardiomyopathy Treated with Cardiac Resynchronization Therapy. *Am J Cardiol 2010; 106(3):389-94.*
59. Antoni ML, **Bertini M**, Atary JZ, Delgado V, ten Brinke EA, Boersma E, Holman ER, van der Wall EE, Schalij MJ, Bax JJ, van de Veire NRL. Predictive Value of Total Atrial Conduction Time Estimated with Tissue Doppler Imaging for the

Development of New-Onset Atrial Fibrillation after Acute Myocardial Infarction. *Am J Cardiol 2010; 106(2): 198-203*

60. **Bertini M**, Delgado V, den Uijl DW, Nucifora G, Ng ACT, van Bommel RJ, Borleffs CJW, Boriani G, Schalij MJ, Bax JJ. Prediction of cardiac resynchronization therapy response: value of calibrated integrated backscatter imaging. *Circ Cardiovasc Imaging 2010 Jan;3(1):86-93*
61. Biffi M, **Bertini M**, Saporito D, Ziacchi M, Frabetti L, Martignani C, Diemberger I, Boriani G. Actual Pacemaker Longevity: the Benefit of Stimulation by Automatic Capture Verification. *Pacing Clin Electrophysiol 2010; 33(7):873-81.*
62. **Bertini M**, Sengupta PP, Nucifora G, Delgado V, Ng ACT, Ajmone Marsan N, Shanks M, van Bommel RJ, Schalij MJ, Narula J, Bax JJ. Left Ventricular Twist Mechanics in Heart Failure: Evolving Role in the Assessment of Cardiac Dyssynchrony. *JACC Cradiovasc Imaging 2009; 2: 1425-1435.*
63. ten Brinke EA, **Bertini M**, Klautz RJ, Antoni ML, Holman ER, Van de Veire NRL, Bax JJ, Steendijk P. Non-Invasive Estimation of Left Ventricular Filling Pressures in Heart Failure Patients after Surgical Ventricular Restoration and Restrictive Mitral Annuloplasty. *J Thorac Cardiovasc Surg. 2010; 140(4):807-15.*
64. van Bommel RJ, Claudia Ypenburg, Borleffs CJW, Delgado V, Ajmone Marsan N, **Bertini M**, Holman ER, Schalij MJ, Bax JJ. Value of Tissue Doppler Echocardiography in Predicting Response to Cardiac Resynchronization Therapy in Patients with Heart Failure. *Am J Cardiol 2010; 105(8):1153-8.*
65. Shanks M, Ng ACT, Van de Veire NRL, Antoni ML, **Bertini M**, Nucifora G, Delgado V, Holman ER, Choy JB, Leung DY, Schalij MJ, van der Wall EE, Bax JJ. Incremental Prognostic Value of the Novel Diastolic Indices for Prediction of Clinical Outcome in Patients with ST- Elevation Myocardial Infarction. *Am J Cardiol 2010;105:592-97*
66. Ng ACT, Delgado V, van der Kley F, Shanks M, Van de Veire NRL, **Bertini M**, Nucifora G, van Bommel RJ, Tops LF, de Weger A, Tavilla G, de Roos A, Kroft LJ, Leung DY, Schuijf J, Schalij MJ, Bax JJ. Comparison of Aortic Root Dimensions and Geometries Pre- and Post-Transcatheter Aortic Valve Implantation by 2- and 3-Dimensional Transesophageal Echocardiography and Multi-slice Computed Tomography. *Circ Cardiovasc Imaging 2010 Jan;3(1):94-102*
67. Nucifora G, Schuijf JD, Delgado V, **Bertini M**, Scholte AJHA, Ng ACT, van Werkhoven JM, Jukema JW, Holman ER, van der Wall EE, Bax JJ. Incremental Value of Subclinical Left Ventricular Systolic Dysfunction for the Identification of Patients with Obstructive Coronary Artery Disease. *Am Heart J 2010; 159:148-157*
68. **Bertini M**, Ajmone Marsan N, Delgado V, van Bommel RJ, Nucifora G, Borleffs CJ, Boriani G, Biffi M, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Effects of cardiac resynchronization therapy on left ventricular twist. *J Am Coll Cardiol 2009; 54:1317-1325*

69. **Bertini M**, Nucifora G, Marsan NA, Delgado V, Scholte A, Ng ACT, van Werkhoven JM, Siebelink HMJ, Holman ER, Schalij MJ, van der Wall EE, Bax JJ. Impact of Left Ventricular Dyssynchrony Early on Left Ventricular Function After First Acute Myocardial Infarction. *Am J Cardiol 2009 2010 Feb 1;105(3):306-11.*
70. Mollema SA, Delgado V, **Bertini M**, Antoni ML, Boersma E, Holman ER, Stokkel MP, Van der Wall EE, Schalij MJ, Bax JJ. Viability Assessment With Global Left Ventricular Longitudinal Strain Predicts Recovery of Left Ventricular Function After Acute Myocardial Infarction. *Circ Cardiovasc Imaging 2010 Jan;3(1):15-23*
71. **Bertini M**, Nucifora G, Ajmone Marsan N, Delgado V, van Bommel RJ, Boriani G, Biffi M, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Left ventricular rotational mechanics in acute myocardial infarction and in chronic (ischemic and non-ischemic) heart failure patients. *Am J Cardiol 2009 103(11):1506-12.*
72. **Bertini M**, Mollema SA, Delgado V, Antoni ML, Ng ACT, Holman ER, Boriani G, Schalij MJ, Bax JJ. Impact of Time to Reperfusion After Acute Myocardial Infarction on Myocardial Damage Assessed by Left Ventricular Longitudinal Strain. *Am J Cardiol 2009* 15;104(4):480-5
73. **Bertini M**, Valzania C, Biffi M, Martignani C, Ziacchi M, Pedri S, Domenichini G, Diemberger I, Saporito D, Rocchi G, Rapezzi C, Branzi A, Boriani G. Interventricular delay optimization: a comparison among three different echocardiographic methods. *Echocardiography 2010; 27(1):38-43.*
74. Rocchi G, **Bertini M**, Biffi M, Ziacchi M, Biagini E, Gallelli I Martignani C, Cervi E, Ferlito M, Rapezzi C, Branzi A, Boriani G Exercise Stress Echocardiography is Superior to Rest Echocardiography in Predicting Left Ventricular Reverse Remodeling and Functional Improvement after Cardiac Resynchronization Therapy. *Eur Heart J. 2009 Jan; 30(1):89-97.*
75. Biffi M, Moschini C, **Bertini M**, Saporito D, Ziachi M, Diemberger I, Valzania C, Domenichini G, Cervi E, Martignani C, Sangiorgi D, Branzi A, Boriani G. Phrenic Stimulation: A Challenge for Cardiac Resynchronization Therapy. *Circ Arrhythm Electrophysiol 2009; 2:402-410*
76. **Bertini M**, Delgado V, Bax JJ, Van de Veire NRL. Why, how and when do we need to optimize the setting of cardiac resynchronization therapy? *Europace 2009;11: v46-v57*
77. Boriani G, Biffi M, Martignani M, Valzania C, Diemberger I, **Bertini M**, Domenichini G, Ziacchi M, and Branzi A. Is cardiac resynchronization therapy cost-effective? *Europace 2009;11 (5): v93-v97*
78. Ajmone Marsan N, Bleeker GB, Van Bommel RJ, Borleffs JW, **Bertini M**, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Cardiac resynchronization therapy in patients with ischemic versus non-ischemic heart failure: differential effect of optimizing inter-ventricular pacing interval. *Am Heart J 2009; 158:769-776.*

79. Ng ACT, Stiges M, Pham PN, Tran DT, Delgado V, **Bertini M**, Nucifora G, Vidaic J, Allman C, Holman ER, Bax JJ, Leung DY. Incremental Value Of Two-Dimensional Speckle Tracking Strain Imaging To Wall Motion Analysis For Detection Of Coronary Artery Disease In Patients Undergoing Dobutamine Stress Echocardiography. *Am Heart J 2009;158:836-844.*
80. Ng ACT, Delgado V, **Bertini M**, Nucifora G, Shanks M, Ajmone Marsan N, Holman ER, Van de Veire NRL, Leung DY, BaxJJ. Advanced Applications of 3-Dimensional Echocardiography. *Minerva Cardioangiologica 2009; 57(4):415-41.*
81. **Bertini M**, Ziacchi M, Biffi M, Martignani C, Saporito D, Valzania C, Diemberger I, Cervi E, Frisoni J, Sangiorgi D, Branzi A, Boriani G. Interventricular Delay Interval Optimization in Cardiac Resynchronization Therapy Guided by Echocardiography Versus Guided by Electrocardiographic QRS Interval Width. *Am J Cardiol 2008 Nov 15; 102 (10): 1373-7*
82. **Bertini M**, Biffi M, Ziacchi M, Boriani G. Reply to Reader's comment: "Electrocardiographic Optimization of Cardiac Resynchronization Devices: Simple, but Not So Simple!" by Mont et al. *Am J Cardiol 2009 103(11):1625-6*
83. Delgado V, Tops LF, Trines SA, Zeppenfeld K, Ajmone Marsan N, **Bertini M**, Holman ER, Schalij MJ, Bax JJ. Acute effects of right ventricular apical pacing on left ventricular synchrony and mechanics. *Circ Arrhythm Electrophysiol 2009;2:135-145*
84. Boriani G, **Bertini M**, Diemberger I, Biffi M, Martignani C. The QRS interval in patients treated with resynchronization therapy: which value? *Eur J Heart Fail. 2009 Jul;11(7):635-7.*
85. Biffi M, **Bertini M**, Saporito D, Ziacchi M, Stabellini S, Valsecchi S, Ricci V, Boriani G. Automatic Management of Left Ventricular Stimulation: Hints for Technologic Improvement. *Pacing Clin Electrophysiol 2009; 32:346–353.*
86. Ng CTA, Delgado V, **Bertini M**, van der Meer RW, Rijzewijk LJ, Smit JWA, Diamant M, Romijn JA, de Roos A, Leung DY, LambHJ, Bax JJ. Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus. Am J Cardiol 2009;104:1398-1401
87. Martignani C, Diemberger I, Biffi M, Ziacchi M, Saporito D, Valzania C, **Bertini M**, Domenichini G, Branzi A, Boriani G. Troponin I Rise After Pacemaker Implantation at the Time of "Universal Definition of Myocardial Infarction. *Am J Cardiol 2009 103(8):1061-5*
88. Boriani G, Valzania C, Biffi M, Martignani C, Diemberger I, **Bertini M**, Domenichini G, Saporito D, Ziacchi M, Marziali A, Branzi A. Cost-effectiveness of CRT. *Device Therapy for Heart Failure 2009; Vol 2 (No 2): 38-44.*
89. Boriani G, Biffi M, Martignani C, Diemberger I, Valzania C, **Bertini M**, Branzi A. Expenditure and value for money: the challenge of implantable cardioverter defibrillators. *QJM. 2009 Mar 10*

90. Biffi M, **Bertini M,** Ziacchi M, Martignani C, Valzania C, Diemberger I, Branzi A, Boriani G Clinical implications of Left Superior persistence in candidates for pacemaker or cardioverter-defibrillator implantation. *Heart and Vessels 2009; 24(2):142-6.*
91. **Bertini M**, Biffi M, Ziacchi M, Valzania C, Saporito D, Boriani G Automatic verification of ventricular stimulation: fusion management algorithm. *Pacing Clin Electrophysiol. 2008 Jan;31(1):64-9*
92. Biffi M, Ziacchi M, **Bertini M**, Sangiorgi D, Corsini D, Martignani C, Boriani G Longevity of implantable cardioverter-defibrillators: implications for clinical practice and health care systems. *Europace 2008 Nov; 10(11): 1288-95.*
93. Boriani G, Diemberger I, Martignani C, Biffi M, Valzania C, **Bertini M**, Domenichini G, Saporito D, Ziacchi M, Branzi A. Telecardiology and remote monitoring of implanted electrical devices: the potential for fresh clinical care perspectives. *J Gen Intern Med. 2008 Jan;23 Suppl 1:73-7. Review.*
94. Valzania C, Rocchi G, Biffi M, Martignani C, **Bertini M**, Diemberger I, Biagini E, Ziacchi M, Domenichini G, Saporito D, Rapezzi C, Branzi A, Boriani G. Left ventricular versus biventricular pacing: a randomized comparative study evaluating mid-term electromechanical and clinical effects. *Echocardiography. 2008 Feb;25(2):141-8*
95. Martignani C, Diemberger I, Biffi M, Valzania C, **Bertini M**, Boriani G How to assess the efficacy of catheter ablation of atrial fibrillation? *Eur Heart J. 2008 Jul 2.*
96. Martignani C, Diemberger I, Biffi M, Valzania C, **Bertini M**, Domenichini G, Boriani G. Atrial fibrillation ablation: beyond electro-mechanical matters.*Eur Heart J. 2008 Sep 14*
97. Marsan NA, Breithardt OA, Delgado V, **Bertini M**, Tops LF. Predicting response to CRT. The value of two- and three-dimensional echocardiography. *Europace. 2008 Nov;10 Suppl 3:iii73-9.*
98. Biffi M, **Bertini M**, Ziacchi M, Boriani G.Transvenous Cardioverter-defibrillator implantation in a patient with tricuspid mechanical prosthesis. *J Cardiovas Electrophysiol 2007;18(3):329-31.*
99. Biffi M, **Bertini M,** Ziacchi M, Boriani G. Left ventricular pacing by automatic capture verification. *Europace. 2007;12:1177-81*
100. Boriani G, Valzania C, Fallani F, Biffi M, Martignani C, Saporito D, Ziacchi M, Diemberger I, Greco C, **Bertini M**, Domenichini G, Levorato M, Franchi R, Branzi A. Effects of cardiac resynchronization therapy on diastolic function: evaluation by radionuclide angiography. *Pacing Clin Electrophysiol. 2007;30 Suppl 1:S43-6.*
101. Boriani G,Diemberger I, Biffi M,Martignani C, Ziacchi M, **Bertini M**, Valzania C, Bronzetti G, Rapezzi C, Branzi A.How, why, and when may atrial defibrillation find

a specific role in implantable devices? A clinical viewpoint. *Pacing Clin Electrophysiol. 2007 Mar;30(3):422-33*

102. Valzania C, Biffi M, Martignani C, Diemberger I, **Bertini M**, Ziacchi M, Bacchi L, Rocchi G, Rapezzi C, Branzi A, Boriani G. Cardiac resynchronization therapy: variations in echo-guided optimized atrioventricular and interventricular delays during follow-up. *Echocardiography. 2007 Oct;24(9):933-9*
103. Boriani G, Artale P, Biffi M, Martignani C, Frabetti L, Valzania C, Diemberger I, Ziacchi M, **Bertini M**, Rapezzi C, Parlapiano M, Branzi A. Outcome of cardioverter-defibrillator implant in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Vessels. 2007 May;22(3):184-92. Epub 2007 May 21*
104. Boriani G, Valzania C, Diemberger I, Biffi M,Martignani C, **Bertini M**, Ziacchi M, Domenichini G, Saporito D, Rapezzi C, Branzi A. Potential of non-antiarrhythmic drugs to provide an innovative upstream approach to the pharmacological prevention of sudden cardiac death. *Expert Opin Investig Drugs. 2007 May;16(5):605-23. Review*
105. Boriani G, Diemberger I, Biffi M, Martignani C, Valzania C, Ziacchi M, **Bertini M**, Specchia S, Grigioni F, Rapezzi C, Branzi A. Cardiac resynchronization therapy in clinical practice: Need for electrical, mechanical, clinical and logistic synchronization.. *J Interv Card electrophysiol. 2006 Dec;17(3):215-24.*
106. Boriani G, Biffi M, Martignani C, Ziacchi M, Saporito D, Grigioni F, Domenichini G, Valzania C, Diemberger I, **Bertini M**, Specchia S, Branzi A Electrocardiographic remodeling during cardiac resynchronization therapy. *Int. J. Cardiol. 2006;108(2):165-70.*
107. Biffi M, **Bertini M,** Boriani G, Martignani C, Branzi A Heart Failure after myocardial revascularization: risk markers. *Int. J Cardiol. 2005;105(1):11-4*
108. Biffi M, Boriani G, **Bertini M**, Silvestri P, Martignani C, Branzi A Pacing with capture verification in candidates for resynchronisation therapy: a feasibility study. *Europace 2005;7(3):255-65*
109. Biffi M, Boriani G, Bartolotti M, **Bertini M**, Gallina C, Martignani C, Zannoli R, Branzi A. Which will be the indications for dual defibrillator? *Giornale Italiano di Aritmologia e Cardiostimolazione 2002;5 (Suppl. 1):106-11*
110. Biffi M, Boriani G, Bartolotti M, **Bertini M**, Bacchi-Reggiani L, Martignani C, Gallina C, Branzi A. Neurocardiogenic syncope in pediatric patients: long term follow up. *Giornale Italiano di Aritmologia e Cardiostimolazione 2002;5 (Suppl. 1):183-5*
111. Boriani G, Biffi M, Martignani C, Ziacchi M, Saporito D, Valzania C, Diemberger I, **Bertini M**, Domenichini G, Artale P, Frabetti L, Branzi A. Cardiac resynchronization therapy: Update on clinical studies. *Mediterranean Journal of pacing and electrophysiology 2004; 6 (2): 70-5.*

CURRICULUM VITAE

Matteo Bertini was born in Forlimpopoli (FC) on 19.06.1976. He started his studies at the Faculty of Mechanical Engineering of the University of Bologna in 1995. After successfully having defended the exams of Mathematical Analysis, Design, Algebra and Geometry and Physics, he joined the Faculty of Medicine of the University of Bologna in 1996. He attended the Institute of Cardiovascular Diseases directed by Professor Angelo Branzi Chiarissimo as medical student in the years 2001-2002. He obtained the bachelor degree with honors in Medicine and Surgery at the University of Bologna in 2002 and discussing with Chiarissimo Prof. Angelo Branzi the thesis entitled "Prognostic significance of intraventricular conduction disturbances in patients undergoing myocardial revascularization".

He completed his Master degree in Cardiology with honors with the dissertation entitled " Cardiac resynchronization therapy in patients with dilated heart disease: evaluation with rest and stress echocardiography " in 2006. From 2007 to 2010, he followed the PhD degree in "Pathophysiology of heart failure" at the Institute of Cardiovascular Diseases (Prof. Branzi) University of Bologna and defended the PhD thesis entitled "Cardiac resynchronization therapy: Rational, Patient Selection and optimization of therapy" in 2010. From 2008 to 2010, he also followed a technical and professional training fellowship in the field of heart failure, particularly in cardiac resynchronization therapy, under the supervision of Prof. dr. Jeroen Bax at the Department of Cardiology at the University Medical Center in Leiden (Netherlands), pioneer center in Europe in the field of diagnosis and treatment of cardiovascular diseases and in particular for cardiac resynchronization therapy. During this period he also learnt the diagnosis and risk stratification of patients with acute and chronic ischemic heart disease using new imaging techniques. The research at the Department of Cardiology at the University Medical Center in Leiden (Netherlands) has resulted in numerous publications in international journals and several abstracts accepted in national and international conferences. From 2010 to 2011 he got two consecutive appointments as 'Medical Director of first level at the Department of Cardiology, University Hospital S. Anna Hospital, Ferrara. From 2010 to 2011 he also followed a technical-professional internship in the field of interventional electrophysiology under the supervision of Prof. Carlo Pappone (Maria Cecilia Hospital, Cotignola, RA). In particular, during this internship he acquired skills' practices for diagnosis and ablation of cardiac arrhythmias using modern systems of electroanatomic mapping and acquisition of techniques for access to all the chambers of the heart as the transseptal puncture. Finally, he successfully applied for the position of Medical Director in Cardiology indefinitely at University Hospital Policlinico S. Anna, Ferrara and has been working there since May 2011.

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