Advanced Quantitative Echocardiography: Guiding Therapy for Heart Failure

Osama Ibrahim Ibrahim Soliman

ISBN: 978-90-8559-155-9
Cover: O.I.I. Soliman
Lay out: O.I.I. Soliman
Illustrations: O.I.I. Soliman

Printed by Optima Grafische Communicatie, Rotterdam, The Netherlands

Advanced Quantitative Echocardiography: Guiding Therapy for Heart Failure

Geavanceerde kwantitatieve echocardiografie als leidraad van hartfalen therapie

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
Rector Magnificus

Prof.dr. S.W.J. Lamberts

and in accordance with the decision of the Doctorate Board
The public defence shall be held on

Wednesday, 21 November 2007 at 11.45 h.

by

Osama Ibrahim Ibrahim Soliman
born at Ashmun (Monofia) Egypt

Doctoral Committee

Promoters:	Prof.dr. M.L. Simoons Prof.dr. L.J.L.M. Jordaens
Other members:	Prof.dr. N. de Jong Prof.dr. N.M. van Hemel Prof.dr. Y.M. Pinto
Copromoter:	Dr. F.J. ten Cate

Financial support by the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

To my lovely family

Osama T.T. Soliman

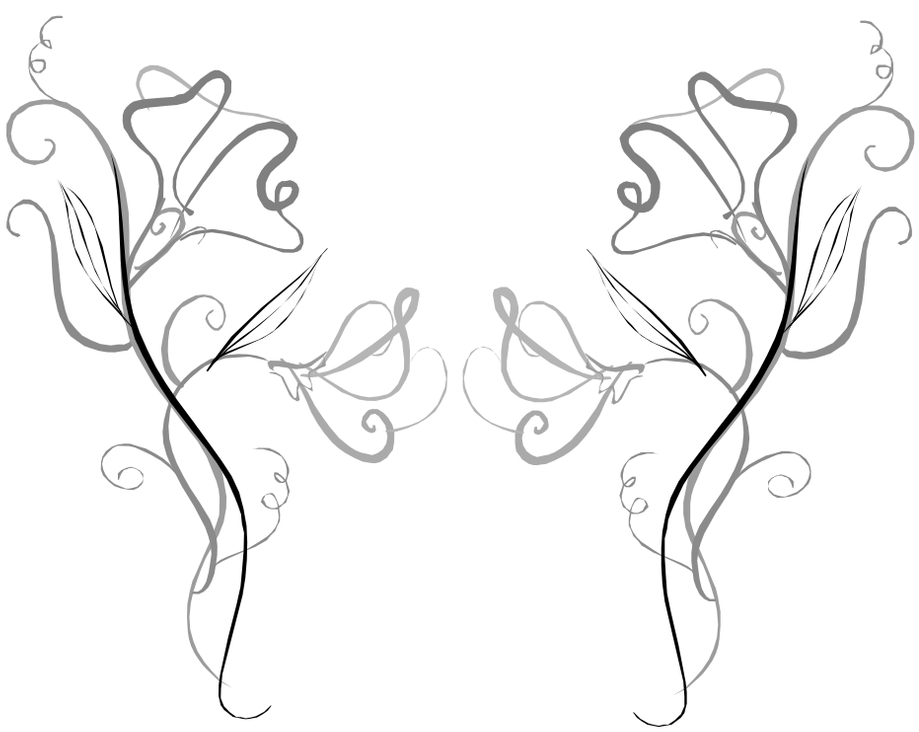


Table of Contents

Part I

Introduction

Includes chapter 1

Chapter 1

General introduction and outline of the thesis

Osama I.I. Soliman MD, MSc., FESC.,
Department of Cardiology, Thoraxcenter,
Erasmus University Medical Center, Rotterdam, The Netherlands

INTRODUCTION

Heart failure (HF) constitutes a major health problem worldwide. It is a complex syndrome that represents interplay of one or more derangements in cardiac functions that eventually results in mechanical inefficiency in the form of inability of the heart to receive or pump sufficient blood for body needs. Clinical presentation of HF patients ranges from asymptomatic left ventricular (LV) dysfunction to a severe form with disabling resting symptoms.[1] The severity of HF symptoms progress over time and is classified according to the New York Heart Association (NYHA) class. The current guidelines of the European Society of Cardiology which, represents countries with a population of over 900 million, suggesting that there are at least 10 million patients with HF in those countries.[1] There are also patients with myocardial systolic dysfunction without symptoms of HF and who constitute approximately a similar prevalence.[2-4] The prevalence of HF increases rapidly with age, and age-adjusted mortality attributed to HF is also increasing.[1, 5] Moreover, the prognosis of HF is uniformly poor if the underlying problem cannot be rectified.[1, 5] Approximately 50% of patients diagnosed with HF die within four years, and within one year in case of severe HF.[4, 6, 7] However, some reports suggesting improved survival over time in Scotland, Sweden, and UK.[8-10] Several clinical and echocardiographic parameters such as NYHA functional class, LV end-systolic volume and LV ejection fraction were identified as major determinants of HF outcome. Data from the Studies of LV Dysfunction (SOLVD) and the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial showed that mortality rates increases significantly as the NYHA functional class progresses from 19% for NYHA I patients to 64% for NYHA IV patients at 4 years follow-up.[11-13] In an earlier study of 605 post myocardial infarction patients, LV end-systolic volume >130 ml was associated with ~50% mortality at 7 years follow-up.[14] Data from the same study demonstrated that LV ejection fraction <40% was associated with ~45% mortality at 7 years follow-up.[14] Drugs that act by inhibiting the neuroendocrine system, such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptors blockers, and aldosterone antagonists have been shown to be effective in reducing morbidity and mortality in patients with HF, and are considered class I indication for the treatment of HF.[1] Yet, and despite optimal pharmacological therapy, their efficacy is limited, mandating an additional therapy for the treatment of HF, especially for patients with advanced HF with NYHA functional class III and IV.[15] Those patients are considered potentials for heart transplantations, which, represents a major dilemma due to lack of donors. In the last decade, cardiac stimulation by biventricular pacing known as cardiac resynchronization therapy (CRT) has been developed as an additional therapy for patients with drug-refractory HF. The efficacy of CRT for selected HF patients has been clearly demonstrated in several randomized and many observational studies (see later).

ECHOCARDIOGRAPHY IN HEART FAILURE

Many patients with HF have symptoms and preserved LV ejection fraction.[6] Studies show that the accuracy of diagnosis by clinical means alone is often inadequate, particularly in women, elderly, and obese.[16] To study properly the natural history and prognosis and to optimize the treatment of HF, the

uncertainty relating to the diagnosis must be minimized or avoided completely. Echocardiography is the most commonly used non-invasive test for the documentation of cardiac dysfunction. It can measure several systolic and diastolic parameters that allow for early detection of myocardial dysfunction such as in asymptomatic patients. The most important measurement of ventricular function is the LV ejection fraction for distinguishing patients with cardiac systolic dysfunction from patients with preserved systolic function. Assessment of diastolic function may be clinically useful to detect abnormalities of diastolic function in patients who present with HF and normal LV ejection fraction, providing a non-invasive estimate of LV diastolic pressure, and may help in determining prognosis in HF patients. Another important role of echocardiography is to determine effects of medical treatment and therapeutic interventions on cardiac parameters hence, treatment success.

Table 1. Current CRT selection criteria

- NYHA class III/IV
- Left ventricular ejection fraction <35%
- QRS duration >120 msec
- Sinus rhythm
- Optimal standard medical therapy for heart failure

CARDIAC RESYNCHRONIZATION THERAPY

The first descriptions of short-term hemodynamic effects of LV pacing or combined bi-ventricular stimulation were published >35 years ago.[17-19] Moreover, the clinical application of myocardial stimulation technique, known as CRT, began in the early 1990's when Cazeau and colleagues [20] in France, described the first cases of biventricular pacemaker implantation in patients with severe HF and no conventional indication of cardiac pacing. The first application by Cazeau et al., was conducted on a 54-year-old man who received a four chamber pacing system for severe congestive HF (NYHA functional Class IV). The patient had ventricular dyssynchrony evidenced by left bundle branch block and 200-msec QRS duration on 12 leads electrocardiogram (ECG) and atrio-ventricular dyssynchrony in the form of 200-msec PR interval. An acute hemodynamic study with insertion of four temporary leads was performed prior to the implant, which demonstrated a significant increase in cardiac output and decrease of pulmonary capillary wedge pressure. Similar data was reported at the same time by Bakker and colleagues in The Netherlands, and later published.[21] In both of these early experiences, the LV lead was implanted epicardially by thoracotomy. Daubert and colleagues first described the transvenous approach through the coronary veins in 1998.[22] Few years later, CRT alone or with combination with an implantable cardiovertor-defibrillator (ICD) has become a largely validated treatment for HF patients with a moderate to severe heart failure and pre-implantation electrical dyssynchrony. CRT by atrio-biventricular pacing

improves heart failure symptoms, reducing HF hospitalization and reduces mortality including sudden cardiac deaths, in selected HF patients when compared to standard optimal medical therapy for HF. The current selection criteria for CRT are listed in Table 1.[1, 5]

Mechanisms of cardiac resynchronization

The rational of CRT using multisite stimulation involves atrio-ventricular, inter-ventricular and intra-ventricular resynchronization. Atrio-ventricular resynchronization can generally be achieved by setting an optimal atrio-ventricular delay between atrial and LV pacing leads. This will provide an effective LV filling period and eliminate diastolic mitral regurgitation. Inter-ventricular resynchronization can be achieved via either simultaneous or sequential left and right ventricular pacing. The most important form is intra-ventricular resynchronization which can be achieved by intra-ventricular activation, organized ventricular activation sequence, coordinated septal and free-wall contraction, and thus improved LV pumping efficiency. These effects lead to reverse LV remodeling and eventually improved morbidity and mortality.

Clinical evidence of cardiac resynchronization therapy

Since the first clinical application of the concept of CRT in early 1990's, the efficacy and safety of CRT in patients with refractory HF symptoms despite standard optimal pharmacological therapy have been widely investigated. A recent meta-analysis of ~10,000 HF patients, who received CRT from major randomized trials and many observational studies, have been demonstrated that CRT is an effective and safe procedure for selected HF patients.[23-26] The clinical benefits of CRT were demonstrated in the first published randomized trial by Cazeau et al. the Multisite biventricular pacing in patients with HF and intra-ventricular conduction delay (MUSTIC) trial and then from other randomized trials that were published in the following years.[27] However, the Cardiac Resynchronization-HF (CARE-HF) trial was the first randomized trial that was designed to evaluate the mortality benefits from CRT compared to optimal standard medical therapy for HF.[23, 28] The data from large randomized studies have led to the adoption of CRT, as class I level of evidence A, in the Heart Rhythm Society/European Society of Cardiology/American College of Cardiology/American Heart Association guidelines on diagnosis and treatment of HF.[29, 30] However, these impressive results were hampered by the significant percentage of non-responders to CRT.

Evaluation of effectiveness of CRT

Several clinical and echocardiographic parameters were used as primary or secondary end-points in the major randomized trials and non-randomized studies for the evaluation of effectiveness of CRT (Table 2). The end-points that were used in major randomized trials ranged from a subjective NYHA class improvement to a hard end-point of mortality. LV reverse remodeling was demonstrated in the MIRACLE

trial as significant reductions in LV internal dimensions at end-diastole and end-systole or as a reduction in LV end-diastolic volume.[31, 32]

Table 2, Primary and secondary end-points used in the major CRT randomized trials.

Clinical parameters

- NYHA class
- Quality of life scores
- Six-minute hall walk test
- Hospitalization (for heart failure) rate
- Mortality rate
- Composite end-point (mortality and hospitalization for heart failure)

Echocardiographic parameters

- Left ventricular ejection fraction
- Left ventricular reverse remodeling

In CRT randomized and observational studies, several cut-off values were used for definition of CRT success "responders" (Table 3).

Non-response to CRT

Despite the unsurpassed success of CRT as clearly demonstrated in randomized and observational studies a significant proportion of candidates whom were implanted according to the current guidelines [1, 29] did not benefit and are defined as "non-responders". Non-response rates varied between studies from 43% to 18%.[33, 34] The reasons for this variation are mostly due to the use of different criteria for definition of CRT responders and due to variable durations of the follow-up.

In assessment of a successful outcome in our CRT population at Erasmus University Medical Center clinical definition of responders was a combination of 1 NYHA class improvement plus >25% improvement in the six-minute walk distance for patients who were alive free from hospitalization at time of the follow-up. Definition of echocardiographic responders was a >25% reduction in LV end-systolic volume at the time of follow-up.

Table 3, List of cut-off values that were used in the observational studies to define response to CRT

Clinical parameters

- ≥1 NYHA class improvement
- Improvement in Quality of life scores
- Improvement in Quality of life scores by 15 points
- 50 meters increase in six-minute hall walk distance
- ≥10% increase in six-minute hall walk distance
- ≥25% increase in six-minute hall walk distance
- >10% increase in VO_2 max during six-minute walk test
- Freedom from mortality and hospitalization for heart failure
- Combination of one or more of the above

Echocardiographic parameters

- ≥5% absolute increase left ventricular ejection fraction
- ≥10% absolute increase left ventricular ejection fraction
- ≥25% relative increase left ventricular ejection fraction
- ≥10% reduction in left ventricular end-systolic volume
- ≥25% reduction in left ventricular end-systolic volume
- Combination of any of above with or without clinical parameters

Predictors of the lack of response to CRT

In published literature, several clinical and echocardiographic parameters were identified as independent predictors of the lack of response to CRT. Generally, the reasons of non-response to CRT can be classified at three levels: "pre-implantation", "during" and "after" CRT device implantation. First, there are significant issues before CRT implantation due to selection of "wrong" patients, such as lack of mechanical dyssynchrony. During CRT device implantation there are potential reasons for the lack of response to CRT such as placement of the LV lead at the "wrong" site. Other potential issues can be seen after CRT device implantation such as lack of optimization of LV filling due to a prolonged atrio-ventricular interval.

OUTLINE OF THE PRESENT THESIS

The aim of the thesis was to evaluate the potential use of quantitative echocardiographic parameters and modalities aiming at proper management of patients with HF. Clinical and echocardiographic characteristics of HF patients from the CRT registry at the Thoraxcenter, Erasmus University Medical Center were evaluated to examine the effectiveness of CRT and for the prediction of the clinical and echocardiographic outcomes after CRT.

In **Part I** the general introduction of the thesis with an overview of HF and CRT is presented. In **Part II**, patients with HF and severely distorted LV geometry were evaluated for accurate assessment of LV systolic function. In **Chapter 2**, accurate assessment of LV volumes and ejection fraction by real-time three-dimensional echocardiography was evaluated using two different endocardial border detection algorithms

from up-to-date commercially available analysis software program. In **Chapter 3**, two different commercially available analysis software programs were tested against cardiac magnetic resonance imaging aiming at more automated and accurate assessment of LV systolic function. **In Part III**, patients who underwent CRT at Erasmus University Medical Center were evaluated for sound understanding of the optimal use of CRT for HF patients. In **Chapter 4** and **Chapter 5**, LV and left atrial revere remodeling after CRT were evaluated. In **Chapter 6**, tissue Doppler lateral-to-septal mechanical delay was evaluated for the prediction of clinical and echocardiographic outcome after CRT. In **Chapter 7** and **Chapter 8**, clinical and echocardiographic predictors of the long-term adverse outcome (cardiovascular mortality and hospitalization for HF) after CRT were evaluated at baseline and shortly after CRT. In **Chapter 9**, a rational approach for guiding placement of a LV pacing lead during CRT device implantation using a novel technique based on real-time three-dimensional echocardiography parametric imaging was evaluated. In **Chapter 10**, reverse LV remodeling after long-term CRT in diabetic HF patients was evaluated. The last chapter represents the summary and conclusion of the thesis.

REFERENCES

1. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A *et al*: **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**(11):1115-1140.
2. Mosterd A, Hoes AW, de Bruyne MC, Deckers JW, Linker DT, Hofman A, Grobbee DE: **Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study**. *Eur Heart J* 1999, **20**(6):447-455.
3. McDonagh TA, Morrison CE, Lawrence A, Ford I, Tunstall-Pedoe H, McMurray JJ, Dargie HJ: **Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population**. *Lancet* 1997, **350**(9081):829-833.
4. Cleland JG, Khand A, Clark A: **The heart failure epidemic: exactly how big is it?** *Eur Heart J* 2001, **22**(8):623-626.
5. Hunt SA: **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)**. *J Am Coll Cardiol* 2005, **46**(6):e1-82.
6. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J *et al*: **The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis**. *Eur Heart J* 2003, **24**(5):442-463.
7. McMurray J, McDonagh T, Morrison CE, Dargie HJ: **Trends in hospitalization for heart failure in Scotland 1980-1990**. *Eur Heart J* 1993, **14**(9):1158-1162.
8. Blackledge HM, Tomlinson J, Squire IB: **Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993-2001**. *Heart* 2003, **89**(6):615-620.
9. MacIntyre K, Capewell S, Stewart S, Chalmers JW, Boyd J, Finlayson A, Redpath A, Pell JP, McMurray JJ: **Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995**. *Circulation* 2000, **102**(10):1126-1131.
10. Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A: **Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; Data from the Swedish Hospital Discharge Registry 1988 to 2000**. *Eur Heart J* 2004, **25**(4):300-307.
11. **Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group**. *N Engl J Med* 1987, **316**(23):1429-1435.
12. **Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators**. *N Engl J Med* 1991, **325**(5):293-302.
13. **Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors**. *N Engl J Med* 1992, **327**(10):685-691.
14. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ: **Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction**. *Circulation* 1987, **76**(1):44-51.
15. Jarcho JA: **Biventricular pacing**. *N Engl J Med* 2006, **355**(3):288-294.
16. Remes J, Miettinen H, Reunanen A, Pyorala K: **Validity of clinical diagnosis of heart failure in primary health care**. *Eur Heart J* 1991, **12**(3):315-321.
17. Gibson DG, Chamberlain DA, Coltart DJ, Mercer J: **Effect of changes in ventricular activation on cardiac haemodynamics in man. Comparison of right ventricular, left ventricular, and simultaneous pacing of both ventricles**. *Br Heart J* 1971, **33**(3):397-400.
18. Tyers GF: **Comparison of the effect on cardiac function of single-site and simultaneous multiple-site ventricular stimulation after A-V block**. *J Thorac Cardiovasc Surg* 1970, **59**(2):211-217.
19. Vagnini FJ, Gourin A, Antell HI, Stuckey JH: **Implantation sites of cardiac pacemaker electrodes and myocardial contractility**. *Ann Thorac Surg* 1967, **4**(5):431-439.
20. Cazeau S, Ritter P, Bakdach S, Lazarus A, Limousin M, Henao L, Mundler O, Daubert JC, Mugica J: **Four chamber pacing in dilated cardiomyopathy**. *Pacing Clin Electrophysiol* 1994, **17**(11 Pt 2):1974-1979.
21. Bakker PF, Meijburg HW, de Vries JW, Mower MM, Thomas AC, Hull ML, Robles De Medina EO, Bredee JJ: **Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function**. *J Interv Card Electrophysiol* 2000, **4**(2):395-404.
22. Daubert JC, Ritter P, Le Breton H, Gras D, Leclercq C, Lazarus A, Mugica J, Mabo P, Cazeau S: **Permanent left ventricular pacing with transvenous leads inserted into the coronary veins**. *Pacing Clin Electrophysiol* 1998, **21**(1 Pt 2):239-245.
23. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ: **Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials**. *Eur Heart J* 2006, **27**(22):2682-2688.
24. Bradley DJ: **Combining resynchronization and defibrillation therapies for heart failure**. *Jama* 2003, **289**(20):2719-2721.
25. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, Crumley E, Hartling L, Klassen T, Abraham W: **Systematic review: cardiac resynchronization in patients with symptomatic heart failure**. *Ann Intern Med* 2004, **141**(5):381-390.
26. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH: **Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review**. *Jama* 2007, **297**(22):2502-2514.
27. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M *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.
28. 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**(15):1539-1549.
29. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K *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**(12):e154-235.

30. Strickberger SA, Conti J, Daoud EG, Havranek E, Mehra MR, Pina IL, Young J: **Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society**. *Circulation* 2005, **111**(16):2146-2150.
31. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL *et al*: **Cardiac resynchronization in chronic heart failure**. *N Engl J Med* 2002, **346**(24):1845-1853.
32. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E: **Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE)**. *Circulation* 2006, **113**(2):266-272.
33. Reuter S, Garrigue S, Barold SS, Jais P, Hocini M, Haissaguerre M, Clementy J: **Comparison of characteristics in responders versus nonresponders with biventricular pacing for drug-resistant congestive heart failure**. *Am J Cardiol* 2002, **89**(3):346-350.
34. Yu CM, Fung JW, Chan CK, Chan YS, Zhang Q, Lin H, Yip GW, Kum LC, Kong SL, Zhang Y *et al*: **Comparison of efficacy of reverse remodeling and clinical improvement for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure**. *J Cardiovasc Electrophysiol* 2004, **15**(9):1058-1065.

Part II

Echocardiographic assessment of left ventricular systolic function

Includes chapter 2 and 3

Chapter 2

Quantification of left ventricular volumes and function in patients with cardiomyopathy by real-time three-dimensional echocardiography:
a head-to-head comparison between two different semi-automated endocardial border detection algorithms

Osama I.I. Soliman[1,2], Boudewijn J. Krenning[1], Marcel L. Geleijnse[1], Attila Nemes[1,4], Robert-Jan van Geuns[1,3], Sharon W. Kirschbaum[1,3], Ashraf M. Anwar[1,2], Tjebbe W. Galema[1], Wim B. Vletter[1], and Folkert J. ten Cate[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt; [3]Department of Radiology, Erasmus University Medical Center, Rotterdam, the Netherlands; [4]Second Department of Medicine and Cardiology Center, University of Szeged, Szeged, Hungary

Journal of the American Society of Echocardiography 2007 Sept; 20 (9): 1042-1049

ABSTRACT

Aim of the study. We evaluated two different commercially available TomTec real-time three-dimensional echocardiographic (RT3DE) semi-automated border detection algorithms for left ventricular (LV) volume analysis in patients with cardiomyopathy and distorted LV geometry.

Methods. Fifty-three patients in sinus rhythm with various types of cardiomyopathy (mean age 56 ± 11 years, 28 men), and adequate 2D image quality were included. The TomTec RT3DE multiplane interpolation (MI) and full volume reconstruction (FVR) methods were used for LV volume analysis. Magnetic resonance imaging (MRI) was used as the reference method.

Results. A strong correlation (R^2 >0.95) was found for all LV volume and ejection fraction (EF) measurements by either RT3DE method. Analysis time was shorter with the FVR method (6 ± 2 vs. 15 ± 4 min, P <0.01) as compared to the MI method. Bland-Altman analysis showed greater underestimation of end-diastolic volume and end-systolic volume (ESV) by MI compared to FVR. For the MI method a bias of –24.0 ml (-15.0% of the mean) for EDV and –11.3 ml (-18.0% of the mean) for ESV was found. For FVR analysis these values were –9.9 ml (-6.0% of the mean) and –5.0 ml (-9.0% of the mean), respectively. EF was similar for the MI and FVR method with a mean difference compared to MRI of 0.6 (1.0%) and 0.8 (1.3%), respectively.

Conclusions. In cardiomyopathic patients with distorted LV geometry and good 2D image quality, the TomTec FVR method is faster and more accurate than the MI method in assessment of LV volumes.

INTRODUCTION

Accurate assessment of left ventricular (LV) volume and systolic function forms a routine part of daily echocardiographic practice.[1] However, the geometric assumptions in motion-mode (1D) and two-dimensional (2D) echocardiography and the poor inter- and intra-observer variability limit these techniques.[2, 3] The development of real-time three-dimensional echocardiography (RT3DE) with matrix transducer technology made a more reliable analysis of LV function feasible. The increasing accuracy and reproducibility of RT3DE for LV quantification has been shown in many studies.[4-9] Several online and off-line software programs for LV volume quantification by RT3DE are available. However, these programs use a wide spectrum of endocardial contour tracing algorithms, ranging from manual to fully automated algorithms. In previous reports, semi-automated border detection software has been shown to be fast, accurate and less observer-dependent for RT3DE quantification of LV volumes and function.[6] Patients with cardiomyopathy have a distorted LV geometry, which theoretically may preclude accurate LV quantification using semi-automated border detection. The present study sought to assess the accuracy and inter-observer variability of two different TomTec semi-automated border detection RT3DE analysis programs in patients with cardiomyopathy.

METHODS

Patient selection

Fifty-three patients (mean age 56 ± 11 years, 28 men), in sinus rhythm, with a cardiomyopathy and adequate 2D image quality (no more than 2 LV segments not well visualized) were enrolled in the study. These patients represent in image quality terms the best half of our patients seen at the echo laboratory. All patients underwent 3DE and cardiac magnetic resonance imaging (MRI) on the same day, to ensure comparable hemodynamic conditions between the examinations. The etiology of the cardiomyopathy was ischemic in 9 (17%), non-compaction in 11 (21%), hypertrophic in 20 (38%), and idiopathic dilated in 13 (24%) patients. The institutional review board approved the study and all patients gave informed consent.

Trans-thoracic RT3DE

Image acquisition

RT3DE was performed using a Sonos 7500 equipped with a X4 matrix-array transducer or an iE33 ultrasound system equipped with a X3-1 transducer (Philips Medical Systems, Best, The Netherlands) with the patient in a left lateral decubitus position. Image acquisition was performed from an apical window with the LV as region of interest. To encompass the complete LV into the 3D data set, a full volume of 93° × 84° scan was acquired in harmonic mode from 4 R-wave triggered subvolumes (93° × 21°) during an

end-expiratory breath-hold. The 3D dataset was stored on CD-ROM and transferred to an off-line analysis workstation.

Data analysis

All data were analyzed by a single experienced observer (O.I.I.S.) using the two algorithms on two separate occasions to assess the intra-observer variability. The first 31 patients were also analyzed by a second observer (A.N.) to assess inter-observer variability. All measurements were performed blinded to both the patient data and results of MRI. MRI data were analyzed by an independent third observer (S.K.) who was also blinded to the patient data and results of RT3DE.

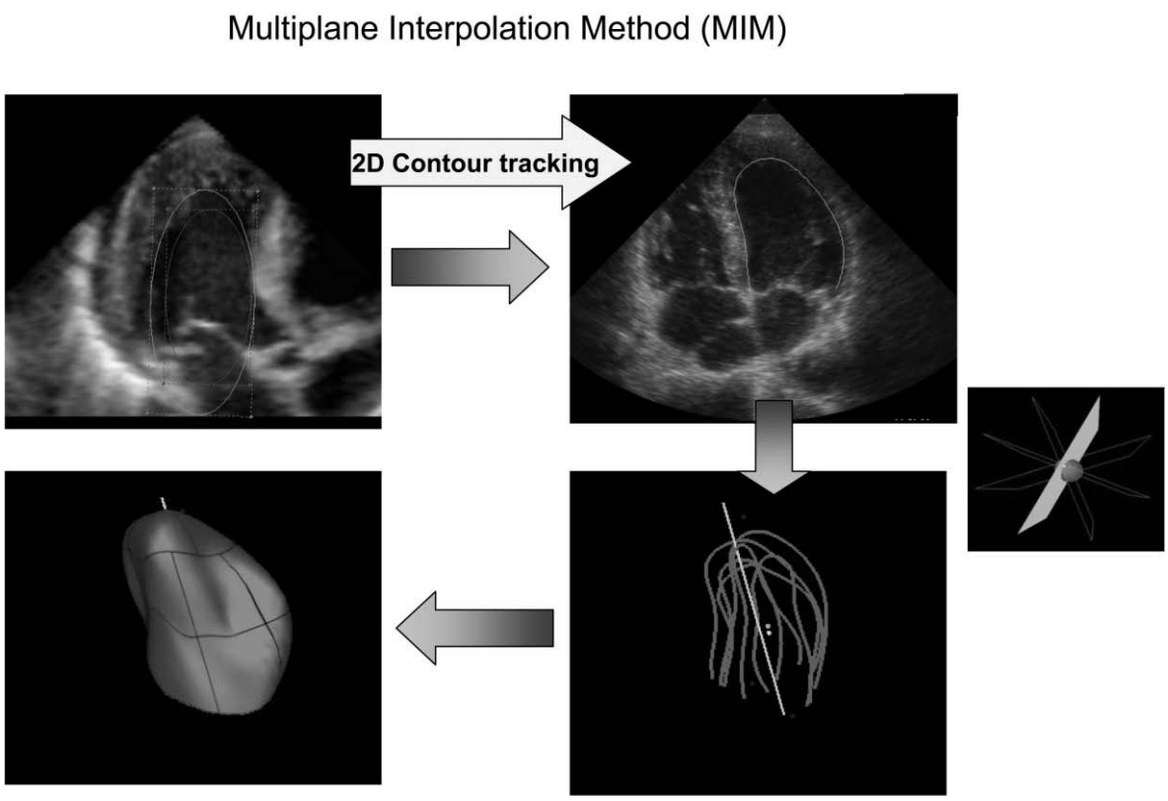


Figure 1. An ellipse is used for initiation of the semi-automatic algorithm in individual cross-sections. After semi automated border detection, an interpolation algorithm is used for LV reconstruction.

Image analysis: Multiplane interpolation (MI) method

As seen in Figure 1, LV volume analysis using MI was performed off-line using commercially available software (4D LV-Analysis, version 1.2, TomTec, Munich, Germany). The algorithm has been described previously.[6] In brief, the orientation of the 3D dataset is determined by manually marking 3 points in a 5-chamber view: the mitral annulus, aortic valve and apex. Subsequently, the data set is divided into 8 equidistant oblique sagittal (or long-axis) and coronal (or frontal) image planes.[10] In each of the 8 planes, the 3 points are manually marked and end-diastolic and end-systolic still frames are manually defined. An

ellipse is then automatically generated by the software and placed in the 8 end-diastolic and end-systolic planes. This ellipse serves for initiation of the semi-automatic algorithm by which the software automatically defines the total endocardial border in all frames. A spatio-temporal spline interpolation model is then used to generate a LV model for both the temporal and spatial domain. The analysis program then displays a reconstruction of the LV as a dynamic surface rendered image in which LV wall motion is shown in 3D. At any stage it is possible to revise the ellipse and corresponding endocardial border tracing. LV ejection fraction (EF) is calculated by the software as (EDV − ESV) / EDV × 100%, where EDV = end-diastolic volume and ESV = end-systolic volume.

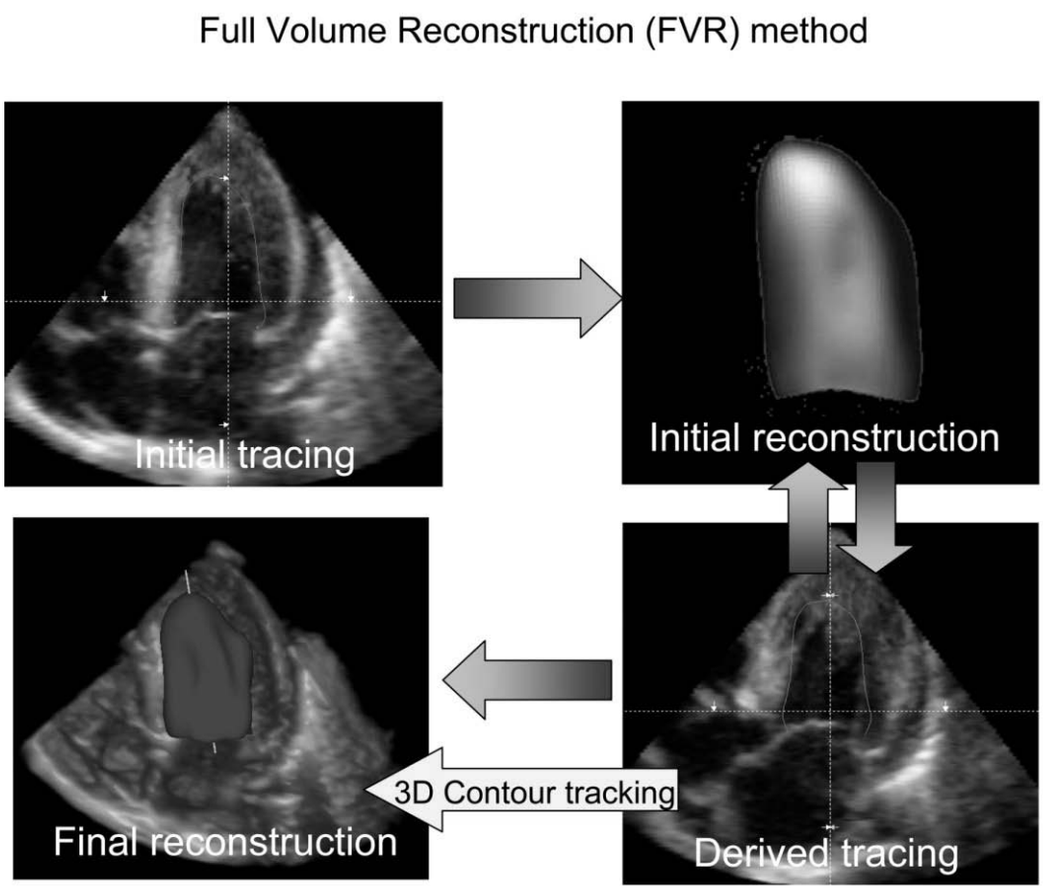


Figure 2. The initial endocardial contour is expanded/rotated 360 degrees and adapted when additional contours are added. According to the initial balloons, the algorithm starts to detect the endocardial border continuously in the entire 4D dataset, e.g. like deforming the balloon in the LV until it best fits the walls in each frame. Adjustments can be made manually after this step and finally a LV reconstruction is created.

Image analysis: Full volume reconstruction (FVR) method

As seen in Figure 2, LV volume analysis using FVR was performed off-line using commercially available software (4D LV-Analysis, version 2.0, TomTec, Munich, Germany). The oblique coronal 4-chamber view and the 60° and 120° incremental views are the (tri) planes used for primary analysis. To avoid

foreshortening, the meeting points of the three oblique sagittal and coronal planes are adjusted to meet in the middle of the LV cavity. The end-diastolic and end-systolic frames are identified automatically in this software version. Subsequently, the endocardial border in the three planes is manually traced (LV trabeculations and papillary muscles are included within the LV volume) in both the end-diastolic and end-systolic images for initialization of the algorithm. Based on these 6 initial contours, a spatio-temporal spline interpolation model (like a pulsating balloon) is created by rotational and temporal interpolation of these contours.
According to the initial balloons, the algorithm starts to detect the endocardial border continuously in the entire 4D dataset (without large gaps due to interpolation as in the MI method), e.g. like deforming the balloon in the LV until it best fits the walls in each frame.

The detection itself employs the same local boundary estimates as the MI method. Adjustments can be made manually after this step in approximately 30 single oblique sagittal and coronal planes. EF is calculated by the software as described in the previous section.

Magnetic resonance imaging

MRI images were acquired using a 1.5 Tesla scanner (GE Signa CV/i, Milwaukee, WI). Patients were positioned in the supine position, with a cardiac eight-element phased-array coil placed over the thorax. Repeated breath holds and electrocardiographic gating were applied to minimize the influence of cardiac and respiratory motion on data collection. Cine MRI was performed using a steady-state free-precession technique (FIESTA). Imaging parameters were; repetition time, 3.5 ms; echotime, 1.3 ms; flip angle, 45°; field of view, 36-40 x 36-40 cm; matrix, 196x160; views per segment, 12, resulting in a temporal resolution of 42 ms. To cover the entire LV 10-12 consecutive slices of 8 mm in the short axis view were planned on the four chambers (gap 2 mm). To quantify LV volumes, endocardial contours were detected automatically and corrected manually on short-axis cine-MRI images with a dedicated software program using the centerline method (Mass; Medis, Leiden, the Netherlands). Papillary muscles were considered as part of the LV cavity.

STATISTICAL ANALYSES

All data are expressed as mean ± SD. For comparison between the MI and FVR method, and MRI and RT3DE data, linear regression analysis was performed and a Pearson correlation coefficient was calculated. For paired data, the Student's *t* test was used. For agreement between the MI and FVR method, MRI and RT3DE data, the method of Bland and Altman was used.[11] RT3DE inter- and intra-observer variability were calculated for individual patients as an absolute value of difference between the two readings and then mean value from all patients is expressed as a percentage of mean of the two readings. Statistical Package of the Social Science (SPSS) software version 12.02 (SPSS Inc., Chicago, Illinois) was used for statistical analysis.

RESULTS

The mean time for data analysis was 6 ± 2 minutes for the FVR method compared to 15 ± 5 minutes for the MI method (P <0.001). Mean LV volumes and EF by the two different RT3DE algorithms and MRI are shown in Table 1.

Table 1. Left Ventricular Volumes and Ejection Fraction by Real-Time Three-Dimensional Echocardiography Using the Full Volume Reconstruction and the Multiplane Interpolation Method for Endocardial Contour Definition

	EDV (range), ml	ESV (range), ml	EF (range), %
MRI	175 ± 51 (74 to 328)	74 ± 51 (14 to 208)	61 ± 17 (15 to 86)
FVR	165 ± 50 (67 to 308)	69 ± 48 (15 to 194)	61 ± 18 (16 to 85)
MIM	150 ± 48 (63 to 301)	63 ± 44 (16 to 182)	61 ± 18 (15 to 86)

Values are expressed in mean ± standard deviation (range), EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; FVR = Full Volume Reconstruction method; MIM = Multiplane Interpolation method; MRI = Magnetic Resonance Imaging.

Comparison to MRI

There was an excellent correlation between all values measured by MI, FVR and MRI analysis (Figures 3A to 3I). The lowest values for LV volumes were found by MI analysis; these values were significantly lower than the values found by FVR or MRI analysis. However, FVR still underestimated LV volumes as compared to MRI (Table 2). As seen in Figure 4, Bland-Altman analysis confirmed the greater underestimation of EDV and ESV by MI compared to FVR (when MRI was used as gold standard).

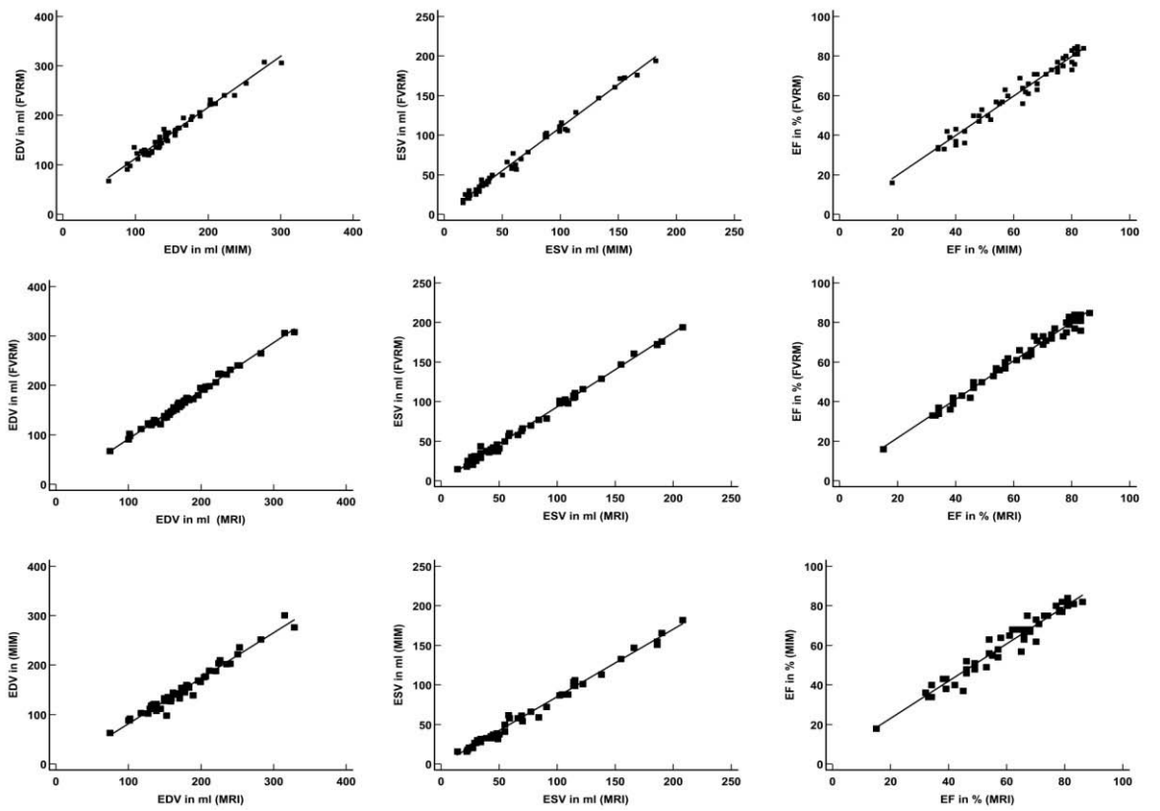


Figure 3. Results of linear regression analysis of real-time three-dimensional echocardiographic values of left ventricular volumes and ejection fraction using the full volume reconstruction method (top) and the multiplane interpolation method (bottom) versus magnetic resonance imaging reference values.

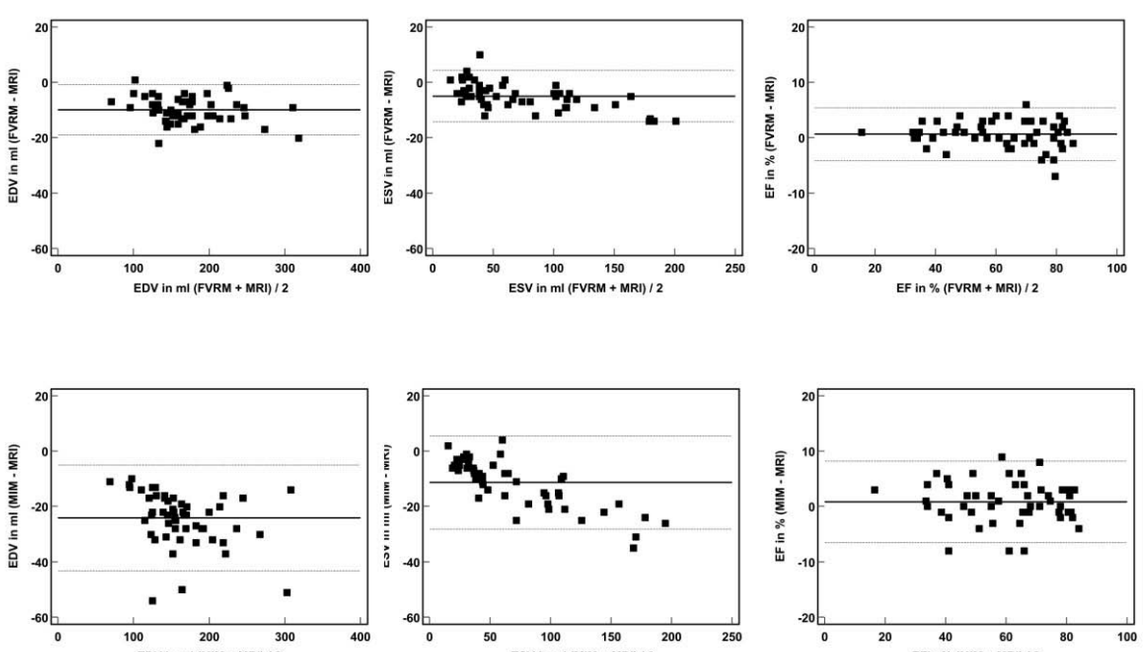


Figure 4. Results of Bland-Altman analysis of real-time three-dimensional echocardiographic values of left ventricular volumes and ejection fraction using the full volume reconstruction method (top) and the multiplane interpolation method (bottom) versus magnetic resonance imaging reference values.

Table 2. Correlation and Comparison Between the Real-Time Three-Dimensional Echocardiographic Methods for Endocardial Contour Definition, and Magnetic Resonance Imaging

	Linear Regression analysis				Paired t-test	
	Regression Equation	R^2	P Value	SEE	Mean Difference ± SD	P Value versus 0
Full Volume Reconstruction Method versus Multiplane Interpolation Method using RT3DE						
EDV, ml	Y = 1.0X + 9.0	0.98	P < 0.001	3.8	14.1 ± 8.4	<0.001
ESV, ml	Y = 1.1X + 0.8	0.99	P < 0.001	1.1	6.4 ± 6.1	<0.001
EF, %	Y = 1.0X - 0.1	0.96	P < 0.001	1.7	0.2 ± 3.3	NS
RT3DE Full Volume Reconstruction method versus MRI						
EDV, ml	Y = 0.98X – 5.7	0.99	P < 0.001	2.2	-9.9 ± 4.7	<0.001
ESV, ml	Y = 0.94X – 0.5	0.99	P < 0.001	1.0	-5.0 ± 4.8	<0.001
EF, %	Y = 0.97X + 2.3	0.98	P < 0.001	1.2	0.6 ± 2.4	NS
RT3DE Multiplane Interpolation method versus MRI						
EDV, ml	Y = 0.92X – 9.9	0.96	P < 0.001	4.3	-24.0 ± 9.7	<0.001
ESV, ml	Y = 0.87X – 0.7	0.98	P < 0.001	1.5	-11.3 ± 8.6	<0.001
EF, %	Y = 0.94X + 4.0	0.95	P < 0.001	2.0	0.8 ± 3.7	NS

Abbreviations as in Table 1. NS = not significant; RT3DE = real-time three-dimensional echocardiography; MRI = magnetic resonance imaging

Table 3. Bland-Altman Analysis and Agreement Between RT3DE Full Volume Reconstruction and Multiplane Interpolation Method and Magnetic Resonance Imaging.

	Mean Difference	95% Limits of Agreement
Full Volume Reconstruction Method versus Multiplane Interpolation Method using RT3DE		
EDV, ml	15.4 (9.0%)	-3.1 to 33.9 (-2.0% to 20.0%)
ESV, ml	9.1 (10.0%)	-6.8 to 24.9 (-7.0% to 26.0%)
EF, %	-0.6 (-1.2%)	-6.4 to 5.2 (-13.0% to 10.0%)
RT3DE Full Volume Reconstruction method Versus MRI		
EDV, ml	-9.9 (-6.0%)	-19.1 to -0.9 (-11.0% to 1.0%)
ESV, ml	-5.0 (-9.0%)	-14.4 to -4.4 (-24.0% to 7.0%)
EF, %	0.6 (1.0%)	-4.1 to 5.4 (-7.0% to 9.0%)
RT3DE Multiplane Interpolation method versus MRI		
EDV, ml	-24.0 (-15.0%)	-43.0 to -5.0 (-26.0% to –3.0%)
ESV, ml	-11.3 (-18.0%)	-28.1 to -5.5 (-45.0% to –9.0%)
EF, %	0.8 (1.3%)	-6.5 to 8.1 (-11.0% to 13.0%)

Values between brackets are percentage of the mean of the two measurements; abbreviations as in Tables 1 and 2.

Table 4. Inter- and Intra-Observer Variability of Real-Time Three-Dimensional Echocardiography-Derived Values of Left Ventricular End-Diastolic, End-Systolic and Ejection Fraction Using the TomTec Multiplane Interpolation and the Full Volume Reconstruction Method

		Inter-observer Variability (%)	Intra-observer Variability (%)
EDV			
	FVR	6.4 ± 7.8	4.7 ± 3.2
	MIM	8.2 ± 11.4	7.8 ± 8.5
ESV			
	FVR	7.8 ± 9.7	6.1 ± 5.8
	MIM	13.5 ± 14.2	9.1 ± 7.2
EF			
	FVR	7.1 ± 6.9	6.6 ± 7.4
	MIM	13.1 ± 7.9	11.1 ± 9.3

Abbreviations as in Table 1

Comparison between the two algorithms and comparison to MRI

As seen in Table 3, a bias of –24.0 ml (-15.0% of the mean) for EDV and –11.3 ml (-18.0% of the mean) for ESV was present with MI analysis compared to –9.9 ml (-6.0% of the mean) and –5.0 ml (-9.0% of the mean) with FVR analysis. As compared to MRI, RT3DE-derived values of EF were similar between the MI and FVR method with mean difference of 0.6 (1.0%) and 0.8 (1.3%), respectively. Results of intra- and inter-observer variability for MI and FVR analysis are summarized in Table 4.

DISCUSSION

The main finding of the present comparative study between two different TomTec semi-automated border detection algorithms is that the newer FVR method (4D LV Analysis, version 2.0) more accurately estimates LV volumes in patients with cardiomyopathic LVs. Because of the systematic underestimation of all LV volumes by both algorithms (compared to MRI), EF values were similar for both methods. LV volume and EF are important predictors of morbidity and mortality in a wide spectrum of cardiac patients.[12, 13] Recent advances in acquisition and software analysis has made accurate measurements of LV volumes possible with RT3DE in large numbers of patients.[4, 6, 14, 15] Currently, several off-line software programs are available for quantification of LV volumes. The method of endocardial border delineation used in the software algorithm for analysis of a 3D dataset affects accuracy and reproducibility. This is of particular interest in patients with difficult and distorted LVs. In the present study, we compared side-by-side the accuracy and reproducibility of the recently developed FVR algorithm against the previously validated MI algorithm for LV volume quantification in patients with cardiomyopathy and substantially altered LV geometry. The two analysis algorithms used in our study fundamentally differ. In

the MI algorithm, the software determines a geometric model for the LV through manual definition of the mitral annulus, aortic valve and apex, and semi-automated border detection in various LV oblique sagittal (or long-axis) and coronal (or frontal) image planes. [6] This method is limited by boundary detection and contour revision in a limited number of cross-sections. In contrast, the newer FVR algorithm performs automated contour detection in the complete 4D dataset, which can be adjusted anywhere by the reviewer. Besides less (only 6 versus 16 planes) user interaction, faster processing time and better review options, significantly more data is used to estimate the endocardial contour for LV reconstruction. This study shows that this results in higher accuracy and reproducibility as seen from the lower biases and narrower limits of agreement.

Table 5. Comparison of Correlation, Agreement, and Variability Between Real-Time Three-Dimensional Echocardiographic Studies of Left Ventricular Volumes and Function Quantification Using TomTec version 1.2 Software Program

	Author	Year	Pts	MRI analysis	R^2	Biases (units)	Inter-observer (%)	Intra-observer (%)
	Soliman	**2007**	**53**	**SAX**	**0.96**	**-24.0 ± 9.7**	**8.2 ± 11.4**	**7.8 ± 8.5**
	Jenkins	2006	110	SAX+ LAX	0.75	-15.0 ± 28.0	-	-
LV-EDV (ml)	Sugeng	2006	31	SAX+ LAX	0.94	-5.0 ± 26.0	13.9 ± 2.0	11.2 ± 8.6
	Nikitin	2006	64	SAX	0.96	7.0 ± 28.0	4.0	3.0
	vd Bosch	2006	29	SAX	0.94	-2.9 ± 12.0	-	-
	Kuhl	2004	24	SAX	0.97	-13.6 ± 18.9	0.9 ± 6.9	0.2 ± 6.6
	Soliman	**2007**	**53**	**SAX**	**0.98**	**-11.3 ± 8.6**	**13.5 ± 14.2**	**9.1 ± 7.2**
	Jenkins	2006	110	SAX+ LAX	0.84	-10.0 ± 22.0	-	-
LV-ESV (ml)	Sugeng	2006	31	SAX+ LAX	0.93	-6.0 ± 26.0	5.6 ± 3.9	14.2 ± 11.8
	Nikitin	2006	64	SAX	0.96	3.0 ± 22.0	6.0	3.0
	vd Bosch	2006	29	SAX	0.96	0.9 ± 10.0	-	-
	Kuhl	2004	24	SAX	0.96	-12.8 ± 20.5	0.7 ± 9.6	-0.0 ± 3.8
	Soliman	**2007**	**53**	**SAX**	**0.95**	**-0.8 ± 3.7**	**11.1 ± 9.3**	**13.1 ± 7.9**
	Jenkins	2006	110	SAX+ LAX	0.78	1.0 ± 8.0	-	-
LV-EF (%)	Sugeng	2006	31	SAX+ LAX	0.93	0.3 ± 4.0	5.6 ± 3.4	10.5 ± 8.3
	Nikitin	2006	64	SAX	0.89	-1.0 ± 10.0	4.0	4.0
	Vd Bosch	2006	29	SAX	0.89	-1.4 ± 7.2		
	Kuhl	2004	24	SAX	0.96	0.9 ± 4.4	-1.5 ± 7.0	-0.6 ± 4.1

Abbreviations as in Table 1

Comparison to previous studies

Our study is the first to assess the new FVR method. Therefore, we can only compare the results of the old MI method (4D LV Analysis, version 1.2) with results published by others. As seen in Table 5, the biases described in our paper for ESV and EF are quite comparable to those described by others. Only the biases for EDV seem somewhat higher (but with a small standard deviation), most likely caused by the inclusion of patients with distorted LV geometry in our study.

Study limitations

MRI analysis uses short axis images with a disk summation method to obtain a LV volume. This analysis is not optimal near the apex because of partial-volume artifacts and has limitations in recognizing the mitral valve.[16] Subsequently, a part of the aortic root or left atrium can be included in the volume of the reconstructed_disk in the most basal cross-section. This may explain the difference between the measured volumes between RT3DE and MRI. This error can theoretically be reduced by increasing the number of disks (and subsequent decrease of slice thickness) resulting in increased review time. In the future incorporation of long-axis analysis can also improve assessment of LV volumes. However, the short-axis MRI method of analysis is still most widely used for LV volume assessment, both in clinical practice and research.[6, 14, 17] and does not influence the head-to-head comparison between the two software programs. In should be noted that these results do not necessarily imply a higher accuracy for detection of wall motion abnormalities, which was not the aim of this study.

CONCLUSIONS

The newer TomTec 4D LV Analysis software, version 2.0 that uses the FVR method provides superior assessment of LV volumes compared to the old 1.2 software version using the MI method.

Acknowledgement: We thank Dr. M. Schreckenberg (TomTec, Munich, Germany) for his description of the algorithms used in this study.

REFERENCES

1. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS: **Natural history of asymptomatic left ventricular systolic dysfunction in the community**. *Circulation* 2003, **108**(8):977-982.
2. Siu SC, Levine RA, Rivera JM, Xie SW, Lethor JP, Handschumacher MD, Weyman AE, Picard MH: **Three-dimensional echocardiography improves noninvasive assessment of left ventricular volume and performance**. *Am Heart J* 1995, **130**(4):812-822.
3. Siu SC, Rivera JM, Guerrero JL, Handschumacher MD, Lethor JP, Weyman AE, Levine RA, Picard MH: **Three-dimensional echocardiography. In vivo validation for left ventricular volume and function**. *Circulation* 1993, **88**(4 Pt 1):1715-1723.
4. Jenkins C, Bricknell K, Hanekom L, Marwick TH: **Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography**. *J Am Coll Cardiol* 2004, **44**(4):878-886.
5. Zeidan Z, Erbel R, Barkhausen J, Hunold P, Bartel T, Buck T: **Analysis of global systolic and diastolic left ventricular performance using volume-time curves by real-time three-dimensional echocardiography**. *J Am Soc Echocardiogr* 2003, **16**(1):29-37.
6. Kuhl HP, Schreckenberg M, Rulands D, Katoh M, Schafer W, Schummers G, Bucker A, Hanrath P, Franke A: **High-resolution transthoracic real-time three-dimensional echocardiography: quantitation of cardiac volumes and function using semi-automatic border detection and comparison with cardiac magnetic resonance imaging**. *J Am Coll Cardiol* 2004, **43**(11):2083-2090.
7. Simpson IA, Sahn DJ: **Adult congenital heart disease: use of transthoracic echocardiography versus magnetic resonance imaging scanning**. *Am J Card Imaging* 1995, **9**(1):29-37.
8. Mao S, Shinbane JS, Girsky MJ, Child J, Carson S, Oudiz RJ, Budoff MJ: **Coronary venous imaging with electron beam computed tomographic angiography: three-dimensional mapping and relationship with coronary arteries**. *Am Heart J* 2005, **150**(2):315-322.
9. Gutierrez-Chico JL, Zamorano JL, Perez de Isla L, Orejas M, Almeria C, Rodrigo JL, Ferreiros J, Serra V, Macaya C: **Comparison of left ventricular volumes and ejection fractions measured by three-dimensional echocardiography versus by two-dimensional echocardiography and cardiac magnetic resonance in patients with various cardiomyopathies**. *Am J Cardiol* 2005, **95**(6):809-813.
10. Nanda NC, Kisslo J, Lang R, Pandian N, Marwick T, Shirali G, Kelly G: **Examination protocol for three-dimensional echocardiography**. *Echocardiography* 2004, **21**(8):763-768.
11. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement**. *Lancet* 1986, **1**(8476):307-310.
12. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ: **Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction**. *Circulation* 1987, **76**(1):44-51.
13. Wong M, Johnson G, Shabetai R, Hughes V, Bhat G, Lopez B, Cohn JN: **Echocardiographic variables as prognostic indicators and therapeutic monitors in chronic congestive heart failure. Veterans Affairs cooperative studies V-HeFT I and II. V-HeFT VA Cooperative Studies Group**. *Circulation* 1993, **87**(6 Suppl):VI65-70.
14. van den Bosch AE, Robbers-Visser D, Krenning BJ, Voormolen MM, McGhie JS, Helbing WA, Roos-Hesselink JW, Simoons ML, Meijboom FJ: **Real-time transthoracic three-dimensional echocardiographic assessment of left ventricular volume and ejection fraction in congenital heart disease**. *J Am Soc Echocardiogr* 2006, **19**(1):1-6.
15. Jacobs LD, Salgo IS, Goonewardena S, Weinert L, Coon P, Bardo D, Gerard O, Allain P, Zamorano JL, de Isla LP *et al*: **Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data**. *Eur Heart J* 2006, **27**(4):460-468.
16. Sugeng L, Mor-Avi V, Weinert L, Niel J, Ebner C, Steringer-Mascherbauer R, Schmidt F, Galuschky C, Schummers G, Lang RM *et al*: **Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference**. *Circulation* 2006, **114**(7):654-661.
17. Nikitin NP, Constantin C, Loh PH, Ghosh J, Lukaschuk EI, Bennett A, Hurren S, Alamgir F, Clark AL, Cleland JG: **New generation 3-dimensional echocardiography for left ventricular volumetric and functional measurements: comparison with cardiac magnetic resonance**. *Eur J Echocardiogr* 2006, **7**(5):365-372.

Chapter 3

Comparison between QLAB and TomTec full volume reconstruction for real-time three-dimensional echocardiographic quantification of left ventricular volumes

Osama I.I. Soliman[1,2], Boudewijn J. Krenning[1], Marcel L. Geleijnse[1], Attila Nemes[1,4], Robert-Jan van Geuns[1,3], Timo Baks[1,3], Ashraf M. Anwar[1,2], Tjebbe W. Galema[1], Wim B. Vletter[1], and Folkert J. ten Cate[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt'; [3]Department of Radiology, Erasmus University Medical Center, Rotterdam, the Netherlands; [4]Second Department of Medicine and Cardiology Center, University of Szeged, Szeged, Hungary

Echocardiography 2007 Oct; 24 (9)967- 974

ABSTRACT

Objectives: To compare the inter-observer variability and accuracy of two different real-time three-dimensional echocardiography (RT3DE) analyzing programs.

Methods: Forty-one patients (mean age 56 ± 11 years, 28 men) in sinus rhythm with a cardiomyopathy and adequate 2D image quality underwent RT3DE and magnetic resonance imaging (MRI) within one day. Off-line left ventricular (LV) volume analysis was performed with QLAB® V4.2 (semi-automated border detection with bi-plane projections) and TomTec® 4D LV analysis V2.0 (primarily manual tracking with tri-plane projections and semi-automated border detection).

Results: Excellent correlations (R^2 >0.98) were found between MRI and RT3DE. Bland-Altman analysis revealed an underestimated LV end-diastolic volume (LV-EDV) for both TomTec (-9.4 ± 8.7 ml) and QLAB (-16.4 ± 13.1 ml). Also, an underestimated LV end-systolic volume (LV-ESV) for both TomTec (-4.8 ± 9.9 ml) and QLAB (-8.5 ml ± 14.2 ml) was found. LV-EDV and LV-ESV were significantly more underestimated with QLAB software. Both programs accurately calculated LV ejection fraction (LV-EF) without a bias. Inter-observer variability was 6.4 ± 7.8% vs. 12.2 ± 10.1% for LV-EDV, 7.8 ± 9.7% vs. 13.6 ± 11.2% for LV-ESV, and 7.1 ± 6.9% vs. 9.7 ± 8.8% for LV-EF for TomTec vs. QLAB, respectively. The analysis time was shorter with QLAB (4 ± 2 minutes vs. 6 ± 2 minutes, P <0.05).

Conclusions: RT3DE with TomTec or QLAB software analysis provides accurate LV-EF assessment in cardiomyopathic patients with distorted LV geometry and adequate 2D image quality. However, LV volumes may be somewhat more underestimated with the current QLAB software version.

INTRODUCTION

Accurate assessment of left ventricular (LV) volume and systolic function is of great importance in cardiac patients and forms a routine part of daily echocardiographic practice.[1] However, the geometric assumptions in motion-mode (1D) and two-dimensional (2D) echocardiography and the poor inter- and intra-observer variability limit these techniques.[2, 3] The development of real-time three-dimensional echocardiography (RT3DE) with matrix transducer technology and analyzing software made a more reliable analysis of LV function feasible. The increasing accuracy and reproducibility of RT3DE for LV quantification has been shown in many studies.[4-9] There are several online and off-line software programs for LV volume quantification by RT3DE. The endocardial border tracking algorithms which can be used for generation of a 3D LV volume represent a continuum spectrum ranging from fully automated to fully manual-based algorithms.[10] At one end of the spectrum, a fully automated endocardial tracking algorithm provides a fast, highly reproducible and operator independent calculation of LV volumes. On the other end of the spectrum, a fully manual-based tracking algorithm is more time-consuming and operator-dependent, but potentially more accurate. For clinical practice, the commercially available software packages have to balance between the pros and cons of the two ends of the spectrum. The TomTec (TomTec, Munich, Germany) and QLAB (Philips, Best, The Netherlands) software packages are two frequently used programs for RT3DE analysis. The analysis used by these software programs is fundamentally different. TomTec requires a tri-plane manual tracing of the endocardial border after which the software selects a fitting geometric model and the total LV endocardial border is automatically delineated with manual corrections possible for each individual longitudinal LV plane. In contrast, the QLAB software does not require manual tracing of the endocardial border but only needs input of five specific identification points (one at the apex and four at the mitral annulus) for selecting a fitting geometric model. Manual corrections are still possible, but each single LV plane correction results automatically in correction of all longitudinal LV planes. The present study was conducted to compare the inter-observer variability and accuracy of these two different RT3DE analysis programs in patients with cardiomyopathic LVs.

METHODS

Patient selection

Forty-one consecutive patients (mean age 56 ± 11 years, 28 men) in sinus rhythm with a LV cardiomyopathy and adequate 2D image quality (no more than 2 LV segments not well visualized) were enrolled in the study. The etiology of the cardiomyopathy was ischemic in 6 (15%), idiopathic dilated in 9 (22%), non-compaction in 9 (22%), and hypertrophic in 17 (41%). The diagnosis of the different forms of cardiomyopathy was based on current guidelines.[11] All patients underwent both RT3DE and magnetic resonance imaging (MRI) within one day to ensure comparable hemodynamic conditions between the examinations. All patients gave informed consent and the institutional review board approved the study.

Transthoracic RT3DE

Image acquisition

RT3DE was performed using a Sonos 7500 (Philips Medical Systems, Best, The Netherlands) ultrasound machine equipped with an X4 matrix-array transducer with the patient in a left lateral decubitus position. Image acquisition was performed from an apical window with the LV as region of interest. To encompass the complete LV into the 3D data set, a full volume (93° × 84°) scan was acquired in harmonic mode from four R-wave triggered subvolumes (93° × 21°) during an end-expiratory breath-hold lasting for 6 to 8 seconds. The 3D data set was stored in Sonos format on CD-ROM and transferred to two separate workstations for off-line data analysis.

Image analysis – QLAB semi-automated border detection method

Semi-automated border detection bi-plane LV volume analysis was performed using off-line QLAB version 4.2, 3DQ Advanced software (Philips, Best, The Netherlands). Once the program starts, a quad screen displaying two orthogonal views (top, left and right), one short-axis view (bottom, left) and one dynamic window for multi-purpose display (bottom, right) are shown. LV quantification starts by definition of the proper 4-chamber view and adjustment of the LV 4-chamber and orthogonal views to avoid foreshortening. Then it is made sure that the intersection point of the displayed horizontal and vertical lines is in the middle of the LV cavity. Subsequently, the end-diastolic (largest LV volume) and end-systolic (smallest LV volume) frames are identified. On both these end-diastolic and end-systolic frames, 5 identification points are marked: the septal, lateral, anterior, and inferior mitral annulus and the apex (from either one of the views). After this the software automatically delineates the LV endocardial border and by sequential analysis the software creates a LV mathematical model or "cast" that represents the LV cavity and LV volumes are calculated. Unsatisfactory delineation of the endocardial border was manually adjusted. LV ejection fraction (LV-EF) is calculated by the software as (LV-EDV − LV-ESV) / LV-EDV × 100%, where EDV = end-diastolic volume and ESV = end-systolic volume.

Image analysis – TomTec semi-automated method

LV volume analysis was performed off-line using TomTec 4D LV-Analysis software, version 2.0 (TomTec, Munich, Germany). The oblique coronal 4-chamber view and the 60° and 120° incremental views are the (tri) planes used for primary analysis. To avoid foreshortening, the meeting points of the three oblique sagittal and coronal planes are adjusted to meet in the middle of the LV cavity. The end-diastolic and end-systolic frames are identified automatically in this software version, which is necessary for initial contour detection. Subsequently, the endocardial border in the three planes is manually traced (LV trabeculations and papillary muscles are included within the LV volume) in both the end-diastolic and end-systolic images for initialization of the algorithm. Based on these six initial contours, a spatiotemporal spline interpolation model (like a pulsating balloon) is created by rotational and temporal interpolation of these contours. According to the initial balloons, the algorithm starts to detect the endocardial border

continuously in the entire 4D dataset (without large gaps due to interpolation), e.g. like deforming the balloon in the LV until it best fits the walls in each frame. Adjustments can be made manually after this step in approximately 30 single oblique sagittal and coronal planes. Subsequently, a final reconstruction of the LV model and a time-volume curve are created. LV-EDV and LV-ESV are calculated as the largest and smallest volume, respectively, from this time-volume curve. LV-EF is calculated as described in the previous section.

Two independent investigators (OIIS, AN) who were blinded to the MRI results performed both the QLAB and TomTec analyses on a separate day. One investigator (OIIS) analyzed all studies twice in separate weeks.

Magnetic resonance imaging

MRI images were acquired using a 1.5 Tesla scanner (GE Signa CV/i, Milwaukee, WI). Patients were positioned in the supine position, with a cardiac eight-element phased-array coil placed over the thorax. Repeated breath holds and electrocardiographic gating were applied to minimize the influence of cardiac and respiratory motion on data collection. Cine MRI was performed using a steady-state free-precession technique (FIESTA). Imaging parameters were; repetition time, 3.5 ms; echo time, 1.3 ms; flip angle, 45°; field of view, 36-40 x 36-40 cm; matrix, 196x160; views per segment, 12, resulting in a temporal resolution of 42 ms. To cover the entire LV 10-12 consecutive slices of 8 mm in the short axis view were planned on the four chambers (gap 2 mm).

To quantify LV volumes, endocardial contours were detected automatically and corrected manually on short-axis cine-MRI images with a dedicated software program using the centerline method (Mass; Medis, Leiden, the Netherlands). End-diastole and end-systole are based on the largest and smallest cavity size on short-axis, respectively, as previously described.[12] Papillary muscles were considered as part of the LV cavity.

STATISTICAL ANALYSES

All data are expressed as mean ± SD. For comparison between MRI and RT3DE, linear regression analysis was performed and a Pearson correlation coefficient was calculated. For paired data, the Student's *t* test was used. For agreement between MRI and RT3DE, and inter- and intra-observer data form RT3DE, the method of Bland and Altman was used.[13] Variability between MRI and RT3DE was expressed as mean difference ± 2 SD between the two measurements. Inter- and intra-observer variability was expressed as the absolute difference between two measurements divided by the average of the two measurements as a percentage. The Statistical Package of the Social Science (SPSS) software version 12.02 (SPSS Inc., Chicago, Illinois) was used for statistical analysis.

Table 1. Comparison of Real-Time Three-Dimensional Echocardiography for Volumes and Ejection Fraction Using QLAB And TomTec Software for the Different Cardiomyopathies.

	Total population n = 41	NCCM n = 9	DCM n = 9	ICM n = 6	HCM n = 17	Inter-group P value
LV-EDV						
TomTec	-5.5	-5.5	-5.0	-4.8	-5.4	NS
QLAB	-9.4*	-12.4*	-10.2*	-10.1*	-7.1*	NS
LV-ESV						
TomTec	-4.9	-5.3	-5.2	-5.2	-4.2	NS
QLAB	-10.2*	-11.3*	-10.7*	11.1*	-9.1*	NS
LV-EF						
TomTec	0.8	0.7	0.6	0.5	0.7	NS
QLAB	1.5	1.2	1.6	1.6	1.7	NS

Differences Between QLAB and TomTec And MRI Data Expressed As A Percentage Volume Underestimation. * = P <0.01 for QLAB vs. TomTec.
DCM = dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, ICM = ischemic cardiomyopathy, LV-EDV = left ventricular end-diastolic volume, LV-ESV = left ventricular end-systolic volume, LV-EF = left ventricular ejection fraction, NCCM = non-compaction cardiomyopathy, NS = non-significant

RESULTS

LV volumes and function

MRI yielded a LV-EDV of 182 ± 54 ml (range 74 to 328 ml), LV-ESV of 85 ± 53 (range 14 to 208) and LV-EF of 58 ± 17% (range 16 to 86%). RT3DE TomTec analysis yielded a LV-EDV of 173 ± 53 ml (range 67 to 308 ml), LV- ESV of 80 ± 49 ml (range 16 to 194 ml) and LV-EF of 57 ± 17% (range 16 to 84%). RT3DE QLAB analysis yielded a LV-EDV of 166 ± 50 ml (range 71 to 298 ml), LV-ESV of 76 ± 48 ml (range 20 to 189 ml) and LV-EF of 57 ± 17% (range 17 to 84%). As seen in Table 1, there were no significant differences in percentage volume underestimation for the four groups of cardiomyopathy.

Comparison of TomTec versus QLAB (paired *t* test)

QLAB measurements were significantly lower than TomTec measurements for LV-EDV (P <0.01) and LV-ESV (P <0.01) with comparable LV-EF values. The time needed for full-volume reconstruction was shorter with the QLAB (4 ± 2 minutes vs. 6 ± 2 minutes, P <0.05) compared to TomTec.

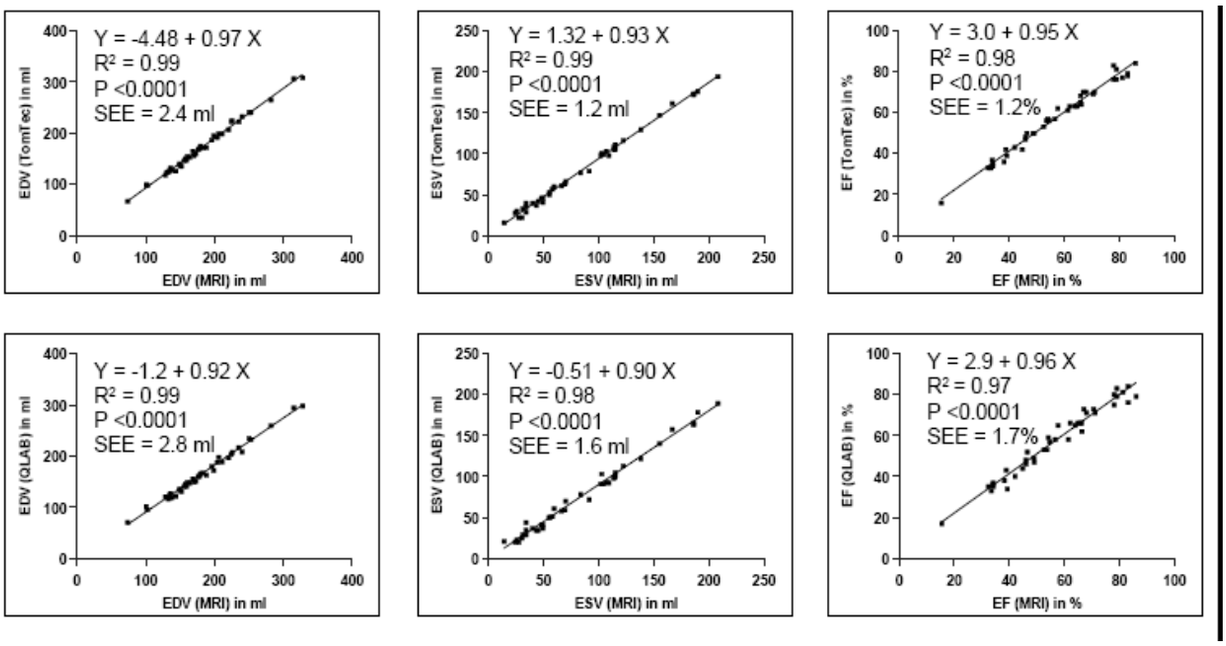


Figure 1. Results of linear regression analysis of real-time three-dimensional echocardiographic values of left ventricular volumes and ejection fraction using TomTec (top) and QLAB (bottom) versus magnetic resonance imaging reference values.

Precision and accuracy

LV end-diastolic volume

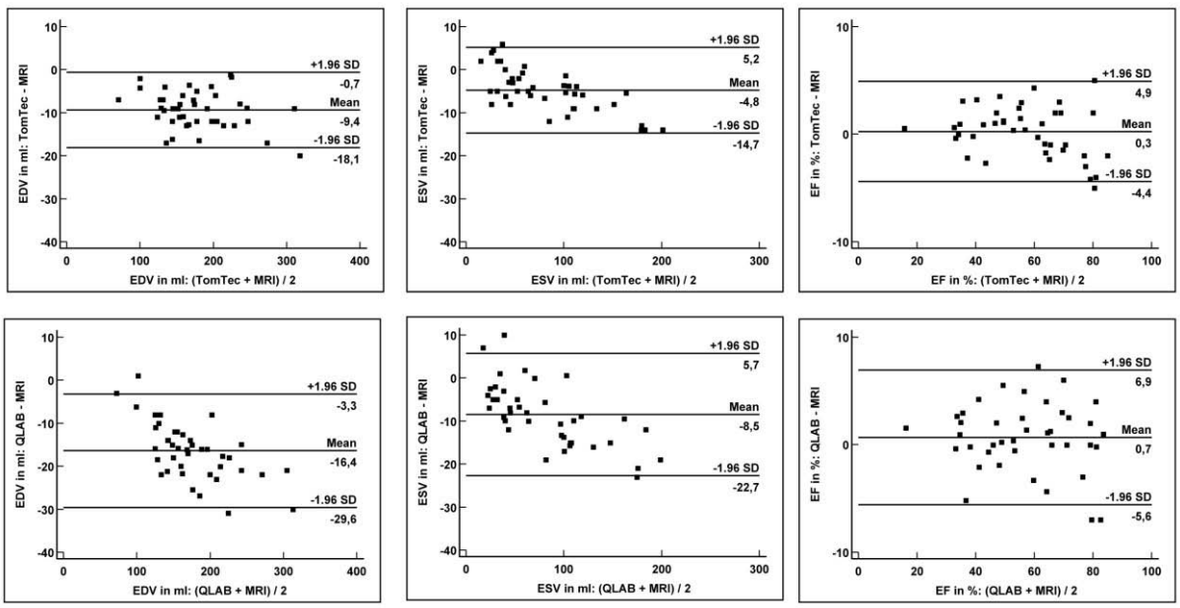
As shown in Figure 1 (top left), linear regression analysis of TomTec- derived LV-EDV revealed an excellent correlation with MRI values, with a coefficient of determination of $R^2 = 0.99$, a regression slope of 0.97, an intercept of –4.5 ml, and SEE of 2.4 ml. Bland-Altman analysis confirmed the underestimation of the TomTec measurements by demonstrating a bias of –9.4 ml (-5.5% of the mean) with 95% limits of agreement at ± 8.7 ml (± 5.3% of the mean) (Figure 2, top left). As shown in Figure 1, bottom left, QLAB-derived values of LV-EDV correlated well with MRI values, with a coefficient of determination of $R^2 = 0.99$, a regression slope of 0.92, an intercept of –1.2 ml, and SEE of 2.8 ml. Bland-Altman analysis confirmed the underestimation of the QLAB by demonstrating a bias of –16.4 ml (-9.4% of the mean) with 95% limits of agreement at ± 13.1 ml (± 6.3% of the mean) (Figure 2, bottom left).

LV end-systolic volume

As shown in Figure 1 (top middle), linear regression analysis of TomTec-derived LV-ESV resulted in excellent correlation with MRI values, with a coefficient of determination of $R^2 = 0.99$, a regression slope of 0.93, an intercept of 1.4 ml, and SEE of 1.2 ml. Bland-Altman analysis confirmed the underestimation of the TomTec measurements by demonstrating a bias of –4.8 ml (-4.9% of the mean) with 95% limits of agreement at ± 9.9 ml (± 18.3% of the mean) (Figure 2, top middle). As shown in Figure 1 (bottom middle), QLAB-derived values of LV-ESV correlated well with MRI values, with a coefficient of determination of R2 = 0.98, a regression slope of 0.90, an intercept of –0.5 ml, and SEE of 1.6 ml. Bland-Altman analysis

confirmed the underestimation of the QLAB by demonstrating a bias of –8.5 ml (-10.2% of the mean) with 95% limits of agreement at ± 14.2 ml (± 24.3% of the mean) (Figure 2, bottom middle).

A.



B.

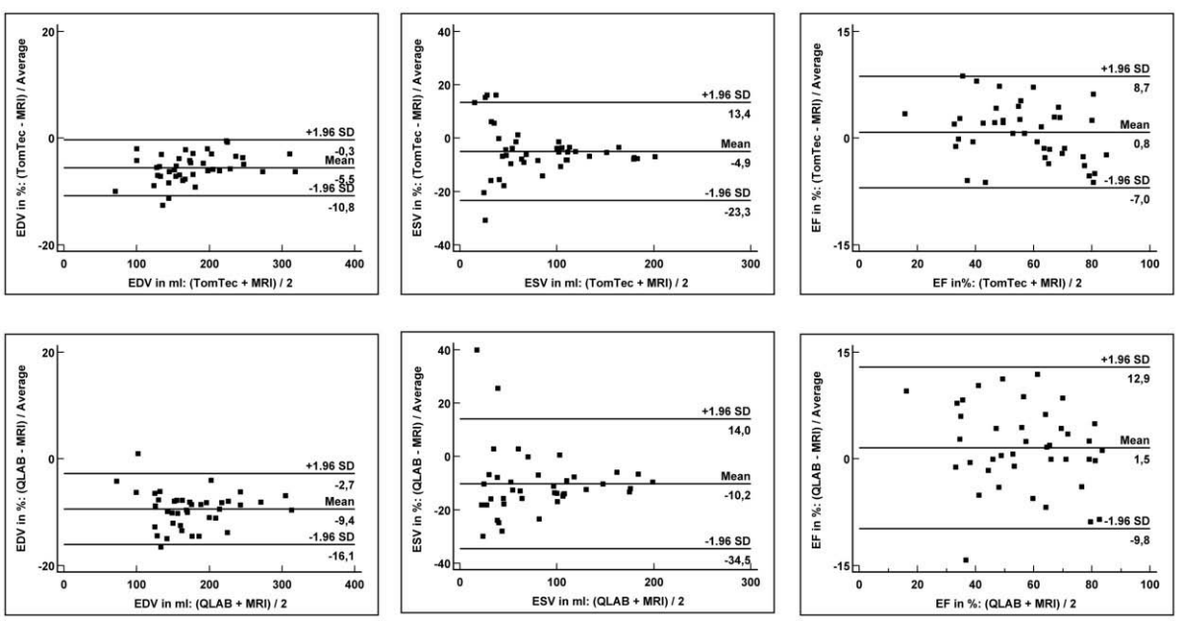


Figure 2. Results of Bland-Altman analysis of real-time three-dimensional echocardiographic values of left ventricular volumes and ejection fraction using TomTec (top) and QLAB (bottom) versus magnetic resonance imaging reference values as an absolute values (A) and percentage of mean (B).

LV ejection fraction

As shown in Figure 1 (top right), linear regression analysis of TomTec-derived LV-EF resulted in excellent correlation with MRI values, with a coefficient of determination of $R^2 = 0.98$, a regression slope of 0.95, an intercept of 3.0%, and SEE of 1.2%. Bland-Altman analysis confirmed the underestimation of the TomTec measurements by demonstrating a bias of 0.3% (0.8% of the mean) with 95% limits of agreement at ± 4.7%

(± 7.8% of the mean) (Figure 1, top right). As shown in Figure 1 (bottom right), QLAB-derived values of LV-EF correlated well with MRI values, with a coefficient of determination of $R^2 = 0.97$, a regression slope of 0.96, an intercept of 2.9%, and SEE of 1.7%. Bland-Altman analysis confirmed the underestimation of the QLAB by demonstrating a bias of 0.7% (1.5% of the mean) with 95% limits of agreement at ± 6.2% (± 11.4% of the mean) (Figure 2, bottom right).

Table 2. Inter- and Intra-Observer Variability of Real-Time Three-Dimensional Echocardiography for Volumes and Ejection Fraction Using the 2 Software Programs.

	Inter-observer Variability (%)	Intra-observer Variability (%)
LV-EDV		
TomTec	6.4 ± 7.8	4.7 ± 3.2
QLAB	12.2 ± 10.1	7.2 ± 8.1
MRI*	3.7 ± 3.1	0.2 ± 1.0
LV-ESV		
TomTec	7.8 ± 9.7	6.1 ± 5.8
QLAB	13.6 ± 11.2	9.1 ± 7.2
MRI*	4.8 ± 4.0	1.4 ± 2.3
LV-EF		
TomTec	7.1 ± 6.9	6.6 ± 7.4
QLAB	9.7 ± 8.8	7.3 ± 9.1
MRI*	5.6 ± 6.0	0.2 ± 6.2

*Data from van Geuns et al.[14] MRI = magnetic resonance imaging. Other abbreviations see Table 1.

Reproducibility (inter- and intra-observer variability)

As seen in Table 2, TomTec analysis seemed somewhat more reproducible, evidenced by smaller 95% limits of agreement for inter- and intra-observer variability for LV-EDV, LV-ESV, and LV-EF.

DISCUSSION

Recent advances in acquisition and software analysis of RT3DE datasets has made accurate measurements of LV volumes possible in large numbers of patients.[4, 6, 15, 16] Currently, several online and off-line software programs are available for quantification of LV volumes and EF. In the present study, for the first time we head-to-head compared the accuracy and reproducibility of two recently developed software programs for LV volume quantification with MRI as the reference technique. Another unique characteristic of our study is that all patients had cardiomyopathic LVs with altered LV geometry that may be prone to pitfalls during acquisition and analysis of LV volumes.

The main finding of the present head-to-head comparative study is that despite a linear relationship between echocardiographic and MRI three-dimensional quantification of LV volumes, evidenced by excellent correlations for LV-EDV, LV-ESV and LV-EF, there is a small underestimation of

LV volumes by both RT3DE software programs. This was somewhat more pronounced for the QLAB semi-automated tracking algorithm, evidenced by higher biases and wider limits of agreement. However, values of LV-EF were accurately calculated, which can be explained by the systematic underestimation of the volume measurements by either algorithm. Another finding is the higher reproducibility of the semi-automated TomTec algorithm as compared to the semi-automated QLAB tracking algorithm, as evidenced by lower inter- and intra-observer variability for LV volumes and LV-EF.

Table 3. Differences and Similarities Between QLAB and TomTec Algorithms.

	Philips QLAB 3DQ Advanced, version 4.2	TomTec 4D LV analysis, version 2.0
Initial identification of ED and ES	User-defined	Software-defined (ECG-triggered)
Initial border tracing	Automated (requires definition of five points in ED and ES frames)	Manual (requires tracing of the whole endocardial borders in ED and ES frames)
Initial border tracing planes	Bi-plane (apical 4 and 2 chamber views)	Tri-plane (apical 4, 2, and 3 chamber views)
Final contour adjustments	Manual with global impact on 3D shell	Manual with local impact on 3D shell
Final 3D shell	From full volume reconstruction in a full cardiac cycle	From full volume reconstruction in a full cardiac cycle
Final ED and ES volume determination	From the time-volume curve	From the time-volume curve

ED = end-diastole; ES = end-systole; ECG = electrocardiogram

These differences may be explained by a number of significant differences between the two software programs used in our study (see Table 3). The QLAB software is a more automated algorithm that requires minimal operator intervention. After definition of end-diastolic and end-systolic frames, only identification of five specific points in 2 apical planes is needed to identify a geometric LV model. In contrast, the TomTec software requires manual tracing in 3 planes of the LV endocardial border. In addition, an important difference in final contour adjustment is present. TomTec software uses manual fine editing which has only local impact on the generated LV shell. On the other hand, in the QLAB software, the adjustment in a single plane automatically results in creation of a new LV model with automatic changes in all planes. This may explain the differences in underestimation between both methods particularly in a group of patients with the very distorted LV geometry. In a newer QLAB software version that is currently under development, this limitation is solved by a more local impact of edited points for the 3D reconstruction. This, together with improved manual editing tools, is likely to increase accuracy of 3D LV volume calculation.

Comparison to previous studies: Our study is the first head-to-head comparison between the newest TomTec algorithm and QLAB software for measurement of LV volumes within the same

cardiomyopathic patients. The biases and limits of agreement published in our study are comparable to those reported in prior bi-plane TomTec and QLAB studies. [4, 6, 9, 16-18] It is remarkable that an approximately two-fold higher underestimation of LV volumes for the QLAB software described in our study was also reported in a head-to-head comparison between bi-plane TomTec and QLAB software by Jenkins et al.[18] and by non-direct comparative data published from the same center by Jacobs et al. and Sugeng et al.[16, 17] However, it should be noticed that the underestimation of LV volumes by QLAB software in our study was somewhat less compared to results published by others.[18] As mentioned before, the newer QLAB software under development will probably make LV volume analysis more accurate. Because of the systematic underestimation of all volumes by QLAB software, the clinically most relevant data on LV-EF are equal for TomTec and QLAB software.

Study limitations: Short-axis MRI analysis was used as a reference technique. This analysis is not optimal near the apex because of partial-volume artifacts and has limitations in recognizing the mitral valve[16]. In the future incorporation of long-axis analysis can improve assessment of LV volumes. However, the short-axis MRI method of analysis is still most widely used for LV volume assessment, both in clinical practice and research [6, 14, 15] and does not influence the head-to-head comparison between the two software programs. Also, it should be recognized that RT3DE has several limitations. Firstly, because currently 4 heart cycles are necessary to acquire a full LV volume, patients with arrhythmias cannot be studied with RT3DE. In addition RT3DE is critically dependent on image quality (of note in our study patients were selected on adequate 2D image quality) and motion and breathing artifacts.

CONCLUSIONS

RT3DE with TomTec or QLAB software can provide accurate LV-EF assessment in cardiomyopathic patients with distorted LV geometry and moderate to good 2D image quality. However, LV volumes may be somewhat more underestimated with the current QLAB software version.

REFERENCES

1. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS: **Natural history of asymptomatic left ventricular systolic dysfunction in the community**. *Circulation* 2003, **108**(8):977-982.
2. Siu SC, Levine RA, Rivera JM, Xie SW, Lethor JP, Handschumacher MD, Weyman AE, Picard MH: **Three-dimensional echocardiography improves noninvasive assessment of left ventricular volume and performance**. *Am Heart J* 1995, **130**(4):812-822.
3. Siu SC, Rivera JM, Guerrero JL, Handschumacher MD, Lethor JP, Weyman AE, Levine RA, Picard MH: **Three-dimensional echocardiography. In vivo validation for left ventricular volume and function**. *Circulation* 1993, **88**(4 Pt 1):1715-1723.
4. Jenkins C, Bricknell K, Hanekom L, Marwick TH: **Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography**. *J Am Coll Cardiol* 2004, **44**(4):878-886.
5. Zeidan Z, Erbel R, Barkhausen J, Hunold P, Bartel T, Buck T: **Analysis of global systolic and diastolic left ventricular performance using volume-time curves by real-time three-dimensional echocardiography**. *J Am Soc Echocardiogr* 2003, **16**(1):29-37.
6. Kuhl HP, Schreckenberg M, Rulands D, Katoh M, Schafer W, Schummers G, Bucker A, Hanrath P, Franke A: **High-resolution transthoracic real-time three-dimensional echocardiography: quantitation of cardiac volumes and function using semi-automatic border detection and comparison with cardiac magnetic resonance imaging**. *J Am Coll Cardiol* 2004, **43**(11):2083-2090.
7. Simpson IA, Sahn DJ: **Adult congenital heart disease: use of transthoracic echocardiography versus magnetic resonance imaging scanning**. *Am J Card Imaging* 1995, **9**(1):29-37.
8. Mao S, Shinbane JS, Girsky MJ, Child J, Carson S, Oudiz RJ, Budoff MJ: **Coronary venous imaging with electron beam computed tomographic angiography: three-dimensional mapping and relationship with coronary arteries**. *Am Heart J* 2005, **150**(2):315-322.
9. Gutierrez-Chico JL, Zamorano JL, Perez de Isla L, Orejas M, Almeria C, Rodrigo JL, Ferreiros J, Serra V, Macaya C: **Comparison of left ventricular volumes and ejection fractions measured by three-dimensional echocardiography versus by two-dimensional echocardiography and cardiac magnetic resonance in patients with various cardiomyopathies**. *Am J Cardiol* 2005, **95**(6):809-813.
10. Krenning BJ, Voormolen MM, van Geuns RJ, Vletter WB, Lancee CT, de Jong N, Ten Cate FJ, van der Steen AF, Roelandt JR: **Rapid and accurate measurement of left ventricular function with a new second-harmonic fast-rotating transducer and semi-automated border detection**. *Echocardiography* 2006, **23**(6):447-454.
11. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB: **Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention**. *Circulation* 2006, **113**(14):1807-1816.
12. Marcus JT, DeWaal LK, Gotte MJ, van der Geest RJ, Heethaar RM, Van Rossum AC: **MRI-derived left ventricular function parameters and mass in healthy young adults: relation with gender and body size**. *Int J Card Imaging* 1999, **15**(5):411-419.
13. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement**. *Lancet* 1986, **1**(8476):307-310.
14. van Geuns RJ, Baks T, Gronenschild EH, Aben JP, Wielopolski PA, Cademartiri F, de Feyter PJ: **Automatic quantitative left ventricular analysis of cine MR images by using three-dimensional information for contour detection**. *Radiology* 2006, **240**(1):215-221.
15. van den Bosch AE, Robbers-Visser D, Krenning BJ, Voormolen MM, McGhie JS, Helbing WA, Roos-Hesselink JW, Simoons ML, Meijboom FJ: **Real-time transthoracic three-dimensional echocardiographic assessment of left ventricular volume and ejection fraction in congenital heart disease**. *J Am Soc Echocardiogr* 2006, **19**(1):1-6.
16. Jacobs LD, Salgo IS, Goonewardena S, Weinert L, Coon P, Bardo D, Gerard O, Allain P, Zamorano JL, de Isla LP *et al*: **Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data**. *Eur Heart J* 2006, **27**(4):460-468.
17. Sugeng L, Mor-Avi V, Weinert L, Niel J, Ebner C, Steringer-Mascherbauer R, Schmidt F, Galuschky C, Schummers G, Lang RM *et al*: **Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference**. *Circulation* 2006, **114**(7):654-661.
18. Jenkins C, Chan J, Hanekom L, Marwick TH: **Accuracy and feasibility of online 3-dimensional echocardiography for measurement of left ventricular parameters**. *J Am Soc Echocardiogr* 2006, **19**(9):1119-1128.

Part III

Echocardiographic assessment of cardiac resynchronization therapy

Includes chapters 4, 5, 6,7,8,9 and 10

Chapter 4

Reverse of left ventricular volumetric and structural remodeling in heart failure patients treated with cardiac resynchronization therapy

Osama I.I. Soliman[1,2], Marcel L. Geleijnse[1], Dominic A.M.J. Theuns[1], Attila Nemes[1], Wim B. Vletter[1], Bas M. van Dalen[1], Luc J. Jordaens MD[1],and Folkert J. ten Cate[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt

Accepted for publication (American Journal of Cardiology)

ABSTRACT

Background: Patients with moderate to severe heart failure (HF) and mechanical dyssynchrony have progressive increase in left ventricular (LV) mass and asymmetrical hypertrophy, which is associated with poor prognosis. We investigated whether cardiac resynchronization therapy (CRT) may reverse these abnormalities.

Methods: From 74 consecutive HF patients included, 66 were alive and completed clinical and echocardiographic evaluation at 12 months after CRT. Echocardiographic response was defined as a >15% reduction in LV end-systolic volume (LV-ESV).

Results: Fifty patients (76%) were echocardiographic responders at 12 months after CRT. LV end-diastolic volume decreased from 260 ± 113 ml to 248 ± 120 ml ($P < 0.05$) at 3 months and to 217 ± 110 ml at 12 months after CRT ($P < 0.01$). LV-ESV decreased from 214 ± 97 ml to 179 ± 88 ml and to 158 ± 86 ml, respectively (all $P < 0.01$). LV ejection fraction increased from 18% ± 4% to 28% ± 7% ($P < 0.001$) and to 27% ± 7%, respectively. Structural remodeling was shown by a reduction in LV mass from 242 ± 52 g to 222 ± 45 g and to 206 ± 50 g (all $P < 0.01$), and an improvement in end-diastolic and end-systolic sphericity indices, respectively. Echocardiographic responders had a marked reduction in LV mass from 240 ± 50 to 210 ± 38 and to 186 ± 37 g, respectively (all $P < 0.01$). In contrast, non-responders had an increase in LV mass (from 248 ± 59 g to 258 ± 54 g and to 269 ± 60 g, respectively, all $P < 0.05$). Likewise, in echocardiographic responders only, regression of asymmetric hypertrophy of the lateral wall and improvement of the tissue Doppler peak myocardial systolic velocities were noted.

Conclusion: CRT results not only in volumetric improvement but also in true structural LV reverse remodeling, evidenced by progressive reduction in LV mass and restoration of regional wall symmetry.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective therapy for selected heart failure (HF) patients resulting in a decrease in morbidity and mortality.[1, 2] The potential mechanisms for CRT success are mainly related to the optimized diastolic filling of the left ventricle (LV), more synchronized electrical and mechanical LV coupling hence myocardial performance, and reduced mitral regurgitation (MR).[3-5] Most of the randomized CRT trials and non-randomized studies have implemented LV volume changes as a marker for LV reverse remodeling. Recently, it was shown that reduction of LV end-systolic volume is the most important predictor for long-term clinical outcome (mortality and re-hospitalization for HF) after CRT.[6] Data about combined volumetric and structural (e.g. LV mass) LV reverse remodeling after CRT are scarce. Recently, it was shown that volumetric changes are associated with echocardiographic evidence of structural LV reverse remodeling as early as three months after CRT.[7-9] However, in an earlier published study, significant LV structural changes were not seen.[10] Therefore, we sought to assess serial global and regional LV structural changes in our CRT patients after 3 and 12 months.

METHODS

Study population

The study enrolment criteria were (1) New York Heart Association (NYHA) functional class ≥III despite optimal drug therapy, (2) impaired LV ejection fraction (LV-EF <35%), and (3) wide QRS complex >120 ms. These CRT indications comply with current guidelines.[11] Patients with acute coronary syndromes or coronary revascularization within 6 months before CRT were excluded. An informed consent was obtained from all patients and the institutional review board approved the study.

From the 74 included patients that underwent CRT, 8 patients developed cardiac events between 3 and 12 months, and because of lacking one-year echocardiographic data they were excluded from the final analysis. These 8 excluded patients had more often an ischemic etiology ($P < 0.05$), diabetes ($P < 0.05$), and restrictive LV filling ($P < 0.05$), and less LV dyssynchrony ($P < 0.05$). LV mass in these 8 patients was not different. After 3 months, these 8 patients had less decrease in LV end-diastolic volume (LV-EDV) ($P < 0.05$), end-systolic volume (LV-ESV) ($P < 0.05$), and LV mass ($P < 0.01$).

Study design

Before CRT device implantation, standard 2D echocardiography, including tissue Doppler imaging (TDI) assessment of mitral annular velocity, was done. Patients were scheduled for regular three months clinical assessment including NYHA class assessment and six-minute walk distance (6MWD) testing.[12] The CRT devices were interrogated to ensure that biventricular pacing was maintained. Echocardiographic follow-up was scheduled at three months and 12 months after CRT. A patient was considered a clinical responder after CRT when a >25% improvement in 6MWD testing was noted and an echocardiographic responder when a >15% reduction in LV-ESV was noted.

Device implantation

CRT device implantation was performed preferably with a single left pectoral incision, a left cephalic vein cutdown and a left subclavian puncture. The defibrillation lead was positioned in the right ventricular apex. The LV pacing lead was placed in a tributary of the coronary sinus. A postero-lateral branch was used in 45 patients (68%), a lateral branch in 15 patients (23%), and an antero-lateral branch in 6 patients (9%) of patients. Adequate pacing and sensing properties of all leads were tested. All implanted biventricular pacing devices were combined with an internal cardioverter-defibrillator. The lowest effective defibrillation energy was assessed in all patients or a safety major ≥10 J was documented. The implanted devices were InSync 7272, 7279, and 7298 (Medtronic Inc, Minneapolis, MN, USA), Renewal II (Guidant Inc, St Paul, MN, USA), and Epic HF V-339 and Atlas HF V-341 (St Jude Medical, Sylmar, CA, USA). For all patients, ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation. The atrio-ventricular delay was optimized by 2D echocardiography to provide the longest filling time for completion of the end-diastolic filling flow before LV contraction with the highest LV outflow tract velocity time integral.

Echocardiography

Two-dimensional echocardiography

All patients were examined using a Sonos 7500 ultrasound system (Philips, Best, The Netherlands) with a S3 transducer according to the recommendations of the American Society of Echocardiography.[13, 14] LV-EDV, LV-ESV, and LV-EF (by modified bi-plane Simpson rule) were calculated from the apical 4-chamber and 2-chamber views. LV mass was measured with the 2D area-length method, as previously described.[15] The septal and lateral wall thickness were measured and LV sphericity indices were calculated by dividing the maximal LV short-axis by the maximum long-axis internal dimension at end-diastole and end-systole, as previously described.[16] The degree of MR (grade I-IV) was assessed as the mid-systolic jet area relative to left atrial area in the apical 4-chamber view.[17] All measurements were done blinded to clinical data and the other echocardiographic studies.

Tissue Doppler Imaging

In brief, spectral pulsed-wave TDI was applied by placing the sample volume at the side of the medial and lateral mitral annulus in an apical 4-chamber view.[18] Gain and filter settings were adjusted as needed to eliminate background noises and to allow for a clear tissue signal. TDI velocities were recorded end-expiratory at a sweep speed of 100 mm/s and measured using electronic calipers with the workstation EnConcert (Philips, Best, The Netherlands). The velocity and timing of mitral annular longitudinal motion waves, the peak systolic velocity (Sm) averaged from the septal and lateral walls and early peak diastolic velocity (E′) were measured. The delay in time-to-onset of Sm between the septal and the lateral wall was calculated to determine the lateral-to-septal delay (LSD). The myocardial performance index (or Tei index)

was calculated as isovolumic contraction time plus isovolumic relaxation time divided by ejection time as previously described.[24] In each patient, the average of three measurements was calculated.

STATISTICAL ANALYSES

Descriptive statistics for nominal data were expressed in absolute numbers and percentages. After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Comparison of continuous variables between groups was made by unpaired Student's t-tests. In the case of a skewed distribution, the Mann–Whitney U test was used. When comparing frequencies, the x^2 test or Fisher's exact test was used, where applicable. Baseline, 3-months and one-year values within each group was compared by ANOVA. All tests were two-tailed, and all P-value less than 0.05 were considered statistically significant. All statistics were performed using SPSS (12.0.2) for Windows (Chicago, IL, USA).

RESULTS

Baseline demographics

Mean age of the 66 patients was 59 ± 11 years and 45 were men (68%). Sixty-three patients (95%) were in NYHA class III, 3 patients were in NYHA class IV. At baseline, β-blockers were used in 76% of patients, angiotensin converting-enzyme inhibitors in 92%, diuretics in 95%, amiodarone in 33%, and digitalis in 32%. There were no significant changes in the number of HF drugs used after CRT. All other pertinent baseline clinical and echocardiographic data of the patients are shown in Table 1.

Three months follow-up data

Clinical data

At 3 months follow-up, QRS duration decreased from 168 ± 26 to 135 ± 21 ms (P <0.001), the number of patients in NYHA class III or IV decreased from 66 to 5 (P <0.0001), and the 6MWD increased from 216 ± 39 to 283 ± 60 m (P <0.001).

Echocardiographic data

As shown in Table 1, CRT-induced volumetric remodeling was evidenced by a decrease in LV-EDV from 260 ± 113 to 248 ± 120 ml (P <0.05), a decrease in LV-ESV from 214 ± 97 to 179 ± 88 ml (P <0.001), an improvement in LV-EF from 18% ± 4% to 28% ± 7% (P <0.001) and an increase in mean TDI systolic velocity from 3.4 ± 1.5 to 4.9 ± 2.4 cm/sec (P <0.001). After three months, 27 patients (41%) were echocardiographic responders. Mean MR grade decreased from 2.6 ± 0.8 to 2.1 ± 0.8 (P <0.01) and cardiac output increased from 3.5 ± 1.4 to 5.3 ± 3.1 L/m (P <0.001). The myocardial performance index (or Tei index) improved from 0.94 ± 0.23 to 0.62 ± 0.27 (P <0.001). Structural remodeling was shown by a reduction

in LV mass from 242 ± 52 to 222 ± 45 g (P <0.001) and an improvement in end-diastolic and end-systolic sphericity indices from 1.64 ± 0.14 to 1.77 ± 0.17 (P <0.001) and 1.63 ± 0.14 to 1.99 ± 0.22 (P <0.001), respectively.

Twelve-month follow-up data

Clinical data

From 3 months to one year, QRS duration further decreased from 135 ± 21 to 127 ± 20 ms (P = NS), four patients (5%) were in NYHA class III, and the 6MWD further increased from 283 ± 60 to 370 ± 107 m (P <0.001).

Echocardiographic data

As shown in Table 1, further volumetric remodeling was evidenced by a decrease in LV-EDV from 248 ± 120 to 217 ± 110 ml (P <0.001), a decrease in LV-ESV from 179 ± 88 to 158 ± 86 ml (P <0.001). After one year, 50 patients (76%) were echocardiographic responders. Mean MR grade decreased further from 2.1 ± 0.8 to 1.9 ± 0.8 (P <0.05). No further improvements in cardiac output, the myocardial performance index, and end-diastolic and end-systolic sphericity indices were seen. Extended structural Remodeling was shown by a further reduction in LV mass from 222 ± 45 to 206 ± 50 g (P <0.001).

Comparison between responders and non-responders

After one year, 50 patients (76%) were echocardiographic responders. Differences between responders and non-responders are listed in Table 2. Echocardiographic responders had a marked reduction in LV mass from 240 ± 50 to 210 ± 38 and 186 ± 37 g after 3 months and one year, respectively. Also, a significant improvement in the end-diastolic and end-systolic sphericity indices was seen. In contrast, echocardiographic non-responders had an increase in LV mass (from 248 ± 59 g to 258 ± 54 g and to 269 ± 60 g, respectively, all P <0.05) and a trend towards an increase in end-diastolic (1.63 ± 0.15 to 1.67 ± 0.20 and to 1.67 ± 0.21, respectively) and end-systolic (from 1.67 ± 0.13 to 1.72 ± 0.20 and to 1.77 ± 0.20, respectively) sphericity indices.

Table 1. Demographic, Clinical and Echocardiographic Characteristics at Baseline, Three Months, and One Year after Cardiac Resynchronization Therapy

Parameter	Patient population (n = 66)		
	Baseline	**3- months**	**One year**
Clinical data			
Age, (years)	59 ± 11	–	–
Male gender, n (%)	45 (68)		
NYHA class, n (%)			
I	0 (0)	22 (33)†	27 (41)
II	0 (0)	39 (59)†	35 (53)
III	63 (95)	5 (8)†	4 (6)
IV	3 (5)	0 (0)	0 (0)
6MWD, (meters)	216 ± 39	283 ± 60†	370 ± 107‡
QRS duration, (ms)	168 ± 26	135 ± 21†	127 ± 20
Ischemic HF etiology, n (%)	27 (41)	–	–
Medications, n (%)			
Amiodarone	22 (33)	22 (33)	22 (33)
Beta-blockers	50 (76)	53 (80)	53 (80)
ACE-inhibitors	61 (92)	61 (92)	61 (92)
Diuretics	63 (95)	63 (95)	63 (95)
Digitalis	21 (32)	18 (27)	18 (27)
Echocardiographic data			
LV-EDV, (ml)	260 ± 113	248 ± 120*	217 ± 110‡
LV-ESV, (ml)	214 ± 97	179 ± 88†	158 ± 86‡
LV-EF, (%)	18 ± 4	28 ± 7†	27 ± 7
LV-mass, (g)	242 ± 52	222 ± 45†	206 ± 50‡
SWT, (mm)	10.3 ± 0.3≠	9.9 ± 0.2*≠	9.9 ± 0.3≠
LWT, (mm)	10.9 ± 0.2	10.2 ± 0.2*	10.2 ± 0.2
LV-EDSI	1.64 ± 0.14	1.77 ± 0.17†	1.79 ± 0.22
LV-ESSI	1.63 ± 0.14	1.99 ± 0.22†	1.94 ± 0.25
MR grade, n (%)			
0	1 (2)	1 (2)	1 (2)
1	2 (3)	12 (18)*	15 (23)
2	20 (30)	38 (57)*	38 (57)
3	35 (53)	11 (17)†	8 (12)
4	8 (12)	4 (6)	4 (6)
MPI index	0.94 ± 0.23	0.62 ± 0.27†	0.66 ± 0.36
Cardiac output (L/m)	3.5 ± 1.4	5.3 ± 3.1†	4.8 ± 2.7‡
LSD, (ms)	74 ± 44	30 ± 23†	34 ± 29
Mean Sm, (cm/s)	3.4 ± 1.5	4.9 ± 2.4†	5.3 ± 2.9
Septal Sm, (cm/s)	2.8 ± 1.4≠	5.4 ± 2.5†≠	5.8 ± 2.7≠
Lateral Sm, (cm/s)	4.1 ± 1.5	4.4 ± 1.9	4.9 ± 2.5

*P <0.05 vs. Baseline; † P <0.001 vs. Baseline; #P <0.05 vs. 3 months; ‡ P <0.001 vs. 3 months, ≠P<0.01 vs. lateral wall
6MWD = six-minute walk distance; ACE = angiotensin converting enzyme; HF = heart failure; ; LV-EDSI = LV end-diastolic sphericity index; LV-ESSI = LV end-systolic sphericity index; LV-EDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; LV-ESV = left ventricular end-systolic volume; LWT = lateral wall thickness; MPI = myocardial performance index; MR = mitral valve regurgitation; NYHA = New York Heart Association classification; Sm = TDI peak velocity; SWT = septal wall thickness; TDI = tissue Doppler imaging

Table 2. Comparison of Clinical, Electrocardiographic, and Echocardiographic Characteristics Between One-Year Echocardiographic Responders And Non-responders After Cardiac Resynchronization Therapy

Parameter	Responders (n = 50)			Non-responders (n = 16)		
	Baseline	3- months	One year	Baseline	3- months	One year
Clinical data						
Age, (years)	59 ± 10	-	-	57 ± 12	-	-
Male gender, n (%)	34 (68)	-	-	11 (69)		
NYHA class, n (%)						
I	0 (0)	20 (40)†	27 (54)	0 (0)	2 (13)	0 (0)
II	0 (0)	30 (60)†	23 (46)	0 (0)	9 (56)†	12 (76)
III	49 (98)	0 (0) †	0 (0)	14 (88)	5 (31)†	4 (24)
IV	1 (2)	0 (0)	0 (0)	2 (12)	0 (0)	0 (0)
6MWD, (meters)	217 ± 42	297 ± 56†§	405 ± 81‡§	212 ± 30	239 ± 48	259 ± 106
QRS duration, (ms)	168 ± 26	133 ± 21†	125 ± 20	168 ± 25	140 ± 21†	135 ± 20
Ischemic HF etiology, n (%)	18 (36)	-	-	9 (56)	-	-
Medications, n (%)						
Amiodarone	17 (34)	17 (34)	17 (34)	5 (31)	5 (31)	5 (31)
Beta-blockers	38 (76)	41 (82)	41 (82)	12 (75)	12 (75)	12 (75)
ACE-inhibitors	46 (92)	46 (92)	46 (92)	15 (94)	15 (94)	15 (94)
Diuretics	48 (96)	48 (96)	48 (96)	15 (94)	15 (94)	15 (94)
Digitalis	13 (26)	10 (20)	10 (20)	8 (50)	8 (50)	8 (50)
Echocardiographic data						
LV-EDV, (ml)	256 ± 114	241 ± 120†	199 ± 98‡#	271 ± 111	273 ± 120	274 ± 129
LV-ESV, (ml)	210 ± 98	166 ± 79†#	137 ± 64‡§	225 ± 98	220 ± 103	224 ± 110
LV-EF, (%)	18 ± 4	30 ± 6†§	31 ± 5.0§	18 ± 4	21 ± 6*	19 ± 6
LV-mass, (g)	240 ± 50	210 ± 38†§	186 ± 37‡§	248 ± 59	258 ± 54*	269 ± 60#
SWT, (mm)	10.9 ± 0.3≠	10.1 ± 0.3†§	9.8 ± 0.2†§	8.4 ± 0.3≠	9.4 ± 0.4*≠	10.3 ± 0.3≠
LWT, (mm)	11.3 ± 0.2	10.2 ± 0.2†§	9.8 ± 0.2†§	9.5 ± 0.4	10.4 ± 0.3*	11.3 ± 0.3
LV-EDSI	1.64 ± 0.14	1.80 ± 0.14†#	1.82 ± 0.20#	1.63 ± 0.15	1.67 ± 0.20	1.67 ± 0.21
LV-ESSI	1.62 ± 0.14	2.00 ± 0.19†#	1.99 ± 0.24#	1.67 ± 0.13	1.72 ± 0.20	1.77 ± 0.20
MR grade, n (%)						
0	1 (2)	2 (4)	2 (4)	0 (0)	0 (0)	0 (0)
1	2 (4)	11 (22)*	15 (30)	0 (0)	0 (0)	0 (0)
2	15 (30)	30 (60)†	28 (56)	5 (31)	8 (50)	8 (50)
3	29 (58)	7 (14)†	5 (10)	6 (38)	8 (50)	8 (50)
4	3 (6)	0(0)	0 (0)	5 (31)	0 (0)	0 (0)
MPI	0.94 ± 0.17	0.55 ± 0.24†§	0.44 ± 0.31‡§	0.97 ± 0.36	0.85 ± 0.26	1.28 ± 0.68
Cardiac output (L/m)	3.6 ± 1.4	5.6 ± 1.8†§	5.4 ± 2.4§	3.5 ± 1.2	3.9 ± 1.8	3.7 ± 2.7
LSD, (ms)	79 ± 46	26 ± 18†§	23 ± 20	59 ± 34	44 ± 30	53 ± 31
Mean Sm, (cm/s)	3.5 ± 1.5	5.4 ± 2.5†§	5.9 ± 2.9#§	3.2 ± 1.2	3.5 ± 1.4	3.3 ± 1.6
Septal Sm, (cm/s)	2.9 ± 1.4≠	6.2 ± 2.2†≠	6.4 ± 2.8≠	2.3 ± 1.2≠	2.5 ± 1.4≠	2.6 ± 1.6≠
Lateral Sm, (cm/s)	4.1 ± 1.5	4.5 ± 2.2*	5.4 ± 2.7†	4.1 ± 1.3	4.5 ± 1.5*	4.0 ± 1.5

*P <0.05 vs. Baseline; † P <0.001 vs. Baseline; #P <0.05 vs. 3 months; ‡ P <0.001 vs. 3 months; §P <0.05 vs. Non-responders; ≠P<0.01 vs. lateral wall. Abbreviations as in Table 1

Correlation between reverse of structural and volumetric remodeling

As shown in Figure 1, there was a significant correlation between the relative reduction in LV-ESV and LV mass at three months (r^2 = 0.32, P <0.01) and at one year (r^2 = 0.44, P <0.001). From the linear regression formula, early structural reverse remodeling can be defined as >10% reduction in LV mass. Whereas, at one year after CRT a 15% reduction in LV mass, equals to 15% reduction in LV-ESV.

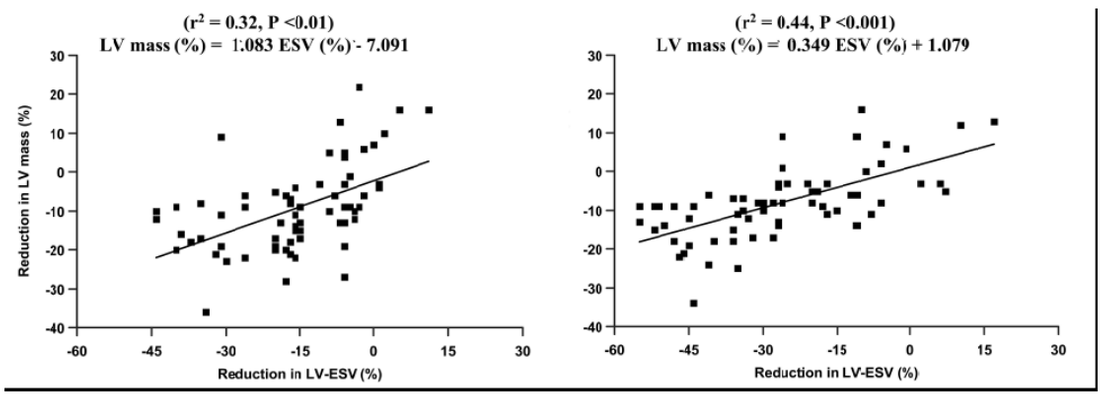


Figure 1: Scatter plots linear regression analysis showing the correlation between the relative reduction in left ventricular end-systolic volume and left ventricular mass at three months (left) and at one-year [19] after cardiac resynchronization therapy.

Correlation between lateral-to-septal delay and regression of LV mass

Echocardiographic responders had more reduction in LSD (79 ± 46 ms vs. 26 ± 18 ms, P <0.001) compared to non-responders (59 ± 34 ms vs. 44 ± 30 ms, P =NS). Moreover, linear regression analysis showed a significant correlation between reductions in LSD and decrease in LV mass (r = 0.53, P <0.05), increase in septal Sm (r = 0.59, P <0.01), and the regional wall symmetry defined as lateral wall thickness/septal thickness ratio (r = 0.55, P <0.05).

DISCUSSION

In agreement with the major CRT trials [1, 20, 21], the majority of patients in this study benefited from CRT implantation. Three months after CRT, volumetric LV reverse remodeling (defined as a reduction in LV-ESV >15%) or more precisely LV unloading had taken place in 41% of patients, evidenced by reductions in LV volumes and improvement in LV-EF. At 12 months after CRT, signs of volumetric LV reverse remodeling became more pronounced, and a new and significant proportion of 35% of patients became echocardiographic responders. This confirms the concept that LV reverse remodeling after CRT is time-dependent.[22] In the present study, we sought to assess the long-term effects of CRT on LV structure and geometry alongside with LV volumetric changes. We found that global and regional structural LV reverse remodeling was evident as early as three months after CRT and became more pronounced at 12 months follow-up. This structural LV reverse remodeling paralleled the improvement in volumetric LV reverse remodeling. Structural LV reverse remodeling was evident by a reduction in LV mass and improvements in end-diastolic and end-systolic sphericity indices. These findings confirm previous short-term results of

structural LV reverse remodeling with LV mass reduction after CRT.[7, 8] Moreover, we found that echocardiographic responders had more favorable structural and functional LV reverse remodeling with more progressive reduction in LV mass and improvement in LV function as evident by improvement in the global myocardial performance index (Tei index) and cardiac output. In contrast, non-responders did not exhibit any signs of structural LV reverse remodeling parallel with failure of volumetric reduction, but rather progressive increase in LV mass and sphericity indices. Another finding in the present study is the differential regression in lateral wall hypertrophy, which is related to the degree of reduction of the LSD on TDI.

Comparison to previous studies

Studies that reported on changes in LV mass and geometry after CRT are scarce. In a report by Saxon et al. [10], neither a reduction in LV mass nor sphericity indices was seen 3 months after CRT. In the MIRACLE trial, a significant 3% to 4% reduction in LV mass was seen after, respectively, 3 and 6 months CRT. In contrast, in the control group (CRT device turned off) LV mass increased 10% after six months CRT.[9] Moreover, our findings confirm the long term structural changes reported in the extension of the MIRACLE trial.[9] In a recent report by Zhang et al. [7], 8% reduction in LV mass was reported 3 to 6 months after CRT. Echocardiographic responders had a significant reduction in LV mass by 15%, whereas non-responders demonstrated an increase in LV mass.[7] Of note, in all studies except the MIRACLE extension, only short-term (3 to 6 months) results were reported. The data on short-term reduction in LV mass reported by Zhang et al. [7] are very similar to those reported by us. In the present study, the relation between change in LV structure (true reverse remodeling) and volume up to one year after CRT was investigated by serial echocardiographic examinations. In echocardiographic responders, both LV volumetric and structural changes at one year were more significant than those observed at 3 months after CRT. Moreover, in the present study the relation between improved LSD and reduction in LV mass and regional symmetry of wall thickness was shown.

Cardiac reverse remodeling patho-physiological and clinical implications

Cardiac remodeling is a process that involves micro- and macroscopic structural LV changes resulting in progressive loss of cardiac function, cardiac dilatation, and hypertrophy particularly in patients has intra-ventricular conduction abnormalities, most commonly left bundle branch block. In such patients the electrical activation wave front takes place in a U-shaped pattern with septal activation first and postero-lateral activation last. This pattern of ventricular activation has great impact on the progression of HF and cardiac remodeling.[23] The early activated septum contracts against low stress and its force is dissipated in generating sufficient energy to open the aortic valve and at the same time it stretches the non-contracting later activated LV parts.[24-26] This energy waste during the early ejection period adds to increased myocardial energy consumption in dilated LVs.[27, 28] The late activated postero-lateral wall is exposed to an increased load and wall stress that increases myocardial energy consumption further. By these mechanisms, myocardial cellular integrity is further disrupted, initiating a vicious circle of LV

remodeling. This substantial role of increased regional mechanical stress in induction of myocardial cellular protein dysregulation has been proven experimentally.[23, 29] In addition chronic overload and wall stress may result in myocellular hypertrophy [30], which eventually ends by programmed cell death (apoptosis).[31] Increased LV mass is a well known independent risk factor for cardiac events.[32] The potential mechanisms proposed for CRT success are mainly related to optimized diastolic LV filling, more synchronized electrical and mechanical coupling hence myocardial performance, and reduced MR. [3-5] The sequelae of these changes are cardiac unloading, decreased myocardial wall stress, and decreased myocardial energy demand. In the present study CRT-induced substantial regression of LV hypertrophy was shown and hence breaks of the aforementioned vicious circle of end-stage HF, potentially contributing to the mortality benefit seen after CRT.[1, 2] Moreover, in the present study, the differential regression of asymmetric hypertrophy of the most delayed lateral wall that is maintained over 12 months after CRT finding may reflect redistribution of the work load between the earliest and latest activated sites. The latter finding that was present only in echocardiographic responders may reflect one of the beneficial mechanisms of CRT. On the other hand, echocardiographic non-responders did not show structural LV reverse remodeling parallel with failure of volumetric reduction, but rather progressive increase in LV mass, wall asymmetry and sphericity indices. This in turn, reflects the progressive nature of HF.

Study limitations

The study is an observational non-comparative and single centre series, which included a rather small number of patients as compared to major randomized trials. However, the present study comprised more CRT patients than the other published single centre series on structural changes after CRT.[7-10]

CONCLUSIONS

CRT results not only in volumetric improvement but also in true structural LV reverse remodeling, evidenced by progressive reduction in LV mass and restoration of regional wall symmetry. The prognostic relevance of these findings should be subject to further studies.

REFERENCES

1. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH: **Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review**. *Jama* 2007, **297**(22):2502-2514.
2. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ: **Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials**. *Eur Heart J* 2006, **27**(22):2682-2688.
3. Nishimura RA, Hayes DL, Holmes DR, Jr., Tajik AJ: **Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study**. *J Am Coll Cardiol* 1995, **25**(2):281-288.
4. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R *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.
5. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B, Nevo E: **Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay**. *Circulation* 1999, **99**(12):1567-1573.
6. 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**(11):1580-1586.
7. Zhang Q, Fung JW, Auricchio A, Chan JY, Kum LC, Wu LW, Yu CM: **Differential change in left ventricular mass and regional wall thickness after cardiac resynchronization therapy for heart failure**. *Eur Heart J* 2006, **27**(12):1423-1430.
8. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M *et al*: **Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure**. *Circulation* 2003, **107**(15):1985-1990.
9. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E: **Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE)**. *Circulation* 2006, **113**(2):266-272.
10. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E: **Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling**. *Circulation* 2002, **105**(11):1304-1310.
11. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A *et al*: **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**(11):1115-1140.
12. Provenier F, Jordaens L: **Evaluation of six minute walking test in patients with single chamber rate responsive pacemakers**. *Br Heart J* 1994, **72**(2):192-196.
13. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR *et al*: **ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography)**. *J Am Coll Cardiol* 2003, **42**(5):954-970.
14. 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**(2):167-184.
15. Reichek N, Helak J, Plappert T, Sutton MS, Weber KT: **Anatomic validation of left ventricular mass estimates from clinical two-dimensional echocardiography: initial results**. *Circulation* 1983, **67**(2):348-352.
16. Lowes BD, Gill EA, Abraham WT, Larrain JR, Robertson AD, Bristow MR, Gilbert EM: **Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure**. *Am J Cardiol* 1999, **83**(8):1201-1205.
17. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP, Jr.: **Color Doppler assessment of mitral regurgitation with orthogonal planes**. *Circulation* 1987, **75**(1):175-183.
18. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA: **Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures**. *J Am Coll Cardiol* 1997, **30**(6):1527-1533.
19. Hillis GS, Moller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, Reeder GS, Oh JK: **Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction**. *J Am Coll Cardiol* 2004, **43**(3):360-367.
20. 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**(15):1539-1549.
21. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL *et al*: **Cardiac resynchronization in chronic heart failure**. *N Engl J Med* 2002, **346**(24):1845-1853.
22. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR *et al*: **Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure**. *Circulation* 2002, **105**(4):438-445.
23. Spragg DD, Kass DA: **Pathobiology of left ventricular dyssynchrony and resynchronization**. *Prog Cardiovasc Dis* 2006, **49**(1):26-41.
24. Prinzen FW, Augustijn CH, Arts T, Allessie MA, Reneman RS: **Redistribution of myocardial fiber strain and blood flow by asynchronous activation**. *Am J Physiol* 1990, **259**(2 Pt 2):H300-308.

25. Prinzen FW, Cheriex EC, Delhaas T, van Oosterhout MF, Arts T, Wellens HJ, Reneman RS: **Asymmetric thickness of the left ventricular wall resulting from asynchronous electric activation: a study in dogs with ventricular pacing and in patients with left bundle branch block**. *Am Heart J* 1995, **130**(5):1045-1053.
26. Prinzen FW, Peschar M: **Relation between the pacing induced sequence of activation and left ventricular pump function in animals**. *Pacing Clin Electrophysiol* 2002, **25**(4 Pt 1):484-498.
27. 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**(25):3053-3059.
28. Curry CW, Nelson GS, Wyman BT, Declerck J, Talbot M, Berger RD, McVeigh ER, Kass DA: **Mechanical dyssynchrony in dilated cardiomyopathy with intraventricular conduction delay as depicted by 3D tagged magnetic resonance imaging**. *Circulation* 2000, **101**(1):E2.
29. Spragg DD, Leclercq C, Loghmani M, Faris OP, Tunin RS, DiSilvestre D, McVeigh ER, Tomaselli GF, Kass DA: **Regional alterations in protein expression in the dyssynchronous failing heart**. *Circulation* 2003, **108**(8):929-932.
30. Sadoshima J, Izumo S: **Molecular characterization of angiotensin II--induced hypertrophy of cardiac myocytes and hyperplasia of cardiac fibroblasts. Critical role of the AT1 receptor subtype**. *Circ Res* 1993, **73**(3):413-423.
31. Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, Schmidt U, Semigran MJ, Dec GW, Khaw BA: **Apoptosis in myocytes in end-stage heart failure**. *N Engl J Med* 1996, **335**(16):1182-1189.
32. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: **Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study**. *N Engl J Med* 1990, **322**(22):1561-1566.

Chapter 5

Effects of cardiac resynchronization therapy on left atrial size and incidence of atrial fibrillation in heart failure patients with implantable defibrillators

Dominic A.M.J. Theuns[1], Osama I.I. Soliman[1,2], Maximo Rivero-Ayerza[1], Emile R. Jessurun[1], Marcel L. Geleijnse[1], Folkert J. ten Cate[1],Luc J. Jordaens[1].

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt

Submitted for publication

ABSTRACT

Introduction: Cardiac resynchronization therapy (CRT) is beneficial for patients with heart failure (HF). The mechanism of CRT benefit comprised of an improved left ventricular (LV) systolic function and reverse LV remodeling. The effect of CRT on left atrial (LA) remodeling is unknown. Accordingly, the purpose of this study was to evaluate LA remodeling and the incidence of atrial fibrillation (AF) after 3 months of CRT.

Methods and Results: Eighty-three consecutive patients with HF (71% NYHA III), LV ejection fraction (LVEF) <35%, and a QRS duration >120 ms were included. Clinical parameters, LA and LV dimensions and volumes, and LVEF were assessed at baseline and after 3 to 6 months of CRT. The presence of AF was determined by use of ECG's, monitoring, and stored electrograms of the defibrillator. At baseline 35% of patients had a history of AF. NYHA class, six-minute walk distance, and LVEF improved significantly after CRT. LV end-diastolic and end-systolic volumes decreased from 228 ± 84 to 206 ± 86 ml, and from 181 ± 66 to 146 ± 66 ml, respectively ($p < 0.001$). Significant reduction in mitral regurgitation was observed. LA diameter and volume decreased from 46 ± 7 to 42 ± 7 mm and from 67 ± 21 to 57 ± 19 ml, respectively ($p < 0.001$). During follow-up, 28% of patients had documented episodes of AF.

Conclusions: Three months of CRT resulted in significant LA and LV reverse remodeling. Despite the remodeling effects, the proportion of patients with AF was not significantly reduced.

INTRODUCTION

Cardiac resynchronization therapy with defibrillation (CRT-D) has shown to improve symptoms, reduce hospitalizations, and reduce mortality in patients with medically refractory heart failure (HF).[1, 2] The proposed mechanisms of the benefit of CRT include improved synchronous left ventricular (LV) contraction, a decrease in mitral regurgitation, and reverse LV remodeling.[3, 4] Recent data suggest that CRT is also associated with left atrial (LA) remodeling.[5] Thus, CRT may have a favorable effect on the presence of atrial fibrillation (AF). This issue is clinically important as AF is common in patients with heart failure, and its prevalence is dependent on the severity of the disease.[6, 7] Furthermore, in patients treated with an implantable cardioverter-defibrillator (ICD), AF can trigger the device to deliver therapy despite the absence of ventricular tachyarrhythmias. Accordingly, the objective of this study was to evaluate the effect of CRT on LA dimensions and the incidence of AF.

METHODS

Study population and device description

The study population consisted of 83 consecutive patients with symptomatic HF, scheduled for implantation of a CRT-D. The following selection criteria for CRT were applied: symptomatic HF, LV ejection fraction (LVEF) ≤ 35%, inter- or intraventricular conduction delay (QRS duration ≥ 120 ms), and LV end-diastolic diameter > 55 mm. The patients were eligible for ICD implantation according to the international guidelines.[8] The implantation method has been previously described in detail.[9] The implanted devices were manufactured by Guidant (Renewal IV; Guidant Inc, St Paul, MN, USA), Medtronic (InSync 7279 and 7298; Medtronic Inc., Minneapolis, MN, USA), and St Jude Medical (Atlas HF and Epic HF; St Jude Medical, Sylmar, CA, USA). ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation. For all patients, the respective arrhythmia discrimination algorithms were activated immediately after ICD implantation.

Echocardiographic evaluation

Transthoracic echocardiography was performed at baseline and 3 to 6 months after implantation. Patients were imaged in the left lateral decubitus position with a commercially available system (Sonos 7500 ultrasound system, Philips, Best, The Netherlands). Standard two-dimensional and colour Doppler data were stored in cineloop format. Quantification of LV dimensions and volumes was performed according to the guidelines.[10] LV internal dimensions (end-systolic and end-diastolic) were determined from the parasternal short axis view at the level of the papillary muscle. LV volumes (end-systolic, end-diastolic) and LV ejection fraction were derived from the apical 2-chamber (A2CH) and apical 4-chamber (A4CH) images using the Simpson's rule. The degree of mitral regurgitation (grade I – IV) was assessed as the mid-systolic percentage jet area relative to LA area in the A4CH view.[11]

Left atrium volume measurement

The following measures were taken to assess the LA volume (LAV): LA area (A1) by manual tracing of the LA endocardial border from a A4CH view. The inferior border of the LA area was a straight line connecting both mitral leaflet base attachment points. The atrial appendage and pulmonary veins were excluded when visualized. The LA area (A2) was assessed by manual tracing at A2CH view. LA long axis (L) was defined as the distance of the perpendicular line measured from the middle of the plane of the mitral annulus to the superior aspect of LA in both apical views and the shortest was used.[12] LAV can be estimated using the formula: Volume = 0.85 X $A1_{A4CH}$ X $A2_{A2CH}$ / L. A physician unaware of the clinical data and the other echocardiographic study did all echocardiographic measurements.

Clinical evaluation and data selection

Patients were evaluated clinically at baseline and after 3 to 6 months of CRT. A surface ECG was obtained to establish QRS morphology and duration. HF symptoms were classified according to the NYHA score. Exercise capacity was determined by using the six-minute hall walk test. A patient was considered a clinical responder when an improvement of ≥1 NYHA class and/or when an increase in exercise capacity (> 25% increase in six-minute walk distance) was noted and an echocardiographic responder when a >15% reduction in LV end-systolic volume was noted. The detection of AF relied on ECGs recorded during outpatient clinic visits, monitoring during hospital admission, and interrogation of the device at every follow-up visit (at 3-monthly intervals) or visit prompted by ICD therapy. Two independent researchers reviewed all stored data of tachyarrhythmia episodes. In case of disagreement between the 2 reviewers about the stored electrograms, a third one was consulted and made a decision. As the atrial electrogram was present, the presence of atrio-ventricular dissociation was used to classify a ventricular tachyarrhythmia. Therapy delivered for atrial tachyarrhythmias (including atrial fibrillation, atrial flutter, atrial tachycardia or sinus tachycardia) was defined as inappropriate.

STATISTICAL ANALYSES

Continuous variables were expressed as mean ± SD, if normally distributed, and compared with the Student's *t* test. In case of non-normal distribution of data, the Mann-Whitney U test was used. Categorical data were expressed as percentages and compared with Fisher's exact test. Simultaneous comparisons of > 2 mean values were performed by one-way analysis of variance. A two-tailed P value < 0.05 was considered as significant.

RESULTS

Patient characteristics

The clinical characteristics of the study population are listed in Table 1.

Table 1 Patients' clinical characteristics

Variable	**(N = 83)**
Male gender	80%
Age (years)	61 ± 13
Ischemic heart failure underlying etiology	52%
QRS duration (ms)	168 ± 28
NYHA class	
II	28%
III-IV	72%
Ejection fraction (%)	21 ± 5
Pharmacological treatment	
Amiodarone	33%
β blocker	76%
Digoxin	42%
ACEi/ARB	86%
Diuretic	83%
Lipid-lowering	55%

Data are given as mean ± SD. Categorical data are shown as percentage.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; NYHA = New York Heart Association

According to the selection criteria for CRT, all patients had a prolonged QRS duration 168 ± 28 ms (range 120 to 252 ms), a mean LV end-diastolic diameter 61 ± 7 mm, and mean LVEF 21 ± 5%. The mean NYHA class was 2.7 ± 0.5, the majority of patients was in NYHA class III (71%). Twenty-nine patients (35%) had a documented history of AF; 22 patients had paroxysmal AF and 7 patients had permanent AF. The ICD was indicated as primary prevention in 69 patients (83%) and as secondary prevention in 14 patients (17%). The mean ventricular tachycardia detection cycle length was programmed at 344 ± 23 ms and ventricular fibrillation detection cycle length at 282 ± 16 ms. All included patients had successful ICD placement and appropriate device function at hospital discharge.

Clinical parameters

After 3 months of CRT, the NYHA class significantly decreased from 2.7 ± 0.5 at baseline to 2.2 ± 0.4 ($p < 0.01$) at 3 months' follow-up. The exercise capacity significantly improved, as reflected by the increase in the six minute walk distance from 330 ± 119 m to 395 ± 111 m ($p < 0.001$).

Table 2 Echocardiographic data at baseline and at 3 to 6 months' follow-up

Variable	Baseline	3 to 6 Months' Follow-up	p Value
LV ejection fraction (%)	21 ± 5	30 ± 8	< 0.001
LV end-diastolic diameter (mm)	61 ± 7	55 ± 7	< 0.001
LV end-systolic diameter (mm)	52 ± 7	43 ± 7	< 0.001
Interventricular septal wall thickness (mm)	8.8 ± 1	9.2 ± 0.8	< 0.001
LV posterior wall thickness (mm)	9.6 ± 1.4	8.9 ± 1.1	< 0.001
LV end-diastolic volume (ml)	228 ± 84	206 ± 86	< 0.001
LV end-systolic volume (ml)	181 ± 66	146 ± 66	< 0.001
LA diameter (mm)	46 ± 7	41 ± 7	< 0.001
LA volume (ml)	67 ± 21	57 ± 19	< 0.001

LA = left atrial; LV = left ventricular

Table 3. Echocardiographic data at baseline and after 3 to 6 months of CRT in patients with AF (n=23) and without AF (n=60) during follow-up.

	Patients with AF (n=23)			Patients without AF (n=60)			
Variable	Baseline	3 to 6 Months' Follow-up	p Value	Baseline	3 to 6 Months' Follow-up	p Value	§ p Value
LV-EF, (%)	20 ± 6	29 ± 9	< 0.001	21 ± 5	30 ± 7	< 0.001	NS
LV-EDV, (ml)	247 ± 118	236 ± 129	NS	225 ± 71	195 ± 62	< 0.001	NS
LV-ESV, (ml)	200 ± 93	171 ± 95	< 0.05	178 ± 57	138 ± 51	< 0.001	NS
LV-EDD, (mm)	62 ± 11	55 ± 10	< 0.001	61 ± 6	55 ± 6	< 0.001	NS
LV-ESD, (mm)	53 ± 11	43 ± 9	< 0.001	52 ± 5	44 ± 6	< 0.001	NS
LA diameter (mm)	46 ± 9	42 ± 9	< 0.001	46 ± 6	42 ± 6	< 0.001	NS
LA volume (ml)	71 ± 27	64 ± 23	< 0.05	66 ± 19	55 ± 17	< 0.001	0.08

AF = atrial fibrillation; LA = left atrial; LV = left ventricular; LV-EDD = left ventricular end-diastolic diameter; LV-EDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; LV-ESD = left ventricular end-systolic diameter; LV-ESV =left ventricular end-systolic volume; NS = non significant;
§ Comparison of echocardiographic dimensions and volumes at baseline and 3 months follow-up between patients with and without AF (one-way analysis of variance).

Reverse of LV and LA remodeling

In the entire cohort, there was a significant increase in LVEF compared with baseline (21 ± 5% vs. 30 ± 8%, p < 0.001). In addition, significant reverse volumetric LV remodeling was observed, as evidenced by the decrease in LV diameters and the reduction in LV volumes (Table 2). In line with reverse remodeling of the LV, CRT also resulted in a significant reverse remodeling of the LA at 3 months' follow-up. LA size significantly decreased after 3 months of CRT. LA diameter significantly decreased from 46 ± 7 mm to 41 ±

7 mm ($p < 0.001$), and LAV decreased from 67 ± 21 ml to 57 ± 19 ml ($p < 0.001$). LA reverse remodeling was also associated with a reduction in mitral regurgitation from 1.8 ± 0.8 to 1.5 ± 0.7 ($p < 0.001$).

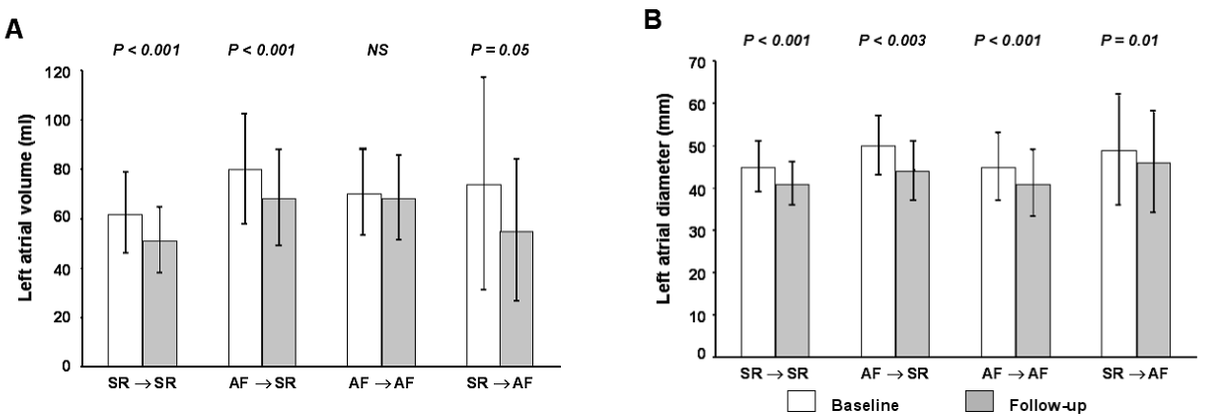


Figure 1. Changes in left atrial volume (*Panel A*) and left atrial diameter (*Panel B*) at 3 to 6 months follow-up according to the documented rhythm at baseline and during follow-up.

Reverse remodeling versus atrial fibrillation

At baseline, 29 patients (35%) had a documented history of AF, including 7 patients with permanent AF. After a follow-up of 12 ± 6 months, 23 patients (28%) had documented episodes of AF. Of these patients, 7 had new-onset AF. In order to assess the reverse remodeling effect by CRT on the presence of AF, we compared dimensions and volumes of LA and LV between patients with and without AF during follow-up (Table 3). In both groups, CRT resulted in significant reverse remodeling of LA and LV. However, LA reverse remodeling is more significant in patients without AF compared to patients with AF during follow-up (Figure 1).

DISCUSSION

This study shows that CRT improved exercise capacity, functional status, LV systolic function, and LV reverse remodeling in heart failure patients. In addition, LA reverse remodeling was observed in this study population. Despite the beneficial remodeling of the LA, CRT was not associated with a favorable effect on the incidence of AF. CRT has consistently proven to improve symptoms, quality-of-life, and exercise tolerance in heart failure patients.[2, 13-15] The proposed mechanisms of the benefit of CRT include improved synchronous LV contraction, a decrease in mitral regurgitation, and reverse LV remodeling.[3, 4, 16]

The present study confirmed the significant decrease in LV diameters and the reduction in LV volumes. Similar to LV reverse remodeling, LA diameter and volume decreased significantly in the present study. This LA remodeling has been described previously in both randomized and nonrandomized studies of CRT.[2, 17-19] The possible mechanism for LA reverse remodeling is the improvement in LA volume overload.[5, 19]

Given the fact that CRT has beneficial remodeling effects, it seems intuitive that CRT might positively influence the development of AF. A small nonrandomized study did demonstrate a reduced incidence of AF by CRT[20], but we could not confirm this. Despite LA remodeling, the proportion of patients with AF was not significantly reduced. In the present study, 35% of patients had a history of AF, and the incidence of AF was 28% during a mean follow-up of 12 months. These data are consistent with the results of the Cardiac Resynchronization in Heart Failure (CARE-HF) trial and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study.[2, 18]

Because patients with heart failure who develop AF have a worse outcome[18], the question arises whether outcome can be improved by CRT. In several studies, the benefits of CRT on cardiac function, functional class, and reverse remodeling remained, despite the development of AF.[18, 19, 21] CRT can induce remodeling of the LA by decreasing the LA size, but CRT probably cannot reverse the structure of interstitial fibrosis.

Study limitations

The study was not designed prospectively to analyze the effect of CRT on the burden of AF during follow-up. The incidence of AF was assessed by ECGs recorded during outpatient clinic visits, monitoring during hospital admission, and interrogation of the device at every follow-up visit (at 3-monthly intervals) or visit prompted by ICD therapy. The results of our study are based on the incidence of AF on per-patient basis, and not on AF burden as such. Further, both persistent and paroxysmal AF were included.

CONCLUSIONS

Cardiac resynchronization therapy results in significant reverse remodeling of the left atrium and ventricle. Despite the beneficial remodeling effects, the incidence of AF is not reduced by cardiac resynchronization.

REFERENCES

1. Abraham W, Fisher A, Smith A, Delurgio D, Leon A, Loh E, Kocovic D, Packer M: **Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure.** *N Engl J Med* 2002, **346**:1845-1853.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG *et al*: **Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure**. *N Engl J Med* 2004, **350**(21):2140-2150.
3. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E: **Effects of long-term biventricular stimulation for resynchronization on echocardiographic measures of remodeling**. *Circulation* 2002, **105**(11):1304-1310.
4. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR *et al*: **Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure**. *Circulation* 2002, **105**(4):438-445.
5. Vural A, Agacdiken A, Ural D, Sahin T, Kozdag G, Kahraman G, Ural E, Akbas H, Suzer K, Komsuoglu B: **Effect of cardiac resynchronization therapy on left atrial reverse remodeling and spontaneous echo contrast**. *Tohoku J Exp Med* 2004, **202**(2):143-153.
6. Carson P, Johnson G, Dunkman W, Fletcher R, Farrell L, Cohn J: **The influence of atrial fibrillation on prognosis in mild to moderate heart failure: The V-HeFT studies**. *Circulation* 1993, **87**:VI102-VI110.
7. Cleland J, Swedberg K, Follath F: **The EuroHeart Failure survey programme - a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis**. *Eur Heart J* 2003, **24**:442-463.
8. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ *et al*: **ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines)**. *Circulation* 2002, **106**(16):2145-2161.
9. Theuns DA, Thornton AS, Klootwijk AP, Scholten MF, Vantrimpont PJ, Balk AH, Jordaens LJ: **Outcome in patients with an ICD incorporating cardiac resynchronisation therapy: Differences between primary and secondary prophylaxis**. *Eur J Heart Fail* 2005.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS *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**(12):1440-1463.
11. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP, Jr.: **Color Doppler assessment of mitral regurgitation with orthogonal planes**. *Circulation* 1987, **75**(1):175-183.
12. Khankirawatana B, Khankirawatana S, Porter T: **How should left atrial size be reported? Comparative assessment with use of multiple echocardiographic methods**. *Am Heart J* 2004, **147**(2):369-374.
13. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M *et al*: **Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay**. *N Engl J Med* 2001, **344**:873-880.
14. Abraham WT, Young J, Leon A, Adler S, Bank A, Hall S, Lieberman R, Bing Liem L, O'Connell J, Schroeder J *et al*: **Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure**. *Circulation* 2004, **110**:2864-2868.
15. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ: **Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials**. *Eur Heart J* 2006, **27**(22):2682-2688.
16. Auricchio A, Spinelli JC, Trautmann SI, Kloss M: **Effect of cardiac resynchronization therapy on ventricular remodeling**. *J Card Fail* 2002, **8**(6 Suppl):S549-555.
17. 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**(15):1539-1549.
18. Hoppe UC, Casares JM, Eiskjaer H, Hagemann A, Cleland J, 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.
19. Kies P, Leclercq C, Bleeker GB, Crocq C, Molhoek SG, Poulain C, van Erven L, Bootsma M, Zeppenfeld K, van der Wall EE *et al*: **Cardiac resynchronization therapy in chronic atrial fibrillation: impact on left atrial size and reversal to sinus rhythm**. *Heart* 2006, **92**:490-494.
20. Fung JW, Yu CM, Chan JY, Chan HC, Yip GW, Zhang Q, Sanderson JE: **Effects of cardiac resynchronization therapy on incidence of atrial fibrillation in patients with poor left ventricular systolic function**. *Am J Cardiol* 2005, **96**(5):728-731.
21. Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, Ceriotti C, Gronda E, Klersy C *et al*: **Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation**. *J Am Coll Cardiol* 2006, **48**(4):734-743.

Chapter 6

Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy

Osama I.I. Soliman[1,2], Dominic A.M.J. Theuns[1], Marcel L. Geleijnse[1], Ashraf M. Anwar[1,2], Attila Nemes[1,3], Kadir Caliskan[1], Wim B. Vletter[1], Luc J. Jordaens MD[1], and Folkert J. ten Cate[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt; [3]Second Department of Medicine and Cardiology Center, University of Szeged, Szeged, Hungary

Europace 2007 Feb; 9(2): 113-118. Epub 2007 Jan 11.

ABSTRACT

Aim: The current study sought to assess if pre-implantation lateral-to-septal delay (LSD) ≥60 msec assessed by spectral pulsed-wave myocardial tissue Doppler imaging (PW-TDI) could predict successful long-term outcome after cardiac resynchronization therapy (CRT).

Methods and results: Sixty patients (72% males, mean age 59 ± 10 years) who were referred for CRT according to ACC/ESC guidelines were enrolled into the study. All patients underwent spectral PW-TDI before and one year after CRT. Two left ventricular (LV) dyssynchrony time intervals, T_O and T_P (time to onset and peak of LV myocardial velocity, respectively) LSD were recorded. LV dyssynchrony was defined as LSD ≥60 msec. Clinical response was defined as an improvement in >1 NYHA class plus improvement in six-minute walking distance (6MWD) ≥25%, echocardiographic response was defined as a ≥15% reduction in LV end-systolic volume (LV-ESV). One-year after CRT, 50 patients (83%) were clinically responders and 47 patients (78%) were echocardiographic responders. Both T_O and T_P LV dyssynchrony indices failed to predict echocardiographic CRT outcome. In addition, there were no significant differences between "synchronous" and "dyssynchronous" patient populations at baseline or follow-up in both clinical (NYHA class and 6MWD) and echocardiographic (LV ejection fraction, LV end-diastolic, and end-systolic) variables.

Conclusion: The great majority of patients referred for CRT benefit clinically from it. However, spectral PW-TDI failed to predict CRT outcome. When PW-TDI dyssynchrony was applied for selection of proper CRT patients, up to 90% of the patients with synchronous LSD that had proven clinical and echocardiographic benefit from CRT would have been denied CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) with biventricular pacing improves functional status and cardiac function in patients with the triad of severe systolic dysfunction, wide QRS complex, and symptomatic heart failure. [1, 2] However, approximately one third of patients are either echocardiographic or clinical non-responders to CRT.[3] Baseline left ventricular (LV) dyssynchrony assessed by tissue Doppler imaging (TDI) has been shown to predict responders to CRT.[4] However, most of these studies have been done with color-coded Doppler TDI [4-7], whereas in real practice most clinicians use spectral PW-TDI to assess LV dyssynchrony. Unfortunately, studies using spectral PW-TDI are limited and not uniform in presentation.[8-11] Therefore, we investigated the role of spectral PW-TDI in the proper selection of our CRT candidates.

METHODS

Study Population

Sixty-nine consecutive heart failure patients referred for CRT were enrolled into the study according to the following criteria: (1) New York Heart Association (NYHA) functional class ≥III despite optimal drug therapy, (2) impaired LV ejection fraction (LV-EF <35%), and (3) wide QRS complex >120 msec. These CRT indications comply with current guidelines.[12, 13] Patients with acute coronary syndromes or coronary revascularization within 6 months before CRT were excluded. At baseline and one-year after CRT implantation all patients underwent a standard two-dimensional echocardiographic examination, including PW-TDI of the LV lateral and septal walls [7, 14] and clinical assessment, including a NYHA class assessment and six-minute walk distance (6MWD) testing.[15, 16]

Echocardiography

All patients were examined using a Sonos 7500 ultrasound system (Philips, Best, The Netherlands) in accordance to the guidelines of the American Society of Echocardiography.[17] LV end-diastolic volume (LV-EDV), LV end-systolic volume (LV-ESV), and LV-EF (by modified bi-plane Simpson rule), were calculated from the apical 4-chamber and 2-chamber views.

Tissue Doppler Imaging (PW-TDI)

In brief, spectral PW-TDI was applied by placing the sample volume in the middle of the basal portions of the LV septal and lateral walls in an apical 4-chamber view. Gain and filter settings were adjusted as needed to eliminate background noises and to allow for a clear tissue signal. PW-TDI velocities were recorded end-expiratory at a sweep speed of 100 mm/s and measured using electronic calipers with EnConcert software (Philips, Best, The Netherlands). The myocardial velocity waves were defined by three positive waves: S1 (the first wave representing the isovolumic contraction phase), S2 (after S1, during mechanical systole), and S3 (during isovolumic relaxation phase).

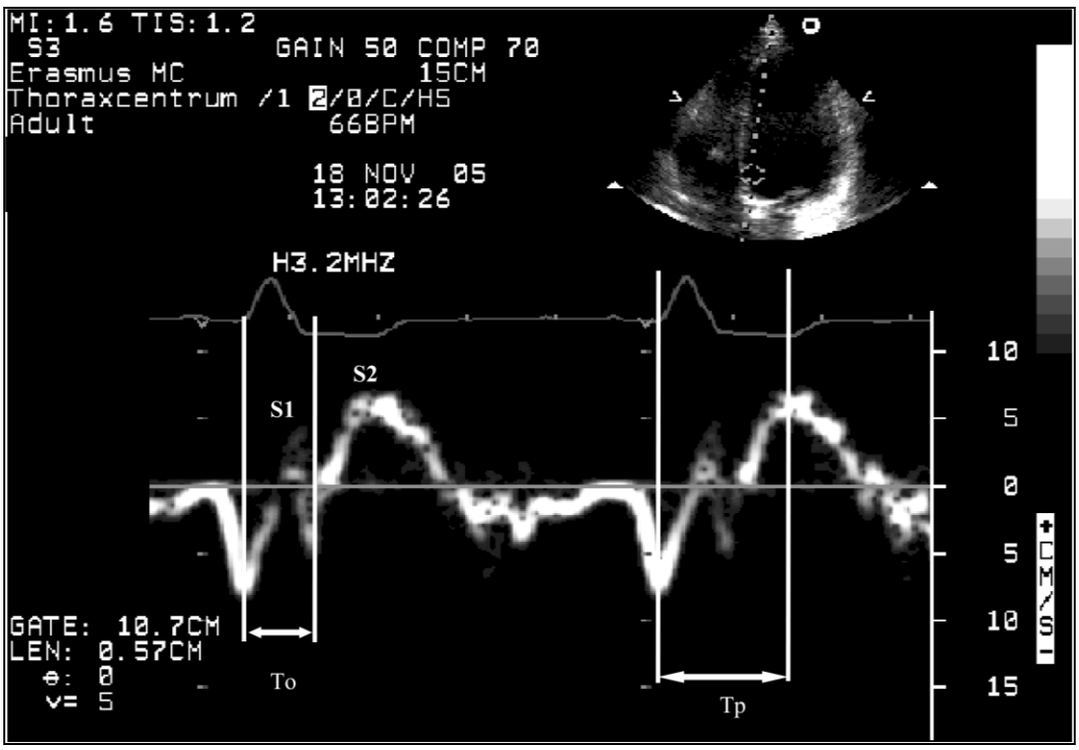


Figure 1. Measurement of time-to-onset and time-to-peak on tissue Doppler imaging: S1and S2 are the myocardial velocity waves during isovolumic contraction phase and during systole respectively, two headed arrow between the two white lines represent time interval from beginning of QRS to onset (To) and to peak of S2 (Tp).

As shown in Figure 1, two time intervals, linked to the start of the QRS complex were recorded: T_O (time-to-onset of S2) and T_P (time-to-peak of S2).[7, 14] These time intervals were rounded of to the nearest 5 msec. Each parameter was measured and averaged over three consecutive beats during sinus rhythm and over 5 consecutive beats for non-sinus rhythm. LV dyssynchrony was defined as a lateral-to-septal delay (LSD) ≥60 msec, in accordance to published data from color TDI.[7, 14, 18] Three, highly experienced, sonographers performed all echocardiograms. All TDI time intervals were measured by one single observer (OIIS). For testing reproducibility of TDI time intervals, a second observer (AMA) who was blinded to the patient's data performed the measurements again on the same data in all patients.

Device implantation

The CRT device-implanting electrophysiologist was blinded to the measured T_O and T_P results. Device implantation was performed preferably with a single left pectoral incision, a left cephalic vein cutdown and a left subclavian puncture. The defibrillation lead was positioned in the right ventricular apex. The left ventricular pacing lead was placed in a tributary of the coronary sinus. A postero-lateral branch was used in 39 patients (65%), a lateral branch in 8 patients (13%), and an antero-lateral branch in 13 patients (22%). Adequate pacing and sensing properties of all leads were tested. All implanted biventricular pacing devices were combined with an internal cardioverter-defibrillator. The lowest effective defibrillation energy was assessed in all patients or a safety major ≥10 J was documented. The implanted devices were

InSync 7272, 7279, and 7298 (Medtronic Inc, Minneapolis, MN, USA), Renewal II (Guidant Inc, St Paul, MN, USA), and Epic HF V-339 and Atlas HF V-341 (St Jude Medical, Sylmar, CA, USA). For all patients, ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation. The atrio-ventricular delay was optimized by 2D echocardiography to provide the longest filling time for completion of the end-diastolic filling flow before left ventricular contraction.

Definition of responders

A patient was considered a clinical responder when at least reduction of 1 NYHA class plus an improvement of ≥25% increase in the 6MWD [19] was noted and an echocardiographic responder when a ≥15% reduction in LV-ESV was noted.

STATISTICAL ANALYSES

Data were expressed as mean ± SD; independent and paired-sample *t* tests were used when appropriate. An alpha level of significance <0.05 was considered significant. All statistics were performed using SPSS (12.0.2) for Windows (Chicago, IL, USA). Bland-Altman method of comparison was used to assess inter-observer variability.[20]

RESULTS

Transvenous implantation of the CRT device was successful in 66 patients (96%), in the remaining three patients the LV lead was surgically implanted. During follow-up, one patient died (due to heart failure exacerbation) at 6 months and three patients underwent heart transplantation. In five patients, PW-TDI measurements could not be performed due to inability to define the systolic S2 wave accurately. These nine patients were excluded from further analysis. So, at one year 60 patients (mean age 59 ± 10 years, 43 males) were considered for analysis of which 50 patients (83%) were clinically responders and 47 patients (78%) were echocardiographic responders. As seen in Table 1, echocardiographic responders and non-responders had comparable baseline clinical and echocardiographic characteristics. During follow-up, echocardiographic responders had a significantly greater improvement in the NYHA class, and the 6MWD compared to non-responders.

Table 1. Baseline and One-Year Follow-Up Clinical and Echocardiographic Data of Echocardiographic Responders versus Non-Responders

	Echo responders (n = 47)		Echo non-responders (n =13)	
	Baseline	Follow-up	Baseline	Follow-up
Age, years	60 ± 11		58 ± 5	
Men, n	33 (70)		10 (77)	
NYHA class	3.0 ± 0.3	1.2 ± 0.4†	3.0 ± 0.4	1.5 ± 0.3†
6MWD, meters	212 ± 36	410 ± 73†	224 ± 26	247 ± 80†‡
QRS, msec	170 ± 27	139 ± 36†	172 ± 31	145 ± 32†
Ischemic cardiomyopathy, n	19 (40)		7 (54)	
Amiodarone, n	12 (26)	12 (26)	7 (54)	7 (54)
Beta-blockers, n	38 (80)	38 (80)	10 (77)	10 (77)
ACE-inhibitors, n	44 (94)	44 (94)	11 (85)	11 (85)
Diuretics, n	44 (94)	44 (94)	11 (85)	11 (85)
Sinus rhythm, n	38 (80)	38 (80)	11 (85)	11 (85)
LSD-Time to onset, msec	78 ± 48	25 ± 18†	65 ± 24	49 ± 33†
LSD-Time to peak, msec	81 ± 48	33 ± 27†	78 ± 48	67 ± 32†‡
LV-EDV, ml	245 ± 84	190 ± 72†	284 ± 113	297± 130‡
LV-ESV, ml	200 ± 72	131 ± 50†	239 ± 99	245 ± 110‡
*Relative change in LV-ESV, %		-34 ± 12		2 ± 8
LV-EF, %	19 ± 4	31 ± 6†	17 ± 3	18 ± 4†
*Relative increase in LV-EF, %		72 ± 44		10 ± 17‡

Values are presented as mean ± SD and values in parenthesis indicate percentages. †P < 0.0001, for follow-up vs. baseline data, ‡p < 0.001 for follow-up responders vs. non-responders. NYHA, New York Heart Association; 6MWD, Six-Minute Walk Distance; LSD = Lateral-to-septal delay; LV-EDV, Left Ventricular End-Diastolic Volume; LV-ESV, Left Ventricular End-Systolic Volume; LV-EF, Left Ventricular Ejection Fraction. *Relative to pre CRT implantation.

Relation of pre-implantation PW-TDI to CRT response

As shown in Table 1 and Figure 2, in the total population CRT significantly reduced the LSD-T_O from 76 ± 44 to 30 ± 24 msec (P <0.001), and LSD-T_P from 80 ± 47 to 40 ± 32 msec (P <0.001). In the echocardiographic responders LSD-T_O reduced from 78 ± 48 to 25 ± 18 msec and LSD-T_P reduced from 81 ± 48 to 33 ± 27 msec (both P <0.0001). Less change were found in the echocardiographic non-responders, in whom LSD-T_O reduced from 65 ± 24 to 49 ± 33 msec, and LSD-T_P reduced from 78 ± 48 to 67 ± 32 msec (both P <0.0001). The study population was classified according to the baseline (pre-CRT) 60 msec LSD cut-off value into synchronous patients (LSD <60msec) and dyssynchronous patients (LSD ≥60msec).

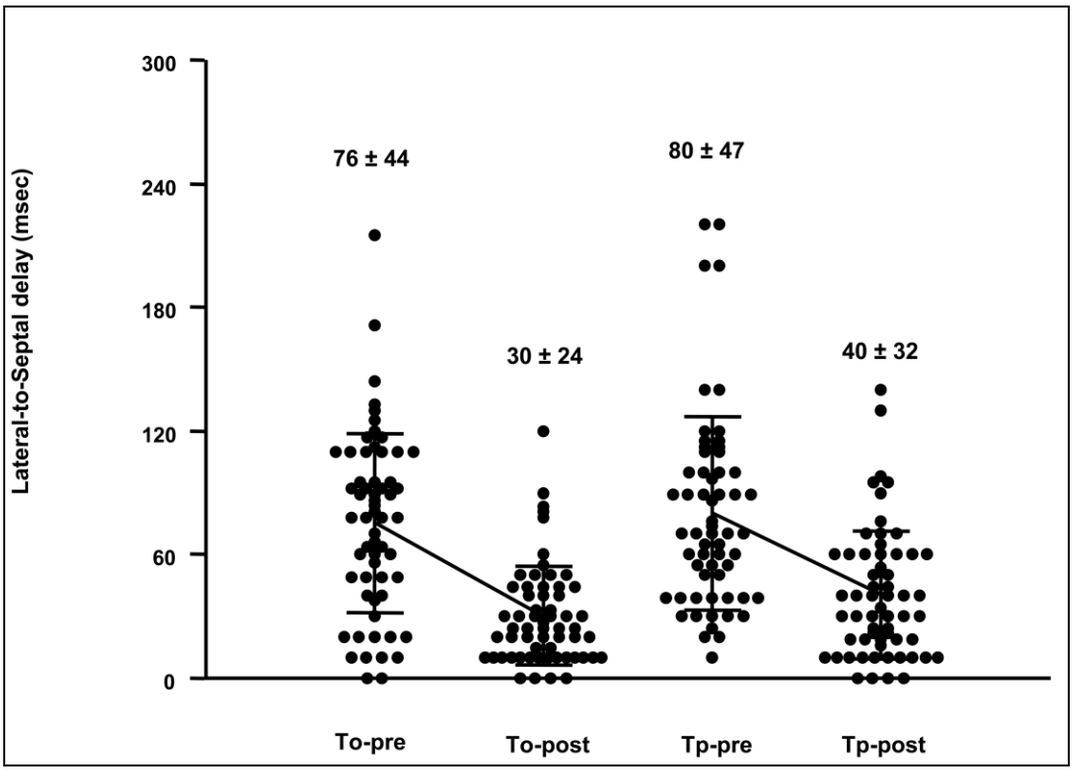


Figure 2. Individual values of pre and post-CRT lateral-septal delay, To = time-to-onset, Tp = time-to-peak, Pre = pre CRT, Post = post CRT implantation in the total population.

Table 2. Baseline and One-Year Follow-Up Clinical and Echocardiographic Data in Synchronous and Dyssynchronous Patients.

		All patients (n = 60)			
	Total population (n = 60)	**T_O <60 msec (n = 20)**	**T_O ≥60 msec (n = 40)**	**T_P <60 msec (n = 21)**	**T_P ≥60 msec (n = 39)**
Age, years	59 ± 10	65 ± 8	57 ± 10	60 ± 10	59 ± 10
Men, n (%)	43 (72)	13 (65)	30 (75)	15 (71)	28 (72)
QRS, msec.	170 ± 27	173 ± 27	168 ± 27	168 ± 25	170 ± 28
Change in - NYHA class	1.6 ± 0.4	1.6 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	1.6 ± 0.5
Change in- 6MWD, meters	160 ± 100	155 ± 81	163 ± 109	162 ± 87	159 ± 107
Change in -LV-EDV, ml	41 ± 42	49 ± 47	36 ± 39	39 ± 47	41 ± 47
Change in -LV-ESV, ml	53 ± 46	66 ± 50	47 ± 43	50 ± 47	55 ± 46
Change in - LV-EF, %	10 ± 7	12 ± 8	9 ± 6	8 ± 5	11 ± 7
Echo responders, n (%)	47 (78)	16 (80)	31 (78)	18 (86)	29 (75)
Clinical responders, n (%)	50 (83)	17 (85)	33 (83)	19 (90)	31 (79)
		Sinus rhythm patients (n = 49)			
	Total population (n =49)	**T_O <60 msec (n = 16)**	**T_O ≥60 msec (n = 33)**	**T_P <60 msec (n = 17)**	**T_P ≥60 msec (n = 32)**
Echo responders, n (%)	38 (78)	12 (75)	26 (79)	13 (76)	25 (78)
Clinical responders, n (%)	45 (92)	14 (88)	31 (94)	15 (88)	30 (94)

Abbreviations as in Table 1. All comparisons between synchronous and dyssynchronous patients non-significant.

As seen in Table 2, for both T_O and T_P assessment there were no significant differences in baseline to follow-up changes in NYHA class, 6MWD testing, LV-EDV, LV-ESV, and LV-EF for patients with and without LV dyssynchrony. Eighteen patients (86%) with LSD-T_P <60 msec and 16 patients (80%) with LSD-T_O <60 msec were echocardiographic responders. Likewise 19 patients (90%) with LSD-T_P <60 msec and 17 patients (85%) with LSD-T_O <60 msec were clinical responders (Table 2).

Reproducibility of TDI measurements: There was a fair inter-observer agreement for baseline T_O (mean difference = -1.2 ± 5.5 msec, 95% limits of agreement = -11.9, 9.6), and T_P (mean difference = -0.3 ± 5.6 msec, 95% limits of agreement = -11.4, 10.9). Likewise, there was a good inter-observer agreement for follow-up T_O (mean difference = 0.3 ± 6.1 msec, 95% limits of agreement = -11.9, 12.4) and T_P (mean difference = -0.2 ± 4.5 msec, 95% limits of agreement = -9.2, 8.9).

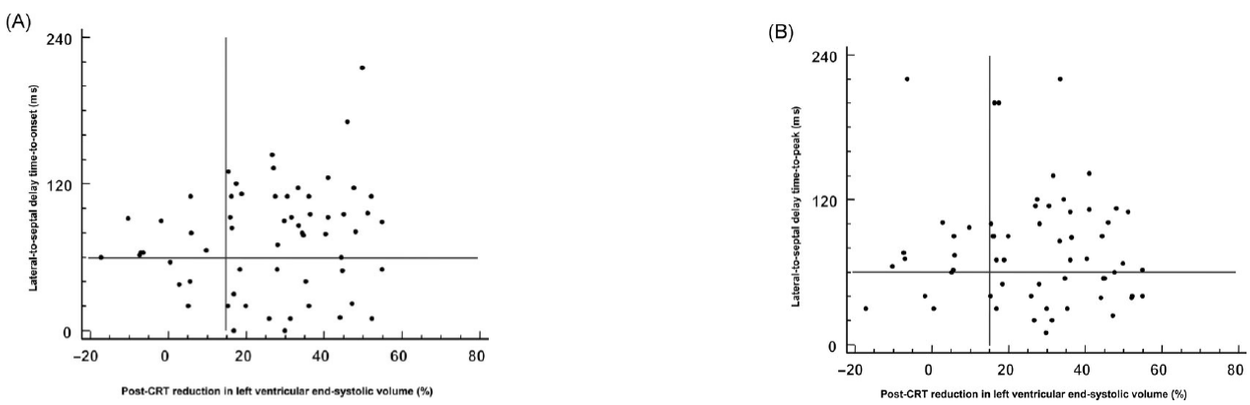


Figure 3. Distribution of individual values of post-CRT changes (% from pre-CRT implantation) in left ventricular end-systolic volume according to pre-CRT time-to-onset (Figure 3A), and time-to-peak lateral-to-septal delay (Figure 3B). The vertical line represents the definition of echocardiographic responders (≥15% reduction in left ventricular end-systolic volume). The horizontal line represents the cut-off value (≥60 msec) of left ventricular mechanical dyssynchrony.

DISCUSSION

In the present study, 60 patients with severe heart failure, impaired LV ejection fraction, and a wide QRS complex underwent CRT according to current guidelines. [12, 13] All patients were assessed with spectral PW-TDI before and one year after CRT. One year after CRT, 50 patients (83%) were clinically responders (reduction of 1 NYHA class plus an improvement of ≥25% increase in the 6MWD) and 47 patients (78%) were echocardiographic responders (≥15% reduction in LV-ESV) (Figure 3). Baseline (pre-CRT) LV dyssynchrony was assessed with spectral PW-TDI and defined as a LSD ≥60 msec.[8, 14] The main finding of our study is that both LSD-T_O (time delay to onset of mechanical LV contraction) and LSD-T_P (time delay to peak of mechanical LV contraction) could not predict changes in functional class, 6MWD testing, LV-EDV, LV-ESV, and LV-EF. Actually, if CRT therapy had only been offered to patients with LV dyssynchrony, 18 patients (86%) with synchronous LSD-T_P and 16 patients (80%) with synchronous LSD-

T_O that demonstrated reverse remodeling and likewise 19 patients (90%) with synchronous LSD-T_P and 17 patients (85%) with synchronous LSD-T_O who clinically benefited from CRT would have been denied CRT.

Reasons for use of spectral PW-TDI in the current study: At present time, evaluation of myocardial tissue velocity can be achieved by either spectral PW-TDI or color-coded TDI. Spectral PW-TDI has a high temporal resolution of 3 to 4 msec (250 to 333 frames per second) and relatively low spatial resolution, whereas color-coded TDI has a somewhat lower temporal resolution of 6 to 10 msec (100-166 frames per second) but higher spatial resolution. Both techniques can assess myocardial velocity and timing of TDI-derived waves of cardiac motion. However, to achieve reproducible data, color-coded TDI necessitates a high (80-100) frame rate, which is not available in most echocardiographic machines. On the other hand, spectral PW-TDI is widely available in nearly every echocardiography laboratory and can be accurately performed by a fairly experienced sonographer. Previous data suggests that LSD derived from color-coded TDI can be used for patient selection for CRT.[7] In the real world spectral PW-derived measurements of LSD are often used instead of color-coded TDI derived measurements for selection of candidates for CRT. Thus, it is necessary to test if these widely available measurements of LSD based on spectral PW-TDI have a predictive value compared to the more established color-coded TDI measurements.

Reasons for failure of spectral PW-TDI to predict CRT outcome: Despite the fact that spectral PW-TDI is a single-dimensional assessment of myocardial motion, its value in evaluation of regional myocardial velocities has been widely accepted.[21] However, in our study PW-TDI failed to predict CRT outcome and this may be caused by many reasons. PW-TDI is prone to angle related errors and does not allow simultaneous timing of regional myocardial motion in one beat with each beat affected by differences in loading conditions, heart rate, and respiration. The respiratory factor was minimized in our study by recording the PW-TDI measurements at a stable end-expiratory phase. Beat-to-beat variability may have played an important role in the included patients with atrial fibrillation. Patients with atrial fibrillation were, however, also not excluded in some other studies [21-23] and exclusion of these patients did not change our results. Another important limitation of PW-TDI is the difficulty in many patients with poor LV function and in particular in patients with ischemic cardiomyopathy, to identify the peak of mechanical contraction. In our study five patients with non-interpretable PW-TDI studies (technical failure) were excluded from analysis. As a result, the inter-observer agreement of LSD-T_P measurements in our study was fair. In addition, because of this known limitation we analyzed also LSD-T_O. As shown in our study, LV dyssynchrony based on LSD-T_O measurements could also not predict outcome after CRT. Another important factor for the negative results in our study may be the inability for PW-TDI lateral-to-septal delay measurements to detect mechanical LV dyssynchrony (physiological failure). LV dyssynchrony is a complex, three-dimensional issue including electromechanical coupling, the pattern of electrical LV activation, the distribution of myocardial fibers, and torsion forces on the cardiac fibers. Although the short time for acquisition and analysis of a two-segment velocity model is very

practical, optimal LV dyssynchrony analysis should include at least more segments analyzed[23] or even a three-dimensional analysis of myocardial velocities and deformation.[6, 24, 25] Moreover, it should be mentioned that even two-dimensional color-coded TDI measurements based on 12 segments failed to predict CRT outcome in a recent publication from the Mayo clinic and correlated less with acute reduction in LV-ESV than strain imaging. [24, 25] Finally, it should be noticed that although timing of LV muscle displacement is important, the extent of (miss) timed muscle displacement is not measured by PW-TDI and may be a crucial factor (a small dyssynchronous muscle area may not necessarily have a great impact on LV-EF).

Comparison to previous studies: In the literature, only five series of patients are reported that underwent spectral PW-TDI before CRT. [8-11, 26] From only one study the predictive value of LSD <60 msec for CRT outcome could be deducted.[8] Although in the latter study PW-TDI results were called positive in terms of prediction of clinical CRT outcome, it should be emphasized that actually only three of the studied patients were clinical non-responders. Other studies only concluded that more dyssynchronous patients had a better short-term CRT outcome, without reporting a practical cut-off LSD value. [9-11, 26] In one of these studies[26] only acute hemodynamic changes were reported and such changes do not necessarily reflect reverse remodeling that needs long-term follow-up. In another study LV-EF was used to define responders [11], whereas we used a reduction in LV-ESV to define responders because this parameter is known to be more predictive of cardiac events.[27] In a recently published series of patients followed-up for only 3 months [23], a multi-segment model was superior to a two-segment model as used in our study. The main purpose of our study was to implement a simple and practical technique that may be used for patient selection for CRT. Since high frame rate needed for color-coded TDI is not available in every ultrasound machine and analysis of multiple segments is time-consuming we tested the clinically most practiced two-segment spectral PW-TDI model for LSD.

CONCLUSIONS

The great majority of patients referred for CRT benefit clinically from it. However, spectral PW-TDI failed to predict CRT outcome. When PW-TDI dyssynchrony was applied for selection of proper CRT patients, up to 90% of the patients with synchronous LSD that clinically benefited from CRT would have been denied CRT. Further studies using other echocardiographic techniques like 3D regional timing of wall motion are necessary to determine the use of ultrasound for the selection of CRT patients.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL *et al*: **Cardiac resynchronization in chronic heart failure**. *N Engl J Med* 2002, **346**(24):1845-1853.
2. Abraham WT, Hayes DL: **Cardiac resynchronization therapy for heart failure**. *Circulation* 2003, **108**(21):2596-2603.
3. Abraham WT: **Cardiac resynchronization therapy: a review of clinical trials and criteria for identifying the appropriate patient**. *Rev Cardiovasc Med* 2003, **4 Suppl 2**:S30-37.
4. Bax JJ, Abraham T, Barold SS, Breithardt OA, Fung JW, Garrigue S, Gorcsan J, 3rd, Hayes DL, Kass DA, Knuuti J *et al*: **Cardiac resynchronization therapy: Part 1--issues before device implantation**. *J Am Coll Cardiol* 2005, **46**(12):2153-2167.
5. Bax JJ, Ansalone G, Breithardt OA, Derumeaux G, Leclercq C, Schalij MJ, Sogaard P, St John Sutton M, Nihoyannopoulos P: **Echocardiographic evaluation of cardiac resynchronization therapy: ready for routine clinical use? A critical appraisal**. *J Am Coll Cardiol* 2004, **44**(1):1-9.
6. Yu CM, Fung JW, Zhang Q, Chan CK, Chan YS, Lin H, Kum LC, Kong SL, Zhang Y, Sanderson JE: **Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy**. *Circulation* 2004, **110**(1):66-73.
7. Bax JJ, Marwick TH, Molhoek SG, Bleeker GB, van Erven L, Boersma E, Steendijk P, van der Wall EE, Schalij MJ: **Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation**. *Am J Cardiol* 2003, **92**(10):1238-1240.
8. Garrigue S, Jais P, Espil G, Labeque JN, Hocini M, Shah DC, Haissaguerre M, Clementy J: **Comparison of chronic biventricular pacing between epicardial and endocardial left ventricular stimulation using Doppler tissue imaging in patients with heart failure**. *Am J Cardiol* 2001, **88**(8):858-862.
9. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M: **Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing**. *J Am Coll Cardiol* 2002, **39**(3):489-499.
10. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Laurenti A, Fedele F, Santini M: **Doppler myocardial imaging in patients with heart failure receiving biventricular pacing treatment**. *Am Heart J* 2001, **142**(5):881-896.
11. Penicka M, Bartunek J, De Bruyne B, Vanderheyden M, Goethals M, De Zutter M, Brugada P, Geelen P: **Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography**. *Circulation* 2004, **109**(8):978-983.
12. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K *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**(12):e154-235.
13. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A *et al*: **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**(11):1115-1140.
14. Bax JJ, Molhoek SG, van Erven L, Voogd PJ, Somer S, Boersma E, Steendijk P, Schalij MJ, Van der Wall EE: **Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy**. *Am J Cardiol* 2003, **91**(1):94-97.
15. Provenier F, Jordaens L: **Evaluation of six minute walking test in patients with single chamber rate responsive pacemakers**. *Br Heart J* 1994, **72**(2):192-196.
16. Olsson LG, Swedberg K, Clark AL, Witte KK, Cleland JG: **Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: a systematic review**. *Eur Heart J* 2005, **26**(8):778-793.
17. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davidson TW, Davis JL, Douglas PS, Gillam LD: **ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography**. *Circulation* 1997, **95**(6):1686-1744.
18. Burri H: **The quest for an optimal left ventricular lead position for cardiac resynchronization therapy**. *Heart Rhythm* 2006, **3**(11):1293-1294.
19. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ: **Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy**. *J Am Coll Cardiol* 2004, **44**(9):1834-1840.
20. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement**. *Lancet* 1986, **1**(8476):307-310.
21. Garrigue S, Bordachar P, Reuter S, Jais P, Haissaguerre M, Clementy J: **Comparison of permanent left ventricular and biventricular pacing in patients with heart failure and chronic atrial fibrillation: a prospective hemodynamic study**. *Card Electrophysiol Rev* 2003, **7**(4):315-324.
22. Garrigue S, Reuter S, Labeque JN, Jais P, Hocini M, Shah DC, Haissaguerre M, Clementy J: **Usefulness of biventricular pacing in patients with congestive heart failure and right bundle branch block**. *Am J Cardiol* 2001, **88**(12):1436-1441, A1438.
23. Jansen AH, Bracke F, van Dantzig JM, Meijer A, Korsten EH, Peels KH, van Hemel NM: **Optimization of pulsed wave tissue Doppler to predict left ventricular reverse remodeling after cardiac resynchronization therapy**. *J Am Soc Echocardiogr* 2006, **19**(2):185-191.

24. Miyazaki C, Cha Y-M, Espinosa R, Bruce CJ, Miller FA, Hayes DL, Redfield MM, Oh JK: **intraventricular dyssynchrony measured by tissue velocity does not change acuetly after cardiac resynchronization therapy at 1-month follow-up.** *J Am Coll Cardiol* 2006, **47**:103A.
25. Miyazaki C, Redfield MM, Oh JK, Espinosa R, Miller FA: **Baseline dyssynchrony derived by strain imaging correlates with the effect of cardiac resynchronization therapy at 1-month follow-up.** *J Am Coll Cardiol* 2006, **47**:102A.
26. Bordachar P, Lafitte S, Reuter S, Sanders P, Jais P, Haissaguerre M, Roudaut R, Garrigue S, Clementy J: **Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing**. *J Am Coll Cardiol* 2004, **44**(11):2157-2165.
27. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moye LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S *et al*: **Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril**. *Circulation* 1994, **89**(1):68-75.

Chapter 7

Baseline predictors of cardiac events after cardiac resynchronization therapy in patients with heart failure secondary to ischemic or non-ischemic etiology

Osama I.I. Soliman[1,2], Dominic A.M.J. Theuns[1], Folkert J. ten Cate[1], Ashraf M. Anwar[1,2] ,Attila Nemes[1,3], Wim B. Vletter[1], Luc J. Jordaens MD[1], and Marcel L. Geleijnse[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt; [3]Second Department of Medicine and Cardiology Center, University of Szeged, Szeged, Hungary

American Journal of Cardiology 2007 Aug; 100 (3): 464-469. Epub 2007 June 13.

ABSTRACT

Aims. To evaluate the value of baseline tissue Doppler imaging (TDI)-derived parameters for event prediction in heart failure (HF) patients secondary to ischemic and non-ischemic etiology who underwent cardiac resynchronization therapy (CRT).

Methods and results. Seventy-four consecutive HF patients (mean age 59 ± 11 years, 52 men) underwent CRT. Baseline clinical parameters included NYHA class; 6-minute walk distance, HF etiology, and diabetes. TDI derived parameters included the lateral and septal E/E' ratios defined as peak early LV filling velocity (E-wave) to TDI-derived peak early diastolic velocity of the mitral annulus (E'-wave). During a median follow-up of 720 days, 21 patients (28%) had cardiac death or hospitalization for HF. These patients had more often an ischemic etiology ($P < 0.05$), diabetes ($P < 0.05$), and restrictive filling ($P < 0.001$), less often LV dyssynchrony ($P < 0.05$), and higher septal and lateral E/E' ratios (both $P < 0.001$). In a multivariable model using a forward selection algorithm only the lateral E/E' ratio remained an independent predictor of cardiac outcome. After 3 months CRT, the TDI-derived systolic mitral annular systolic and diastolic velocities improved significantly in non-ischemic patients both for the septal and lateral side. In contrast, in ischemic patients no significant improvements were seen. Significant improvements were seen in septal and lateral E/E' ratios in both ischemic and non-ischemic patients. However, the improvement in lateral E/E' ratio was significantly less and absolute 3-months E/E' ratios were worse in ischemic patients.

C**onclusions.** The baseline lateral E/E' ratio is an independent predictor for cardiac events in HF patients treated with CRT. The worse clinical outcome in ischemic patients may be due to failure of improvement in LV filling pressures after CRT, evidenced by E/E' ratio.

INTRODUCTION

Several baseline clinical and echocardiographic parameters such as New York Heart Association (NYHA) functional class[1-3], ischemic etiology [3, 4], left ventricular (LV) end-diastolic diameter [4], mitral regurgitation grade [5, 6], restrictive LV filling [7], and right ventricular systolic pressure [8] have been shown to independently predict clinical events after cardiac resynchronization therapy (CRT). The ratio between early LV filling velocity (E-wave) divided by the tissue Doppler imaging (TDI)-derived early diastolic velocity of the mitral annulus (E' wave) has been shown to predict cardiac events in conventionally treated HF patients.[9] Unlike conventional Doppler parameters of LV filling, the E' wave is relatively load-independent.[9] Recently, the predictive value of the septal E/E' ratio was shown in HF patients that underwent CRT.[5] In this study, the authors found that the septal E/E' ratio improved after CRT in patients with non-ischemic etiology but not in patients with ischemic etiology. Unfortunately, the authors did not report the predictive value of baseline septal E/E' ratio in non-ischemic versus ischemic patients. Since many ischemic patients have septal infarction and few lateral infarction [10], it may be that the lateral E/E' ratio is a better indicator for high LV filling pressures in patients with ischemic etiology and thus a better predictor for events. Therefore, the present study investigated the predictive value of the lateral versus septal E/E' ratio for clinical events in HF patients with non-ischemic and ischemic etiology treated with CRT.

METHODS

Study Population

Seventy-four consecutive HF patients referred for CRT were enrolled into the study according to the following criteria: (1) NYHA functional class ≥III despite optimal drug therapy (2) impaired LV ejection fraction <35%, and (3) wide QRS complex >120 msec. These CRT indications comply with current guidelines. [11, 12] Patients with atrial fibrillation, acute coronary syndromes or coronary revascularization within 6 months before CRT were excluded. An informed consent was obtained from all patients and the institutional review board approved the study.

Study Protocol

Two-dimensional echocardiography, including TDI assessment of mitral annular velocity, was done before CRT and after 3 months. Two days after CRT, LV diastolic filling time was optimized. Patients were scheduled for regular clinical follow-up and the CRT device was interrogated to ensure that biventricular pacing was being maintained, at least every 3 months. Primary study endpoints were either documented cardiac-related death (including urgent cardiac transplantation) and / or hospitalization due to HF.

Device implantation

As described previously [13], CRT device implantation was performed preferably with a single left pectoral incision, a left cephalic vein cutdown and a left subclavian puncture. The defibrillation lead was positioned in the right ventricular apex. Transvenous implantation of the CRT device was successful in 71 patients (96%). The LV pacing lead was placed in a tributary of the coronary sinus. A postero-lateral branch was used in 50 patients (68%), a lateral branch in 13 patients (18%), and an antero-lateral branch in 8 patients (11%) of patients. In the remaining 3 patients the LV lead was surgically implanted. Adequate pacing and sensing properties of all leads, and diaphragmatic stimulation with the LV pacing lead were tested. The lowest effective defibrillation energy was assessed and a safety margin of ≥10 J was used. Devices used were InSync 7272, 7279, and 7298 (Medtronic Inc, Minneapolis, MN, USA), Renewal II (Guidant Inc, St Paul, MN, USA), and Epic HF V-339 and Atlas HF V-341 (St Jude Medical, Sylmar, CA, USA). For all patients, ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation. Atrio-ventricular delay was optimized by 2D echocardiography to provide the longest filling time for completion of the end-diastolic filling flow before LV contraction with the highest LV outflow tract velocity timed integral.

Echocardiography

All patients were examined using a Sonos 7500 ultrasound system (Philips, Best, The Netherlands) with a S3 transducer according to the recommendations of the American Society of Echocardiography.[14, 15] LV end-diastolic volume (LV-EDV), LV end-systolic volume (LV-ESV), and LV-EF (by modified bi-plane Simpson rule) were calculated from the apical 4-chamber and 2-chamber views. The degree of mitral regurgitation (grade I-IV) was assessed as the mid-systolic percentage jet area relative to left atrial area in the apical 4-chamber view.[16] From the mitral inflow peak velocity of early (E) and late (A) diastolic filling, E/A ratio, and E-wave deceleration time were measured.[17] Right ventricular peak systolic pressure was derived from the peak tricuspid valve regurgitation velocity and the estimated right atrial pressure.[18]

Tissue Doppler imaging (pulsed-wave-TDI)

In brief, pulsed-wave-TDI was applied by placing the sample volume at the side of the medial and lateral mitral annulus in an apical 4-chamber view.[19] Gain and filter settings were adjusted as needed to eliminate background noises and to allow for a clear tissue signal. Pulsed-wave -TDI velocities were recorded end-expiratory at a sweep speed of 100 mm/s and measured using electronic calipers with software EnConcert (Philips, Best, The Netherlands). The longitudinal velocity of the mitral annular tissue systolic wave (Sm) and the early diastolic wave (E') and the timing of Sm were measured. The mitral septal and lateral annulus E/E' ratio were calculated as previously described.[19, 20] For each patient, the average of 3 measurements was calculated. Diastolic mitral inflow was classified as restrictive when E/A ≥2 or the combination of E/A >1 and <2 and an E-wave deceleration time ≤140 msec was present.[21]

STATISTICAL ANALYSES

All statistics were performed using SPSS (12.0.2) for Windows (Chicago, IL, USA). Descriptive statistics for nominal data were expressed in absolute numbers and percentages. After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Medians and ranges were computed for continuous variables with non-normal distribution. Baseline values were compared by an unpaired *t* test or a *Mann–Whitney U* test, if appropriate. The *Chi-square* test was used for the comparison of categorical variables. Receiver-operating characteristics curve were applied for all relevant clinical and echocardiographic continuous variable to determine the cut-off values with the best predictive value, hence it was set as a categorical variables to fit in the survival models. Each variable was evaluated by using Cox proportional hazard survival analysis for the combined study endpoint of cardiac death, urgent cardiac transplantation, or hospitalization due to HF. Univariable Cox regression analysis identified baseline variables that were significantly associated with the combined study endpoint. Significantly associated variables were then integrated into multivariate analysis using Cox proportional hazards modelling using forward stepwise selection algorithm. The proportional hazards assumptions were then validated in the final model for each categorical variable through visual inspection of log–log survival curves. For continuous variables, the linearity assumption was checked graphically for all variables using the Martingale residuals. There was no sign of violation of the assumptions. Cumulative Kaplan–Meier survival curves were constructed for each outcome variable and the log–rank test, compared outcome variables. Patients without the combined study endpoint were censored at the date of most recent follow-up. A value of $p<0.05$ was considered significant.

RESULTS

Patient characteristics

The study population included 74 patients (mean age 59 ± 11 years, 52 men). Thirty-six patients (48%) had ischemic HF and 38 patients (52%) had non-ischemic HF.

Table 1. Baseline Characteristics of Patients with and without Cardiac Events after Cardiac Resynchronization Therapy

Variable	Total population (n = 74)	No events (n = 53)	Events (n = 21)
Age, (years)	59 ± 11	60 ± 11	57 ± 11
Men	52 (70%)	36 (68%)	16 (76%)
NYHA class	3.1 ± 0.3	3.0 ± 0.2	3.1 ± 0.4
III/IV	69 (93%)/5 (7%)	51 (96%)/2 (4%)	18 (86%)/3 (14%)
6MWD, (meters)	217 ± 40	219 ± 42	213 ± 36
QRS duration, (msec)	172 ± 27	167 ± 25	179 ± 31
Ischemic etiology	36 (48%)	21 (40%)	15 (71%)*
Diabetes mellitus	11 (15%)	4 (8%)	7 (33%)*
Hypertension	25 (34%)	15 (28%)	10 (48%)
Renal insufficiency	5 (7%)	3 (6%)	2 (10%)
Amiodarone	44 (59%)	30 (56%)	14 (67%)
Beta-blockers	58 (78%)	43 (81%)	15 (71%)
ACE-inhibitors	66 (89%)	50 (94%)	16 (77%)
Diuretics	70 (95%)	51 (96%)	19 (90%)
Digitalis	30 (41%)	22 (39%)	8 (47%)
Echocardiographic data			
LV-EDD, (mm)	65 ± 7	64 ± 7	67 ± 7
LV-ESD, (mm)	55 ± 6	55 ± 6	57 ± 6
LV-EDV, (ml)	255 ± 109	252 ± 113	263 ± 100
LV-ESV, (ml)	210 ± 94	206 ± 96	221 ± 88
LV ejection fraction, (%)	18 ± 4	18 ± 4	17 ± 3
Mitral inflow (PW-Doppler)			
E-wave, (cm/s)	85 ± 13	83 ± 13	90 ± 11*
A-wave, (cm/s)	55 ± 20	60 ± 21	44 ± 12*
E/A ratio	1.7 ± 0.7	1.6 ± 0.5	2.2 ± 0.8**
E-wave deceleration time, (msec)	154 ± 36	160 ± 32	138 ± 29*
Restrictive filling	24 (32%)	10 (20%)	14 (67%)***
Mitral regurgitation, (grade)	2.6 ± 0.8	2.5 ± 0.8	2.8 ± 0.9
RVSP, (mmHg)	48 ± 25	46 ± 26	55 ± 19
Tissue Doppler parameters			
LSD-TO, (msec)	73 ± 44	78 ± 47	59 ± 33*
LSD-TP, (msec)	78 ± 46	81 ± 47	70 ± 41
Septal E/E' ratio	17.3 ± 6.2	15.5 ± 3.8	21.3 ± 7.7***
Lateral E/E' ratio	15.6 ± 6.7	12.2 ± 4.4	24.2 ± 7.1***
Mean E/E' ratio	16.5 ± 5.9	13.9 ± 3.6	22.6 ± 6.5***

Values are presented as mean ± SD. 6MWD = Six-minute walking distance; A = late diastolic filling wave, E = early diastolic filling wave, E' = early diastolic tissue velocity wave, EDD = end-diastolic diameter, EDV = end-diastolic volume, ESD = end-systolic diameter, ESV = end-systolic volume, LSD =Lateral-to-septal delay; LV = Left ventricular, NYHA = New York Heart Association functional class PW = pulsed-wave; RVSP = Right ventricular systolic pressure; TO = time to onset; TP = time to peak. *P <0.05, **P <0.01, ***P <0.001 versus patients without events.

Prediction of outcome after CRT

During a median follow-up of 720 days (210 to 1020 days), 21 patients (28%) had cardiac events. Of these 21 patients, 7 patients died (sudden death in 2, HF in 3, non ST-segment elevation acute myocardial infarction in 2). One patient underwent heart transplantation, and 13 patients were hospitalized for HF. Patients with cardiac events had more often an ischemic etiology (P <0.05) and diabetes (P <0.05), higher E-wave velocity (P <0.05), lower A-wave velocity (P <0.05), higher E/A ratio (P <0.01), more often restrictive filling (P <0.001), less LV dyssynchrony (P <0.05), and higher septal and lateral E/E′ ratios (both P <0.001) (Table 1).

Table 2. Cox-Regression Proportional Hazard Analysis of Baseline Clinical and Echocardiographic Predictors Of Cardiac Events After Cardiac Resynchronization Therapy

	Hazard Ratio	95% CI	P value
Univariable Cox-regression analysis			
Diabetes mellitus	3.703	1.491 – 9.199	0.008
Ischemic etiology	2.004	0.830 – 4.837	0.122
Early mitral inflow, E-wave	1.032	1.000 – 1.065	0.049
Late mitral inflow, A-wave	0.959	0.934 – 0.986	0.003
E/A ratio	3.492	1.901 – 6.414	0.000
Restrictive filling	4.293	2.819 – 18.868	0.000
Lateral-to-septal delay (To)	0.991	0.981– 1.001	0.089
Septal mitral annulus E/E′ ratio	1.133	1.075–1.195	0.001
Lateral mitral annulus E/E′ ratio	1.130	1.075 – 1.188	0.000
Multivariable Cox-regression analysis			
Diabetes mellitus	1.852	0.674 – 5.091	0.232
Early mitral inflow, E-wave	1.019	0.951 – 1.092	0.593
Late mitral inflow, A-wave	0.939	0.839 – 1.052	0.279
E/A ratio	0.273	0.020 – 3.690	0.328
Restrictive filling	2.543	0.407 – 15.913	0.318
Septal mitral annulus E/E′ ratio	0.996	0.904 –1.197	0.931
Lateral mitral annulus E/E′ ratio	1.113	1.023 – 1.211	0.013

Abbreviations are as in Table 1.

Univariable prediction of cardiac events

Univariable analysis using Cox proportional hazard ratios showed that diabetes (P <0.01), higher E-wave velocity (P <0.05), lower A-wave velocity (P <0.01), higher E/A ratio (P <0.001), restrictive filling (P <0.001), and higher septal (P <0.01) and lateral (P <0.001) E/E′ ratios were significantly associated with cardiac outcome (Table 2).

Multivariable prediction of cardiac events

In a multivariable model using a forward selection algorithm only the lateral E/E′ ratio remained an independent predictor of cardiac outcome (Table 2). The Kaplan-Meier event-free cumulative survival curve are presented for the overall patient population as stratified by lateral annulus E/E′ ratio is displayed in Figure 1.

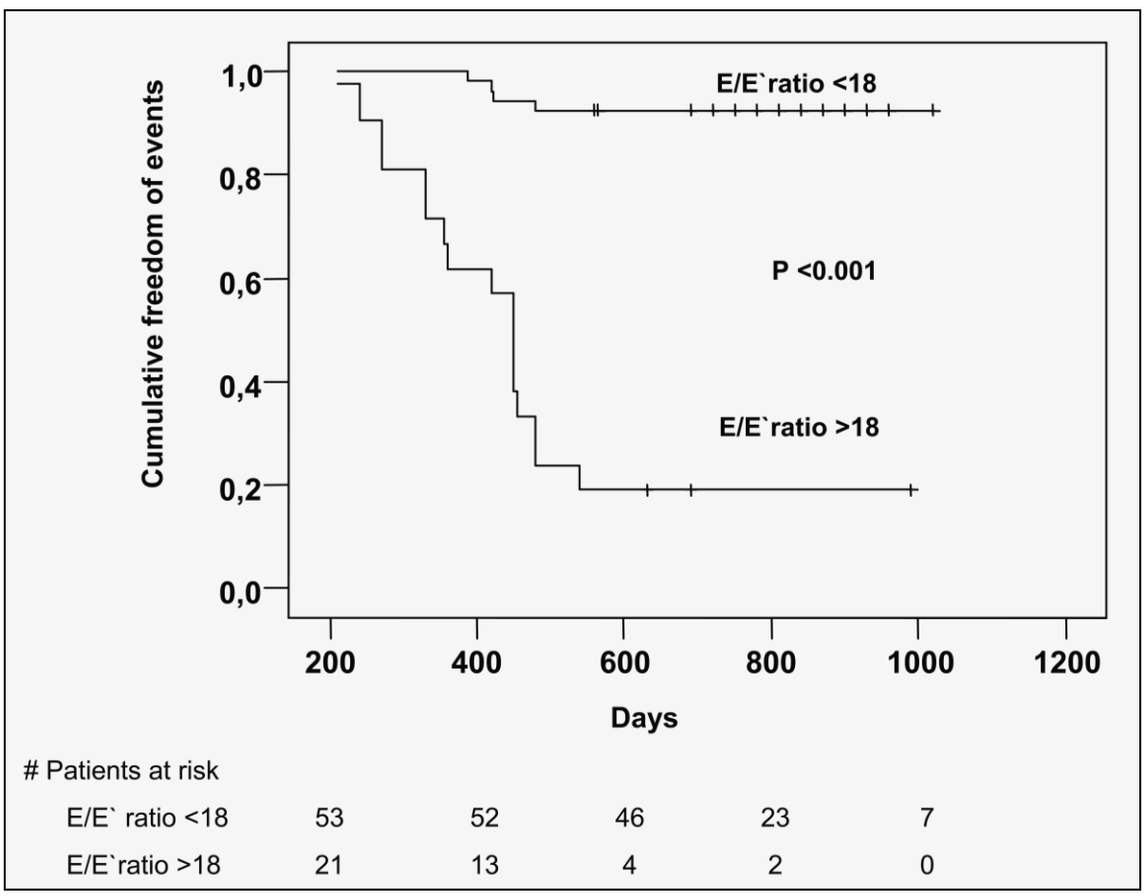


Figure 1. Kaplan-Meier event-free cumulative survival curves are presented for the overall patient population as stratified by lateral annulus E/E` ratio. Log-rank test comparing the survival curves is highly statistically significant (p <0.001). Numbers of patients at risk in each group at interval are displayed below graph.

Prediction of outcome after CRT according to HF etiology

Patients with an ischemic etiology had more often cardiac events (42% vs. 16%, P<0.001). In both patient groups (ischemic and non-ischemic) diabetes (P <0.05), restrictive filling (P <0.001), less LV dyssynchrony (P <0.05), higher septal E/E′ ratio (P <0.05), and higher lateral E/E′ ratio (P <0.001) were predictive of events.

Functional outcome after CRT according to HF etiology

Before CRT there were no significant differences in ischemic and non-ischemic patients in NYHA class and 6-minute walk distance (Table 3). Comparable improvements in ischemic and non-ischemic patients after 3 months CRT were seen in NYHA class (from 3.1 to 1.5, and 3.1 to 1.6, respectively) and 6-minute walk distance (from 216 to 273 meters, and 218 to 287 meters, respectively).

Table 3. Baseline Clinical and Echocardiographic Characteristics of Patients with and without Cardiac Events after Cardiac Resynchronization Therapy According to Etiology Of Heart Failure

	Ischemic cardiomyopathy			Non-ischemic cardiomyopathy		
Variable	Total (n = 36)	No events (n = 21)	Events (n = 15)	Total (n = 38)	No events (n = 32)	Events (n = 6)
Clinical data						
Age, (years)	59 ± 11	60 ± 11	57 ± 11	59 ± 10	60 ± 11	57 ± 11
Men, n (%)	28 (77%)	19 (90%)	9 (60%)	24 (63%)	20 (63%)	4 (67%)
NYHA class	3.1 ± 0.2	3.0 ± 0.2	3.1 ± 0.4	3.1 ± 0.3	3.0 ± 0.2	3.1 ± 0.4
III	34 (94%)	21 (100%)	13 (87%)	35 (92%)	30 (94%)	5 (83%)
IV	2 (6%)	0 (0%)	2 (13%)	3 (8%)	2 (63%)	1(17%)
6MWD, (meters)	216 ± 39	221 ± 41	208 ± 47	217 ± 40	216 ± 42	201 ± 36
QRS duration, (msec)	169 ± 29	169 ± 29	167 ± 27	172 ± 27	170 ± 25	183 ± 31
Diabetes mellitus	9 (25%)†	3 (15%)	6 (40%)*	2 (5%)	1(3%)	1(17%)*
Echocardiographic data						
LV-EDD, (mm)	64 ± 7	63 ± 7	65 ± 8	67 ± 7	66 ± 6	64 ± 4
LV-ESD, (mm)	54 ± 6	55 ± 6	54 ± 6	57 ± 6	56 ± 7	59 ± 6
LV-EDV, (ml)	231 ± 91	212 ± 69	263 ± 94	277 ± 121	280 ± 130	265 ± 74
LV-ESV, (ml)	189 ± 78	169 ± 54	219 ± 100	231 ± 106	233 ± 113	223 ± 65
LV ejection fraction, (%)	19 ± 4	20 ± 4	17 ± 3	17 ± 4	171 ± 4	16 ± 3
Restrictive filling, n (%)	15 (42%)	4 (19%)	11 (73%)***	9 (24%)	4 (13%)	5 (83%)***
RVSP, (mmHg)	45 ± 24	40 ± 27	53 ± 17	51 ± 25	50 ± 26	60 ± 25
Tissue Doppler parameters						
LSD-TO, (msec)	80 ± 40	91 ± 46	65 ± 24*	65 ± 47	71± 46	34 ± 41*
LSD-TP, (msec)	87 ± 48	96 ± 49	76 ± 47	69 ± 42	72 ± 44	54 ± 61
Septal E/E′ ratio	19.7 ± 6.9‡	17.5 ± 3.8	22.4 ± 7.7*	14.9 ± 6.2	14.2 ± 3.8	18.7 ± 7.1*
Lateral E/E′ ratio	16.1 ± 6.4	10.7 ± 4.4	24.1 ± 7.1***	15.1 ± 6.7	13.2 ± 5.2	25.2 ± 6.5***
Mean E/E′ ratio	17.9 ± 5.7†	14.1 ± 3.6	23.3 ± 6.5**	15.0 ± 6.5	13.7 ± 4.6	22.0 ± 6.6***

Values are presented as mean ± SD. Abbreviations are as in Table 1.
*P <0.05, **P <0.01, ***P <0.001 versus patients without events. †P <0.05, ‡P <0.01 versus non-ischemic.

Hemodynamic outcome after CRT according to HF etiology

Comparable significant improvements in LV dyssynchrony after 3 months CRT were seen in ischemic and non-ischemic patients. The TDI-derived systolic mitral annular velocities improved significantly in non-

ischemic patients both for the septal side (4.1 ± 0.8 to 4.9 ± 1.6, P <0.01) and lateral side (5.9 ± 1.3 to 6.9 ± 1.5, P <0.01). The relative improvements in septal and lateral systolic mitral annular velocities were similar. In ischemic patients no significant improvements were seen in septal and lateral systolic mitral annular velocities. The TDI-derived early diastolic mitral annular velocities improved significantly in non-ischemic patients both for the septal side (5.6 ± 1.3 to 6.2 ± 1.3, P <0.05) and lateral side (5.4 ± 1.3 to 6.0 ± 1.5, P <0.01). The relative improvements in septal and lateral velocities were similar. In ischemic patients no significant improvements were seen in septal and lateral early diastolic mitral annular velocities, septal early diastolic mitral annular velocity even worsened. Significant improvements were seen in septal and lateral E/E′ ratios in both ischemic and non-ischemic patients. However, the improvement in lateral E/E′ ratio was significantly less and absolute 3-months E/E′ ratios were worse in ischemic patients (Table 4).

Table 4. Tissue Doppler Changes in Ischemic vs. Non-Ischemic Cardiomyopathy Patients After Resynchronization Therapy

Variable	Ischemic cardiomyopathy (n = 36)				Non-ischemic cardiomyopathy (n = 38)			
	Baseline	3-months	Relative %	P-Value	Baseline	3-months	Relative %	P-Value
To, (ms)	79 ± 41	32 ± 25	-59%	<0.01	67 ± 47	29 ± 22	-57%	<0.01
Tp, (ms)	88 ± 48	50 ± 35	-43%	<0.01	68 ± 42	33 ± 25	-52%	<0.01
Septal Sm, (cm/s)	2.7 ± 0.8	2.9 ± 1.3	7%	NS	4.1 ± 0.8	4.9 ± 1.6	24%	<0.01
Lateral Sm, (cm/s)	3.9 ± 1.2	4.1 ± 1.2	5%	NS	5.9 ± 1.3	6.9 ± 1.5	17%	<0.01
Mean Sm, (cm/s)	3.3 ± 1.1	3.5 ± 1.2	6%	NS	5.0 ± 1.1	5.9 ± 1.6	21%	<0.01
Septal E′, (cm/s)	5.6 ± 0.8	4.3 ± 1.0	-23%	<0.01	5.6 ± 1.3	6.2 ± 1.3	11%	<0.05
Lateral E′, (cm/s)	5.3 ± 1.2	5.7 ± 1.5	8%	NS	5.4 ± 1.3	6.0 ± 1.5	11%	<0.01
Mean E′, (cm/s)	5.5 ± 1.1	5.0 ± 1.3	-15%	<0.05	5.5 ± 1.3	6.1 ± 1.5	11%	<0.01
Septal E/E′ ratio	19.7 ± 6.9	13.9 ± 5.8	-29%	<0.01	14.9 ± 6.2	9.8 ± 6.3	-34%	<0.01
Lateral E/E′ ratio	16.1 ± 6.4	14.2 ± 6.5	-11%	<0.05	15.1 ± 6.7	12.0 ± 6.2	-24%	<0.01
Mean E/E′ ratio	17.9 ± 5.7	14.0 ± 6.6	-20%	<0.01	15.0 ± 6.5	10.9 ± 6.4	-29%	<0.01

Abbreviations are as in Table 1. Sm = peak mitral annular systolic velocity; To = Lateral-to-septal delay - time to onset in msec, Tp = Lateral-to-septal delay - time to peak, in msec

Table 5. Summary of Studies on Baseline Clinical and Echocardiographic Variables For The Prediction of Cardiac Events After Cardiac Resynchronization Therapy

Authors	Year	Patients	FU (months)	NYHA	Etiology	LV-EDD	MR	RFP	RVSP	E/E′ ratio
De Sisti et al.[1]	2005	102	24	U, M	x	x	x		U	
Molhoek et al.[2]	2005	125	23 ± 10	U, M	x		x			
Infante et al.[6]	2005	143	12	x	U, M	U, M	U, M			
Pitzalis et al.[25]	2005	60	14	x	U	x	x		U	
Waggoner et al.[5]	2006	57	20 ± 11	x	x		x	U, M		U, M*
Porciani et al.[7]	2006	65	12	x	x	x	x	U, M		
Tedrow et al.[8]	2006	75	12 ± 8	x	x	x	x		U, M	
Gasparini et al.[3]	2006	317	36	U, M	U, M					
Achilli et al.[26]	2006	133	6							
Soliman et al.	2007	74	24 ± 7	x	U	x	x	U	x	U, M

x = included in univariable analysis. U = significant in univariable analysis. M = significant in multivariable analysis (independent predictor)
* Septal E/E′ ratio. FU = Follow-up, LV-EDD = left ventricular end-diastolic diameter, MR = mitral regurgitation, RFP = restrictive filling pattern, RVSP = right ventricular peak systolic pressure.

DISCUSSION

CRT is an accepted intervention in end-stage HF patients.[12, 22] Unfortunately, in about 30% of patients no clinical benefit is seen.[22] In the most recent years several baseline (pre-CRT) clinical or echocardiographic predictors for post-CRT clinical events have been identified (Table 5).

Only restrictive LV filling and increased right ventricular pressures have emerged as convincing (at least significant in univariable analysis in all studies that included these variables) predictors for post-CRT clinical events. Waggoner et al. were the first to investigate the predictive role of the septal E/E′ ratio as a marker for increased LV filling pressures in CRT patients.[5] In their study, the septal E/E′ ratio was a significant predictor of clinical events in the multivariable analysis. Our study confirms the role of this marker for LV filling pressure.[19] In several studies ischemic HF was also a predictor for poor prognosis after CRT (Table 5). In the studies of Waggoner et al. [5] and us, ischemic patients had higher baseline E/E′ ratios, and the improvement in E/E′ ratio was less pronounced. This may be explained by a lack of improvement in systolic and diastolic mitral annular velocities seen in the ischemic patients, in contrast to the significant improvements in the non-ischemic patients. Although in our study the predictive value of the septal E/E′ ratio is confirmed the lateral E/E′ ratio better discriminated between patients with and without events and was the only significant predictor of cardiac events in a multivariable analysis. Each of the 2 E/E′ ratios has its specific benefits. Translational movement of the heart less affects septal mitral

annular velocity and Doppler beam angle errors are less likely to occur when septal mitral annular velocities are measured. Also, it was shown that the septal E/E' ratio best correlated to LV filling pressures in subjects with preserved systolic LV function.[23] On the other hand, Nagueh et al. found that the lateral E/E' ratio was more easy to quantify.[19, 24] Furthermore, many ischemic CRT patients have a history of acute myocardial infarction and it is well known that the interventricular septum is more often involved in the infarction than the lateral wall. [10] So, in ischemic CRT patients a prior septal infarction may limit the value of the septal E/E' ratio and the lateral E/E' may a better indicator for high LV filling pressures in such patients and thus a better predictor for events.

REFERENCES

1. de Sisti A, Toussaint JF, Lavergne T, Ollitrault J, Abergel E, Paziaud O, Ait Said M, Sader R, JY LEH, Guize L: **Determinants of mortality in patients undergoing cardiac resynchronization therapy: baseline clinical, echocardiographic, and angioscintigraphic evaluation prior to resynchronization**. *Pacing Clin Electrophysiol* 2005, **28**(12):1260-1270.
2. Molhoek SG, Bax JJ, Bleeker GB, Holman ER, Van Erven L, Bootsma M, Boersma E, Steendijk P, Van Der Wall EE, Schalij MJ: **Long-term follow-up of cardiac resynchronization therapy in patients with end-stage heart failure**. *J Cardiovasc Electrophysiol* 2005, **16**(7):701-707.
3. Gasparini M, Lunati M, Santini M, Tritto M, Curnis A, Bocchiardo M, Vincenti A, Pistis G, Valsecchi S, Denaro A: **Long-term survival in patients treated with cardiac resynchronization therapy: a 3-year follow-up study from the InSync/InSync ICD Italian Registry**. *Pacing Clin Electrophysiol* 2006, **29 Suppl 2**:S2-10.
4. Diaz-Infante E, Mont L, Leal J, Garcia-Bolao I, Fernandez-Lozano I, Hernandez-Madrid A, Perez-Castellano N, Sitges M, Pavon-Jimenez R, Barba J *et al*: **Predictors of lack of response to resynchronization therapy**. *Am J Cardiol* 2005, **95**(12):1436-1440.
5. Waggoner AD, Rovner A, de las Fuentes L, Faddis MN, Gleva MJ, Sawhney N, Davila-Roman VG: **Clinical outcomes after cardiac resynchronization therapy: importance of left ventricular diastolic function and origin of heart failure**. *J Am Soc Echocardiogr* 2006, **19**(3):307-313.
6. Diaz-Infante E, Berruezo A, Mont L, Osorio P, Garcia-Moran E, Marigliano A, Sitges M, Azqueta M, Pare C, Muxi A *et al*: **[Predictors of lack of clinical improvement at mid-term follow-up with cardiac resynchronization therapy]**. *Rev Esp Cardiol* 2004, **57**(4):306-312.
7. Porciani MC, Valsecchi S, Demarchi G, Colella A, Michelucci A, Pieragnoli P, Musilli N, Gensini GF, Padeletti L: **Evolution and prognostic significance of diastolic filling pattern in cardiac resynchronization therapy**. *Int J Cardiol* 2006, **112**(3):322-328.
8. Tedrow UB, Kramer DB, Stevenson LW, Stevenson WG, Baughman KL, Epstein LM, Lewis EF: **Relation of right ventricular peak systolic pressure to major adverse events in patients undergoing cardiac resynchronization therapy**. *Am J Cardiol* 2006, **97**(12):1737-1740.
9. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, Lee MM, Park YB, Choi YS, Seo JD *et al*: **Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function**. *J Am Coll Cardiol* 1997, **30**(2):474-480.
10. **A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators**. *N Engl J Med* 1997, **337**(16):1118-1123.
11. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K *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**(12):e154-235.
12. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A *et al*: **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**(11):1115-1140.
13. Soliman OI, Theuns DA, Geleijnse ML, Anwar AM, Nemes A, Caliskan K, Vletter WB, Jordaens LJ, Cate FJ: **Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy**. *Europace* 2007, **9**(2):113-118.
14. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davidson TW, Davis JL, Douglas PS, Gillam LD: **ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography**. *Circulation* 1997, **95**(6):1686-1744.
15. 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**(2):167-184.
16. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP, Jr.: **Color Doppler assessment of mitral regurgitation with orthogonal planes**. *Circulation* 1987, **75**(1):175-183.
17. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F: **Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications. Heart Muscle Disease Study Group**. *J Am Coll Cardiol* 1993, **22**(3):808-815.
18. Otto CM: **Left and Right ventricular Systolic Function**. In: *textbook of clinical Echocardiography*. Edited by Saunders E: Elsevier Saunders; 2004: 131-165.
19. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA: **Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures**. *J Am Coll Cardiol* 1997, **30**(6):1527-1533.
20. Diwan A, McCulloch M, Lawrie GM, Reardon MJ, Nagueh SF: **Doppler estimation of left ventricular filling pressures in patients with mitral valve disease**. *Circulation* 2005, **111**(24):3281-3289.
21. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN: **Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure**. *J Am Coll Cardiol* 1994, **24**(1):132-139.
22. Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, Kass DA, Powe NR: **Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials**. *Jama* 2003, **289**(6):730-740.

23. Firstenberg MS, Levine BD, Garcia MJ, Greenberg NL, Cardon L, Morehead AJ, Zuckerman J, Thomas JD: **Relationship of echocardiographic indices to pulmonary capillary wedge pressures in healthy volunteers**. *J Am Coll Cardiol* 2000, **36**(5):1664-1669.
24. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA: **Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue doppler imaging**. *Circulation* 1998, **98**(16):1644-1650.

Chapter 8

Predictors of cardiac events after cardiac resynchronization therapy with tissue Doppler-derived parameters

Osama I.I. Soliman[1,2], Dominic A.M.J. Theuns[1], Folkert J. ten Cate[1], Attila Nemes[1,3], Kadir Caliskan[1], Aggie H.M. Balk[1], Wim B. Vletter[1], Luc J. Jordaens MD[1], and Marcel L. Geleijnse[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt; [3]Second Department of Medicine and Cardiology Center, University of Szeged, Szeged, Hungary

Journal of Cardiac Failure (in press)

ABSTRACT

Aim of the study: To evaluate the prognostic value of tissue Doppler imaging (TDI)-derived parameters (E/E′ ratio and Tei index) in heart failure (HF) patients who underwent cardiac resynchronization therapy (CRT).

Methods: The study comprised 74 consecutive HF patients (mean age 60 ± 11 years) who underwent CRT. Echocardiography including TDI measurements was performed in all patients at baseline and 3 months after CRT.

Results: During a median follow-up period of 720 days (range 210 to 1020 days), 21 patients (28%) had events (8 deaths, and hospitalization for HF in the remaining 13).
From the baseline clinical and echocardiography data univariable Cox-regressions analysis revealed that only diabetes (hazard ratio (HR) 3.703, P <0.01), E/A ratio (HR 3.492, P <0.001), and E/E′ ratio (HR 1.130, P <0.001) were predictors for cardiac events. From the 3-months follow-up data, the E/A ratio (HR 2.988, P <0.005), E/E′ ratio (HR 1.170, P <0.001), left ventricular ejection fraction (HR 0.835, P <0.01), deceleration time (HR 0.977, P <0.05), and the Tei index (HR 15.784, P <0.001) were predictors for cardiac events. After multivariable analysis only diabetes (HR 5.544, P <0.05), the 3-months E/E′ ratio (HR 1.229, P <0.001), and change in Tei index (HR 32.174, P <0.001) were independent predictors for cardiac events. Patients with a high baseline and 3-months follow-up E/E′ ratio had an 88% cardiac event rate.

Conclusion: The Tei index and E/E′ ratio are independent predictors of cardiac events after CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective therapy for selected heart failure (HF) patients resulting in a decrease in morbidity and mortality.[1, 2] The potential mechanisms proposed for CRT success are mainly related to optimized diastolic left ventricular (LV) filling [3], more synchronized electrical and mechanical coupling hence myocardial performance [4], and reduced mitral regurgitation.[4, 5] Echocardiographic signs of reverse LV remodeling become evident as early as three months after CRT.[6] However, in about one third of patients no benefit is seen.[7] Identifying reliable predictors of clinical and echocardiographic outcome remains a great challenge for the physician. Several well known clinical and echocardiographic parameters such as New York Heart Association (NYHA) functional class [8, 9], ischemic etiology [10], restrictive LV filling [11], and LV reverse remodeling [6] have been shown to predict clinical events after CRT. In HF patients not specifically treated with CRT, tissue Doppler imaging (TDI)-derived parameters such as the ratio between mitral early filling velocity divided by the early diastolic velocity of the mitral annulus (E/E') [12] and the myocardial performance index (Tei index) [13, 14] have been shown to predict cardiac events. Unfortunately, these newer TDI predictors for cardiac events were not investigated in CRT patients. Therefore, the aims of the present study were: (i) to investigate the predictive value of TDI parameters for cardiac events in CRT patients and (ii) to determine cut-off values for optimal identification of patients with events after CRT.

METHODS

Study Population

Seventy-four consecutive heart failure patients referred for an implantable cardiac defibrillator and CRT were enrolled into the study according to the following criteria: (1) New York Heart Association (NYHA) functional class ≥III despite optimal drug therapy, (2) impaired LV ejection fraction (LV-EF <35%), and (3) wide QRS complex >120 msec. These CRT indications comply with current guidelines.[15, 16] Patients with acute coronary syndromes or coronary revascularization within 6 months before CRT were excluded. A written informed consent was obtained from all patients and the institutional review board approved the study. From the 76 initially included patients that underwent CRT, 2 patients died in the first month, and because of lacking three-month echocardiographic data they were excluded from the final analysis. There were no significant differences in baseline characteristics between these excluded patients and the final study group.

Study Protocol

Before CRT, two-dimensional echocardiography, including TDI assessment of mitral annular velocity, was done. Patients were scheduled for regular clinical follow-up and the CRT device was interrogated to

ensure that biventricular pacing was being maintained, at least every three months. Three months after CRT implantation, two-dimensional echocardiography was repeated. A patient was considered an echocardiographic responder when 3 months after CRT implantation a >15% reduction in LV-ESV was noted. The primary study endpoint was a composite of cardiovascular mortality (including urgent cardiac transplantation) and unplanned hospitalization for heart failure.

Device implantation

Device implantation was performed preferably with a single left pectoral incision, a left cephalic vein cutdown and a left subclavian puncture. The defibrillation lead was positioned in the right ventricular apex. Transvenous implantation of the CRT device was successful in 71 patients (96%). The LV pacing lead was placed in a tributary of the coronary sinus. A postero-lateral branch was used in 50 patients (68%), a lateral branch in 13 patients (18%), and an antero-lateral branch in 8 patients (11%) of patients. In the remaining three patients the LV lead was surgically implanted. Adequate pacing and sensing properties of all leads, and diaphragmatic stimulation with the LV pacing lead were tested. All implanted biventricular pacing devices were combined with an internal cardiovertor-defibrillator. The lowest effective defibrillation energy was assessed and a safety margin of ≥10 J was used. Devices used were InSync 7272, 7279, and 7298 (Medtronic Inc, Minneapolis, MN, USA), Renewal II (Guidant Inc, St Paul, MN, USA), and Epic HF V-339 and Atlas HF V-341 (St Jude Medical, Sylmar, CA, USA). For all patients, ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation. Atrio-ventricular delay was optimized by 2D echocardiography to provide the longest filling time for completion of the end-diastolic filling flow before LV contraction with the highest LV outflow tract velocity timed integral.

Echocardiography

All patients were examined using a Sonos 7500 ultrasound system (Philips, Best, The Netherlands) with a S3 transducer according to the recommendations of the American Society of Echocardiography.[17, 18] LV end-diastolic volume (LV-EDV), LV end-systolic volume (LV-ESV), and LV-EF (by modified bi-plane Simpson rule) were calculated from the apical 4-chamber and 2-chamber views. The degree of mitral regurgitation (grade I-IV) was assessed as the mid-systolic jet area relative to left atrial area in the apical 4-chamber view.[19] From the mitral inflow peak velocity of early (E) and late (A) diastolic filling, E/A ratio, and the E-wave deceleration time were measured.

Tissue Doppler Imaging

TDI was applied by placing the sample volume at the side of the medial and lateral mitral annulus in an apical 4-chamber view.[20] Gain and filter settings were adjusted as needed to eliminate background noises and to allow for a clear tissue signal. To acquire the highest tissue velocities the angle between the Doppler beam and the longitudinal motion of the investigated structure was adjusted to a minimal level.

The velocity and timing of the mitral annulus systolic wave (Sm) and early diastolic wave (E') were recorded end-expiratory at a sweep speed of 100 mm/s and measured using electronic calipers with EnConcert software (Philips, Best, The Netherlands). The Tei index, defined as isovolumic contraction time plus isovolumic relaxation time divided by LV ejection time, and the dimensionless mitral E/E' ratio were calculated as previously described.[20, 21] For each patient, the average of three measurements was calculated. Diastolic mitral inflow was classified as restrictive when E/A ≥2 or the combination of E/A >1 and <2 and an E-wave deceleration time ≤140 msec was present.[12] All measurements were done blinded to clinical data and the other echocardiographic study.

STATISTICAL ANALYSES

All statistics were performed using SPSS (12.0.2) for Windows (Chicago, IL, USA). Descriptive data were computed as a mean value ± SD Baseline and 3-months data (and changes) were compared by an unpaired *t* test or a *Mann–Whitney U* test, if appropriate. The *Chi-square* test was used for the comparison of categorical variables. A value of $p<0.05$ was considered significant. Receiver-operating characteristics curve were applied for all clinical and echocardiographic continuous variable to determine the cut-off values with the best predictive value, hence it was set as a categorical variables to fit in the survival models. Each variable was evaluated by using Cox proportional hazard survival analysis for the combined study endpoint of cardiac death or hospitalization due to HF. Univariable Cox regression analysis identified baseline clinical and echocardiographic variables that were significantly associated with the combined study endpoint. Significantly associated variables were then integrated into a multivariable analysis using Cox proportional hazards modeling using a forward stepwise selection algorithm. The proportional hazards assumptions were then validated in the final model for each categorical variable through visual inspection of log–log survival curves. For continuous variables, the linearity assumption was checked graphically for all variables using the Martingale residuals. There were no signs of violation of the assumptions. To test the inter-observer variability, a second observer who was unaware of the results of the first examination performed repeat measurements. Variability was calculated as the mean percent error, derived as the difference between the two sets of measurements, divided by the mean of the two observations. Inter-observer variability for TDI-derived parameters of lateral mitral annulus velocity (Sm, E', and E/E' ratio) ranged from 4% to 8%.

Table 1. Baseline Characteristics of Patients with and Without Cardiac Events

	Total population (n = 74)	No events (n = 53)	Events (n = 21)
Clinical data			
Age, (years)	59 ± 11	60 ± 11	57 ± 11
Men, n (%)	52 (70)	36 (68)	16 (76)
Follow-up, (days)	478 ± 100	505 ± 88	410 ± 99
NYHA class	3.1 ± 0.3	3.0 ± 0.2	3.1 ± 0.4
6MWD, (meters)	217 ± 40	219 ± 42	213 ± 36
QRS duration, (msec)	171 ± 27	167 ± 25	179 ± 31
Ischemic etiology, n (%)	36 (48)	21 (40)	15(71)*
Diabetes mellitus, n (%)	11 (15)	4 (8)	7 (33)*
Hypertension, n (%)	25 (34)	15 (28)	10 (48)
Amiodarone, n (%)	44 (59)	30 (56)	14 (67)
Beta-blockers, n (%)	58 (78)	43 (81)	15 (71)
ACE-inhibitors, n (%)	66 (89)	50 (94)	16 (77)
Diuretics, n (%)	70 (95)	51 (96)	19 (90)
Digitalis, n (%)	30 (41)	22 (39)	8 (47)
Echocardiographic data			
LV-EDV, (ml)	255 ± 109	252 ± 113	263 ± 100
LV-ESV, (ml)	210 ± 94	206 ± 96	221 ± 88
LV-EF, (%)	18 ± 4	18 ± 4	17 ± 3
Mitral inflow (PW-Doppler)			
E/A ratio	1.7 ± 0.7	1.6 ± 0.5	2.2 ± 0.8**
Deceleration time, (msec)	154 ± 36	160 ± 32	138 ± 29**
Restrictive filling, n (%)	24 (32)	10 (20)	14 (67)***
Mitral regurgitation, grade	2.6 ± 0.8	2.5 ± 0.8	2.8 ± 0.9
Tissue Doppler imaging			
LSD time-to-onset, (msec)	73 ± 44	78 ± 47	59 ± 33*
LSD time-to-peak, (msec)	78 ± 46	81 ± 47	70 ± 41
Sm, (cm/s)	4.1 ± 1.1	4.4 ± 0.7	3.4 ± 0.7**
E', (cm/s)	5.5 ± 1.3	6.0 ± 0.8	4.3 ± 0.8*
Tei index	0.92 ± 0.31	0.91 ± 0.20	1.01 ± 0.33
E/E' ratio	15.6 ± 6.7	12.2 ± 4.4	24.2 ± 7.1*

Values are presented as mean ± SD. 6MWD = Six-minute walk distance; A = Late diastolic wave, E and E' = Early diastolic wave, ET = Ejection time, LSD = lateral-to-septal delay, LV-EDV = Left ventricular end-diastolic volume, LV-EF = Left ventricular ejection fraction, LV-ESV = Left ventricular end-systolic volume, NYHA = New York Heart Association, Sm = systolic contraction wave. *P <0.05, **P <0.01, ***P <0.001 versus patients without events.

RESULTS

Baseline demographics

Mean age of the patients was 59 ± 11 years and 52 were men (70%). Seventy-two patients (97%) were in NYHA class III, 2 patients were in NYHA class IV. All other pertinent baseline clinical and echocardiographic data are shown in Table 1.

Three months follow-up data

Clinical data

At 3-months follow-up, QRS duration decreased from 171 ± 27 to 127 ± 28 msec (P <0.001). NYHA class improved from 3.1 ± 0.3 to 1.6 ± 0.5 (P <0.001), and the 6MWD increased from 217 ± 40 to 280 ± 63 m (P <0.001).

Echocardiographic data

LV-EDV decreased from 255 ± 109 to 248 ± 115 ml (P <0.10), LV-ESV decreased from 210 ± 94 to 183 ± 85 ml (P <0.001), and LV-EF improved from 18% ± 4% to 26% ± 7% (P <0.001). Twenty-six patients (35%) were echocardiographic responders. The number of patients with restrictive filling decreased from 24 to 17 (P <0.05). Mean MR grade decreased from 2.6 ± 0.8 to 2.2 ± 0.8 (P <0.001).

Tissue Doppler data

Lateral-to-septal time-to-onset decreased from 73 ± 44 to 30 ± 23 msec (P <0.001) and lateral-to-septal time-to-peak decreased from 78 ± 46 to 41 ± 31 msec (P <0.001). Mean Sm increased from 4.1 ± 1.1 to 4.8 ± 1.1 cm/sec (P <0.001), E′ increased from 5.5 ± 1.3 to 6.2 ± 1.2 cm/sec (P <0.0001), E/E′ ratio decreased from 15.6 ± 6.7 to 13.2 ± 5.2 (P <0.001), and the Tei index improved from 0.92 ± 0.31 to 0.73 ± 0.30 (P <0.001). All other pertinent 3-months data are shown in Table 2.

Cardiac events

During a median follow-up duration of 720 days (range 210 to 1020 days), 21 patients (28%) had cardiac events. Of these 21 patients, 7 patients died (sudden death in 2, HF in 3, non ST-segment elevation acute myocardial infarction in 2). One patient underwent urgent heart transplantation, and 13 patients were hospitalized for HF.

Univariable prediction of cardiac events (Tables 1 and 2)

Baseline data

Patients with cardiac events had more often an ischemic etiology (P <0.05) and diabetes (P <0.05), a higher E/A ratio (P <0.01), more often restrictive LV filling (P <0.001), more LV dyssynchrony (P <0.05), lower mean Sm (P <0.01), lower E' (P <0.05), and a higher E/E' ratio (P <0.05).

Three-month data

Patients with cardiac events had less reduction in QRS duration (P <0.01) and less improvement in 6MWD (P <0.001). Echocardiographically they had less reduction in LV-ESV (P <0.001) and less increase in LV-EF (P <0.001), a higher E/A ratio (P <0.01), more often restrictive filling (P <0.001), and more severe mitral regurgitation (P <0.001). At TDI, patients with cardiac events had more LV dyssynchrony (P <0.05), lower mean Sm (P <0.05), lower E' (P <0.001), a higher E/E' ratio (P <0.001), and worse Tei index (P <0.001).

Univariable Cox-regression analysis of cardiac events

Baseline data

From the baseline clinical and echocardiography data only diabetes (hazard ratio (HR) 3.703, P <0.01), E/A ratio (HR 3.492, P <0.001), and E/E' ratio (HR 1.130, P <0.001) were predictors for cardiac events.

Three-month data

The E/A ratio (HR 2.988, P <0.005), E/E' ratio (HR 1.170, P <0.001), LV-EF (HR 0.835, P <0.01), E-wave deceleration time (HR 0.977, P <0.05), and the Tei index (HR 15.784, P <0.001) were predictors for cardiac events.

Multivariable Cox-regression analysis of cardiac events

From all included baseline and 3-months follow-up parameters, only LV-EF at 3-months (HR 0.869, P <0.05) and the 3-months E/E' ratio (HR 1.137, P <0.005) were independent predictors for cardiac events. When changes in parameters from baseline to 3-months follow-up were also included in the analysis, predictors for cardiac events in the univariable analysis were LV-ESV [HR 1.004, P <0.05], LV-EF [HR 0.835, P <0.05], E/E' ratio (HR 1.053, P <0.001), and Tei index [HR 47.930, P <0.001]). Only diabetes (HR 5.544, P <0.05), the 3-months E/E' ratio (HR 1.229, P <0.001), and change in Tei index (HR 32.174, P <0.001) were independent predictors for cardiac events (Table 3).

Table 2. Three-Month Follow-Up Characteristics of Patients with and Without Cardiac Events

	Total population (n = 74)	No events (n = 53)	Events (n = 21)
Clinical data			
NYHA class	1.6 ± 0.5	1.6 ± 0.6	1.6 ± 0.7
Δ NYHA	-46 ± 14	-46 ± 20	-46 ± 11
6MWD, (meters)	280 ± 63	302 ± 54	224 ± 39**
Δ 6MWD	31 ± 30	41 ± 27	6 ± 22***
QRS duration, (msec)	127 ± 28	117 ± 18	152 ± 29**
Δ QRS duration	-26 ± 12	-30 ± 13	-15 ± 11
Echocardiographic data			
LV-EDV, (ml)	248 ± 115	242 ± 118	265 ± 108
Δ LV-EDV	-6 ± 18	-8 ± 21	-1 ± 8
LV-ESV, (ml)	183 ± 85	170 ± 80	216 ± 93*
Δ LV-ESV	-13 ± 14	-16 ± 15	-3 ± 7***
LV-EF, (%)	26 ± 7	29 ± 5	19 ± 5**
Δ LV-EF	50 ± 42	64 ± 40	13 ± 21***
E/A ratio	1.5 ± 0.7	1.3 ± 0.5	2.1 ± 0.8**
Δ E/A ratio	-12 ± 30	-20 ± 32	10 ± 15**
Deceleration time, (msec)	154 ± 35	162 ± 34	132 ± 27**
Δ Deceleration time	0 ± 10	1 ± 19	-5 ± 25
Restrictive filling, n (%)	17 (23)	3 (6)	14 (67)***
Δ Restrictive filling	-29	-70	0***
Mitral regurgitation, grade	2.2 ± 0.8	1.9 ± 0.6	2.9 ± 0.8***
Δ Mitral regurgitation	-18 ± 32	-28 ± 20	7 ± 11**
Tissue Doppler imaging			
LSD time-to-onset, (msec)	30 ± 23	26 ± 19	40 ± 31*
Δ LSD time-to-onset	-60 ± 27	-67 ± 32	-32 ± 37*
LSD time-to-peak, (msec)	41 ± 31	38 ± 28	50 ± 37
Δ LSD time-to-peak	-47 ± 31	-53 ± 27	-28 ± 32*
Sm, (cm/s)	4.8 ± 1.1	5.2 ± 0.7	3.7 ± 0.7*
Δ Sm	17 ± 22	21 ± 21	9 ± 18*
E′, (cm/s)	5.6 ± 1.2	6.6 ± 0.8	4.1 ± 0.8**
Δ E′	4 ± 18	9 ± 19	-7 ± 17*
Tei index	0.73 ± 0.30	0.64 ± 0.30	0.92 ± 0.34***
Δ Tei index	-22 ± 31	-32 ± 16	-7 ± 28**
E/E′ ratio	13.2 ± 5.2	10.4 ± 2.2	19.4 ± 4.7***
Δ E/E′ ratio	-17 ± 14	-21 ± 27	-16 ± 14**

Abbreviations as in Table 1
Δ = relative change as a percentage from corresponding baseline values

Table 3. Cox-Regression Analysis of Clinical and Echocardiographic Predictors of Cardiac Events 3-Months after Cardiac Resynchronization

	Hazard Ratio	95% CI	P value
Univariable Cox-regression analysis of baseline predictors			
Baseline predictors			
Diabetes	3.703	1.491 – 9.199	0.008
E/A ratio	3.492	1.901 – 6.414	0.000
E/E′ ratio	1.130	1.075 – 1.188	0.000
Three-months predictors			
LV ejection fraction	0.835	0.786 – 0.887	0.007
E/A ratio	2.988	1.867 – 4.782	0.005
Deceleration time	0.977	0.964 – 0.990	0.011
Tei index	15.784	4.598 – 54.187	0.001
E/E′ ratio	1.170	1.117 – 1.227	0.001
Multivariable Cox-regression analysis: initial model			
LV ejection fraction	0.869	0.777 – 0.971	0.014
E/E′ ratio	1.137	1.039 – 1.243	0.005
Univariable Cox-regression analysis of changes in continuous variables after three-months			
Δ LV-ESV	1.004	1.000 – 1.070	0.014
Δ LV ejection fraction	0.835	0.786 – 0.887	0.022
Δ Tei index	47.930	11.260 – 204.027	0.000
Δ E/E′ ratio	1.053	1.027-1.080	0.001
Multivariable Cox-regression analysis using: final step model			
Diabetes	5.544	1.334 – 23.042	0.018
Δ Tei index	32.174	4.735 – 218.632	0.000
E/E′ ratio at 3 months	1.229	1.106 – 1.366	0.000

Abbreviations are as in Table 1.

Table 4. Predictability of E/E′ Ratio and Tei Index for Cardiac Events after Cardiac Resynchronization Therapy

	Value	Sensitivity	Specificity	AUC	PPV	NPV	P-Value
E/E′ ratio							
Baseline	18	0.81	0.92	0.89	0.81	0.92	0.0001
3-Months months	13	0.90	0.83	0.95	0.74	0.96	0.0001
Δ E/E′	<26%	0.81	0.70	0.78	0.47	0.92	0.0001
Tei index							
Baseline	1.02	0.91	0.28	0.53	0.33	0.89	NS
3-Months months	0.60	0.86	0.74	0.82	0.56	0.93	0.0001
Δ Tei index	<0.24	0.84	0.76	0.85	0.53	0.94	0.0001

Abbreviations are as in Table 1. NPV = Negative predictive value; PPV = Positive predictive value

Cut-off value analysis for TDI predictors (Table 4)

In order to define cut-off values for the prediction of cardiac events by the TDI variables, receiver-operating characteristic curves were generated for baseline, 3-months follow-up and changes in E/E′ ratio and the Tei index (Table 4). In Figure 1, the use of the strongest predictor (E/E′) for cardiac events beyond a volumetric response to CRT is clarified. Only 2 out of 21 patients (10%) with a baseline E/E′ ratio >18 were echocardiographic volumetric responders, in contrast to 29 out of 53 patients (55%) with a baseline E/E′ ratio <18. Patients with a high baseline and 3-months follow-up E/E′ ratio had an 88% cardiac event rate.

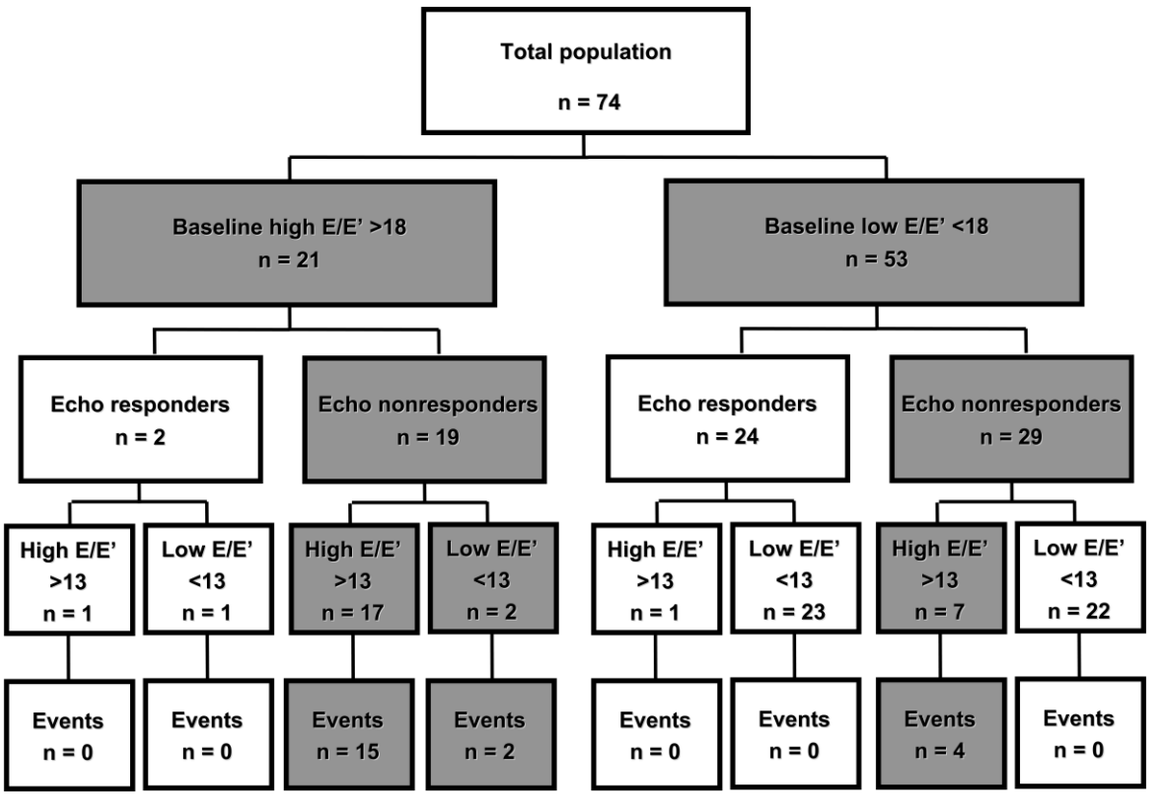
DISCUSSION

In agreement with the major CRT trials [1, 2, 22], the majority of patients in this study clinically benefited from CRT implantation. Three months after CRT reverse LV remodeling had taken place, evidenced by reductions in LV dimensions and improvement in LV-EF, although, the actual echocardiographic volumetric response rate in our study (35%) was quite low. This may be due to the short 3-months period between CRT and echocardiographic assessment. In other studies with even longer follow-up duration, also a low echocardiographic response to CRT varying from 44 to 47% at 6 months was shown.[23, 24] In addition, our criterion for volumetric response was stringent: >15% reduction in LV end-systolic volume compared to >10% reduction in some other studies.[6] Finally, the inclusion of very sick patients in our study with low ejection fractions may have influenced the low response rate. More importantly, 28% of our CRT patients died or were hospitalized for HF during follow-up. Identifying predictors for cardiac events after CRT that are related to LV function and volume status could have an important impact on follow-up management of these patients since such high-risk patients may be more closely and frequently monitored with more tight control of volume status. In previous CRT studies clinical and echocardiographic variables such as NYHA functional class[8, 9], ischemic etiology[10], restrictive LV filling [11], and LV reverse remodeling [6], and myocardial contractile reserve [25], predicted cardiac events. In our study the role of ischemic etiology, restrictive LV filling and reverse LV remodeling was confirmed. Volumetric reverse LV remodeling was an important predictor for cardiac events in our study since all cardiac events took place in patients without 3-months LV remodeling (Figure 1). In addition to these well known predictive parameters important roles for the Tei index and the E/E′ ratio were shown in our study.

Role of the Tei index

The Tei index, also called the myocardial performance index, provides a non-invasive and integrated assessment of systolic and diastolic LV function is reproducible and less dependent on age, heart rate or loading conditions than conventional Doppler measurements.[26, 27] Its potential clinical application was shown in patients with dilated cardiomyopathy [28], mild-to-moderate HF [14], and myocardial infarction.[29] In the present study baseline Tei index was similar in patients with and without events.

Interestingly, CRT resulted in a significant 32% reduction in the 3-months follow-up Tei index in patients



without subsequent events compared to only a 7% reduction in patients with events.

Figure 1. Diagram showing the value of baseline and 3-months follow-up E/E' ratio in the prediction of cardiac events after CRT

Role of the E/E' ratio

Diastolic dysfunction predicts survival in patients with myocardial infarction [30] and dilated cardiomyopathy.[31] Conventional diastolic Doppler measurements such as transmitral early filling velocity, deceleration time and the ratio between early to late LV filling velocities predict prognosis in patients with HF.[32] However, these Doppler transmitral inflow patterns are dependent on many factors such as heart rate and loading conditions [27], whereas Doppler measurements of mitral annular velocity appear to be relatively independent on preload.[20] Diastolic mitral annular velocity reflects the rate of diastolic changes in LV long-axis dimension. The ratio of early transmitral flow velocity to early diastolic mitral annular velocity (E/E' ratio) correlates well with LV filling pressure [20] and predicts survival in patients after acute myocardial infarction.[33] In the present study the 3 months post-CRT transmitral E/A ratio did not change. However, the number of patients with a restrictive LV filling pattern decreased and there was a significant reduction in the E/E' ratio. Baseline and 3-months follow-up persistence of

restrictive LV filling pattern and the E/E' ratio predicted events. Both these parameters provide a simple, reproducible and bedside test.

CONCLUSION

The Tei index and E/E' ratio are independent predictors of cardiac events after CRT.

REFERENCES

1. 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**(15):1539-1549.
2. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ: **Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials**. *Eur Heart J* 2006, **27**(22):2682-2688.
3. Nishimura RA, Hayes DL, Holmes DR, Jr., Tajik AJ: **Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study**. *J Am Coll Cardiol* 1995, **25**(2):281-288.
4. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R *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.
5. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B, Nevo E: **Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay**. *Circulation* 1999, **99**(12):1567-1573.
6. 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**(11):1580-1586.
7. Soliman OI, Theuns DA, Geleijnse ML, Anwar AM, Nemes A, Caliskan K, Vletter WB, Jordaens LJ, Cate FJ: **Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy**. *Europace* 2007, **9**(2):113-118.
8. de Sisti A, Toussaint JF, Lavergne T, Ollitrault J, Abergel E, Paziaud O, Ait Said M, Sader R, JY LEH, Guize L: **Determinants of mortality in patients undergoing cardiac resynchronization therapy: baseline clinical, echocardiographic, and angioscintigraphic evaluation prior to resynchronization**. *Pacing Clin Electrophysiol* 2005, **28**(12):1260-1270.
9. Gasparini M, Lunati M, Santini M, Tritto M, Curnis A, Bocchiardo M, Vincenti A, Pistis G, Valsecchi S, Denaro A: **Long-term survival in patients treated with cardiac resynchronization therapy: a 3-year follow-up study from the InSync/InSync ICD Italian Registry**. *Pacing Clin Electrophysiol* 2006, **29 Suppl 2**:S2-10.
10. Mangiavacchi M, Gasparini M, Faletra F, Klersy C, Morenghi E, Galimberti P, Genovese L, Regoli F, De Chiara F, Bragato R *et al*: **Clinical predictors of marked improvement in left ventricular performance after cardiac resynchronization therapy in patients with chronic heart failure**. *Am Heart J* 2006, **151**(2):477 e471-477 e476.
11. Porciani MC, Valsecchi S, Demarchi G, Colella A, Michelucci A, Pieragnoli P, Musilli N, Gensini GF, Padeletti L: **Evolution and prognostic significance of diastolic filling pattern in cardiac resynchronization therapy**. *Int J Cardiol* 2006, **112**(3):322-328.
12. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN: **Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure**. *J Am Coll Cardiol* 1994, **24**(1):132-139.
13. Acil T, Wichter T, Stypmann J, Janssen F, Paul M, Grude M, Scheld HH, Breithardt G, Bruch C: **Prognostic value of tissue Doppler imaging in patients with chronic congestive heart failure**. *Int J Cardiol* 2005, **103**(2):175-181.
14. Bruch C, Schmermund A, Marin D, Katz M, Bartel T, Schaar J, Erbel R: **Tei-index in patients with mild-to-moderate congestive heart failure**. *Eur Heart J* 2000, **21**(22):1888-1895.
15. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K *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**(12):e154-235.
16. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A *et al*: **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**(11):1115-1140.
17. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR *et al*: **ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography)**. *J Am Coll Cardiol* 2003, **42**(5):954-970.
18. 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**(2):167-184.
19. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP, Jr.: **Color Doppler assessment of mitral regurgitation with orthogonal planes**. *Circulation* 1987, **75**(1):175-183.
20. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA: **Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures**. *J Am Coll Cardiol* 1997, **30**(6):1527-1533.
21. Tei C: **New non-invasive index for combined systolic and diastolic ventricular function**. *J Cardiol* 1995, **26**(2):135-136.
22. Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, Kass DA, Powe NR: **Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials**. *Jama* 2003, **289**(6):730-740.
23. Murphy RT, Sigurdsson G, Mulamalla S, Agler D, Popovic ZB, Starling RC, Wilkoff BL, Thomas JD, Grimm RA: **Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy**. *Am J Cardiol* 2006, **97**(11):1615-1621.

24. Porciani MC, Lilli A, Macioce R, Cappelli F, Demarchi G, Pappone A, Ricciardi G, Padeletti L: **Utility of a new left ventricular asynchrony index as a predictor of reverse remodelling after cardiac resynchronization therapy**. *Eur Heart J* 2006, **27**(15):1818-1823.
25. Da Costa A, Thevenin J, Roche F, Faure E, Romeyer-Bouchard C, Messier M, Convert G, Barthelemy JC, Isaaz K: **Prospective validation of stress echocardiography as an identifier of cardiac resynchronization therapy responders**. *Heart Rhythm* 2006, **3**(4):406-413.
26. St John Sutton M, Wiegers SE: **The Tei index - a role in the diagnosis of heart failure?** *Eur Heart J* 2000, **21**(22):1822-1824.
27. Moller JE, Poulsen SH, Sondergaard E, Egstrup K: **Preload dependence of color M-mode Doppler flow propagation velocity in controls and in patients with left ventricular dysfunction**. *J Am Soc Echocardiogr* 2000, **13**(10):902-909.
28. Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB: **Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy**. *Am J Cardiol* 1998, **82**(9):1071-1076.
29. Sasao H, Noda R, Hasegawa T, Endo A, Oimatsu H, Takada T: **Prognostic value of the Tei index combining systolic and diastolic myocardial performance in patients with acute myocardial infarction treated by successful primary angioplasty**. *Heart Vessels* 2004, **19**(2):68-74.
30. Whalley GA, Gamble GD, Doughty RN: **Restrictive diastolic filling predicts death after acute myocardial infarction: systematic review and meta-analysis of prospective studies**. *Heart* 2006, **92**(11):1588-1594.
31. Pinamonti B, Zecchin M, Di Lenarda A, Gregori D, Sinagra G, Camerini F: **Persistence of restrictive left ventricular filling pattern in dilated cardiomyopathy: an ominous prognostic sign**. *J Am Coll Cardiol* 1997, **29**(3):604-612.
32. Whalley GA, Gamble GD, Doughty RN: **The prognostic significance of restrictive diastolic filling associated with heart failure: a meta-analysis**. *Int J Cardiol* 2007, **116**(1):70-77.
33. Hillis GS, Moller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, Reeder GS, Oh JK: **Noninvasive estimation of left ventricular filling pressure by E/e' is a powerful predictor of survival after acute myocardial infarction**. *J Am Coll Cardiol* 2004, **43**(3):360-367.

Chapter 9

A rational approach to assess optimal left ventricular pacing site for cardiac resynchronization therapy using real-time three-dimensional echocardiography

Osama I.I. Soliman[1,2], Dominic A.M.J. Theuns[1], Marcel L. Geleijnse[1], Bas M. van Dalen[1], Attila Nemes[1], Wim B. Vletter[1], Luc J. Jordaens[1], and Folkert J. ten Cate[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt

Submitted for publication

ABSTRACT

Background: A non-optimal site of left ventricular (LV) lead may be a potential cause for non-responders after cardiac resynchronization therapy (CRT).

Hypothesis: Real-time three-dimensional echocardiography (RT3DE) can define the site of latest activation and thus optimal LV pacing site, which may improve outcome after CRT.

Methods: The site of latest mechanical LV activation was determined by RT3DE bull's eye parametric color maps in 56 patients (61 ± 14 years, 55% male) who received CRT-D according to guidelines. Two blinded observers analyzed both the optimal (site of latest mechanical LV activation by RT3DE) and actual (radiographic) lead position. The RT3DE LV systolic dyssynchrony index (SDI) was defined as the standard deviation of time-to-minimum systolic volume of the 16 LV segments as a percentage of the cardiac cycle.

Results: Matching "paced" to "suggested" RT3DE LV pacing sites resulted in 3 patient groups: concordant (n = 25), intermediate (n = 14) and discordant (n = 17). Baseline characteristics were comparable between the groups. After 3-6 months of CRT, the SDI was reduced in concordant (15.9 ± 5.9% vs. 7.9 ± 4.7%, P <0.001) and intermediate (14.3 ± 6.2% vs. 9.1 ± 7.1%, P <0.05) but not in discordant (12.1 ± 7.1% vs. 13.7 ± 8.2%) patients. Reductions in LV end-diastolic (32%, 24% and 11%), end-systolic (39%, 27% and 12%) volumes and improvement in LV ejection fraction by 60%, 46% and 15%, were seen, respectively in the 3 groups (versus discordant group P <0.01).

Conclusions: RT3DE parametric imaging provides a relatively simple, reproducible technique to identify the site of latest mechanical LV activation. Because pacing at this suggested site is associated with a favorable response to CRT RT3DE may be used for guiding CRT device implantation.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a successful therapy for patients with moderate to severe heart failure (HF) and left ventricular (LV) dyssynchrony.[1] However, a significant proportion of HF patients do not benefit from CRT despite pre-implantation mechanical dyssynchrony.[2-4]The rationale behind CRT is to stimulate the most delayed LV site.[5] One potential mechanism for CRT failure is the non-favorable LV lead position. In several studies non-mechanical (electrical) delay or limited assessment of mechanical delay in one or two-dimensional planes was used to identify the optimal LV pacing site.[3, 6] However, identification of the optimal site of LV pacing based on three-dimensional assessment of mechanical delay has not been described. Real-time three-dimensional echocardiography (RT3DE) can accurately measure global and regional LV function.[7-9] Recently, a novel RT3DE technique for parametric imaging based on quantification of LV mechanical events as a function of time has been developed. It displays the temporal course of LV mechanical events in simple color maps, ranging from monochromatic green maps from homogeneous LV contractility to polychromatic maps from dyssynchronous ventricles. The present study sought to (1) define the site of latest LV contraction using RT3DE in HF patients undergoing CRT, (2) test the inter-observer agreement and normal distribution of LV mechanical contraction using RT3DE in HF patients and healthy volunteers and (3) evaluate the predictive value of LV RT3DE defined optimal pacing site on CRT outcome.

METHODS

Study Population

Fifty-six consecutive HF patients referred for CRT were enrolled into the study according to the following criteria: (1) New York Heart Association (NYHA) functional class ≥III despite optimal drug therapy (2) impaired LV ejection fraction (LV-EF) <35%, and (3) wide QRS complex >120 msec in the form of left bundle branch block and in sinus rhythm. These CRT indications comply with current guidelines.[10, 11] Patients with atrial fibrillation, acute coronary syndromes or coronary revascularization within 6 months before CRT were excluded. In addition, an independent observer who was blinded to CRT device implantation data excluded patients with poor image quality from the study. To define normal values on the novel RT3DE technique 30 healthy volunteers underwent RT3DE and served as control group. An informed consent was obtained from all subjects and the institutional review board approved the study.

Study Protocol

Since this was a prospective study designed to study the usefulness of RT3DE in CRT lead implantation the implanting physicians were unaware of the 3D echo analysis. All CRT patients underwent two-dimensional and RT3DE before CRT and after 3-6 months. Two days after CRT, atrio-ventricular delay was optimized by 2D echocardiography to provide the longest filling time for completion of the end-diastolic filling flow before LV contraction with the highest LV outflow tract velocity timed integral.[12, 13] Patients

were scheduled for regular clinical follow-up and the CRT device was interrogated to ensure that biventricular pacing was being maintained. Two independent observers who were unaware of the patient clinical status, study objectives or other echocardiographic data performed analyses of the follow-up data. Clinical responders to CRT were defined as patients who had an improvement of ≥1 NYHA class plus >25% increase in six-minute walking distance (6MWD). Echocardiographic responders were defined as patients who had >15% reduction in LV end-systolic volume (LV-ESV).

Device implantation

As described previously [12, 13], CRT device implantation was performed preferably with a single left pectoral incision, a left cephalic vein cutdown and a left subclavian puncture. The defibrillation lead of implantable cardiovertor defibrillator (ICD) was positioned in the right ventricular apex. The LV pacing lead was placed in a tributary of the coronary sinus. Adequate pacing and sensing properties of all leads, and diaphragmatic stimulation with the LV pacing lead were tested. The lowest effective defibrillation energy was assessed and a safety margin of ≥10 J was used. Devices used were InSync 7272, 7279, and 7298 (Medtronic Inc, Minneapolis, MN, USA), Renewal II (Guidant Inc, St Paul, MN, USA), and Epic HF V-339 and Atlas HF V-341 (St Jude Medical, Sylmar, CA, USA). For all patients, ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation.

Two-dimensional echocardiography

All patients were examined using the iE33 ultrasound system (Philips, Best, The Netherlands) with a S3 transducer according to the recommendations of the American Society of Echocardiography.[14, 15]. LV end-diastolic volume (LV-EDV), LV-ESV and LV-EF (by modified bi-plane Simpson rule) were calculated from the apical 4-chamber and 2-chamber views. The degree of mitral regurgitation (grade I-IV) was assessed as the mid-systolic percentage jet area relative to left atrial area in the apical 4-chamber view.[16]

Radiographic evaluation of left ventricular leads position

As shown in Figure 1, both the poster-anterior and the lateral radiographic views were used to examine the site of the LV lead. LV lead position was confirmed from the lateral film, where two vertical planes divided the cardiac silhouette into anterior, lateral and posterior, and two horizontal planes divided the cardiac silhouette into basal, mid and apical. Two blinded observers defined the LV lead position.

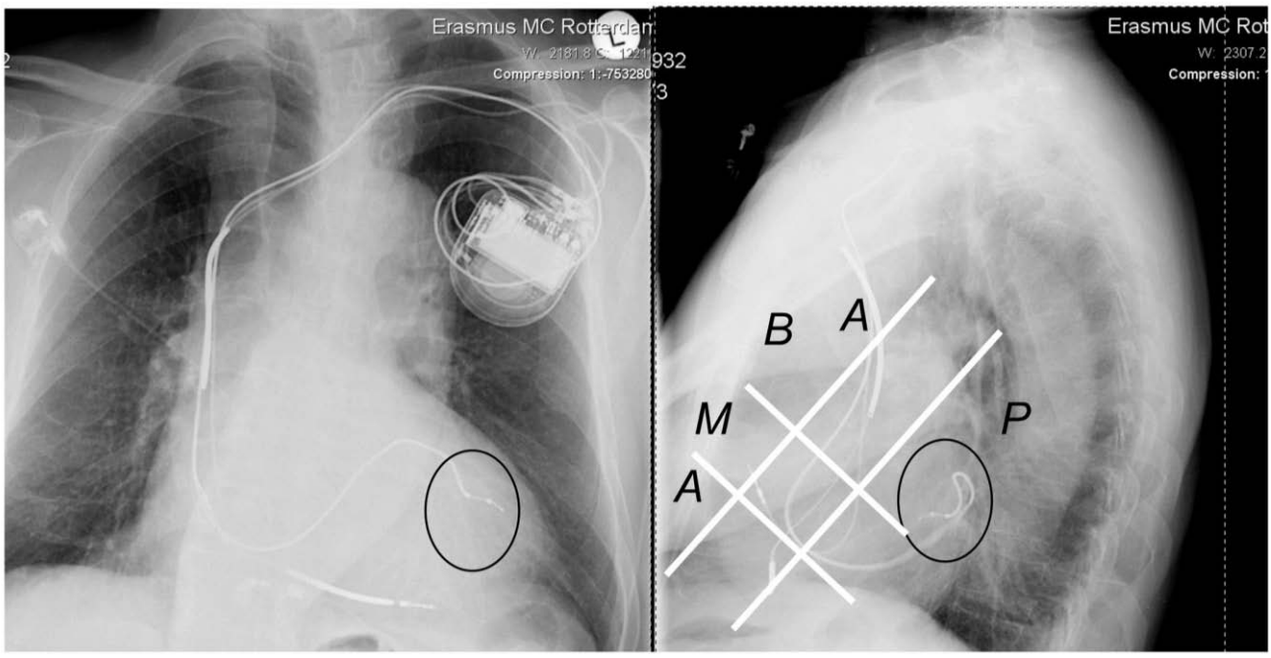


Figure 1. Radiographic images: the postero-anterior view to the left and the lateral view to the right. The exact lead position is confirmed from the lateral image.

Transthoracic RT3DE

Image acquisition

RT3DE was performed using the same iE33 ultrasound machine (Philips Medical Systems, Best, The Netherlands) equipped with a X3 matrix-array transducer with the patient in a left lateral decubitus. Image acquisition was performed from an apical window with the LV as region of interest. Adjustments of the ultrasound machine depth and ultrasound density lines were performed to acquire full-volume data of the LV in the highest possible frame rate. Typical frame rates acquired were 25 to 35 frames per second. To encompass the complete LV into the 3D data set, a full volume (up to 103° × 103°) scan was acquired in harmonic mode from four-to-seven R-wave triggered sub-volumes during an end-expiratory breath-hold lasting for 6 to 8 seconds. The 3D data set was stored digitally and transferred via a network server to QLAB workstation for off-line analysis.

Image analysis

(i)-System start-up and calculation of global function

Analysis of RT3DE datasets was performed on QLAB workstation using the 3D-Advanced quantification (3DAdv, version 6.0, Philips, Best, The Netherlands) software package. The 3DQAdv uses all voxels from 3D datasets to semi-automatically detect the 3D LV endocardial border and timing of regional LV volume changes. It uses a physics-based modeling algorithm that makes no assumptions regarding LV geometry.[7]

(ii)-Regional left ventricular data

The analysis of the global and regional LV function is achieved by creating artificial segments, based on the recommendations of the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association.[17] These segments divide the LV region into four sections relative to the long axis of the heart. Each of these sections is then divided, equally, into subsections around the circumference of the heart.[17] The regional volume waveforms are computed from ~900 small anatomical myocardial segments (not displayed), but only the regional volume curves from the 17 standard LV segments are displayed. 3D Data from LV volume, myocardial radial excursion and timing of systolic and diastolic events can be shown in the form of curves and on two Bull's eye color maps.

(iii)- Radial excursion (spatial map)

The radial excursions of LV segments are displayed on static Bull's eye color maps. The long axis of the LV is used as the spatial reference line. The radial distances (excursion) from ~900 points to the reference line are computed (in mm): maximum, minimum, average and standard deviation (SDof LV radial excursion are extracted and displayed. Three basic color codes refer to LV radial excursion as follows: high excursion amplitude in blue, low excursion amplitude in dark blue and opposite excursion (dysskinetic) in red.

(iv)-**Volumetric timing** (**Temporal map)**

The timing of LV volume changes is displayed on Bull's eye color map. The global time-to-minimum systolic volume (Tmsv) is used as the temporal reference point. Tmsvs for each of ~900 points are computed (in msec) and compared to the global reference Tmsv. The Tmsv from any segments within a SD of ± 30 msec will be coded in green while early points will be coded in blue and late points will show up in red-to-yellow. A SD of ± 35 msec (range 25 to 48 msec) was found as the normal distribution of LV regional Tmsv in reference to global Tmsv in 30 healthy volunteers. A color map from a healthy volunteer is seen in Figure 2.

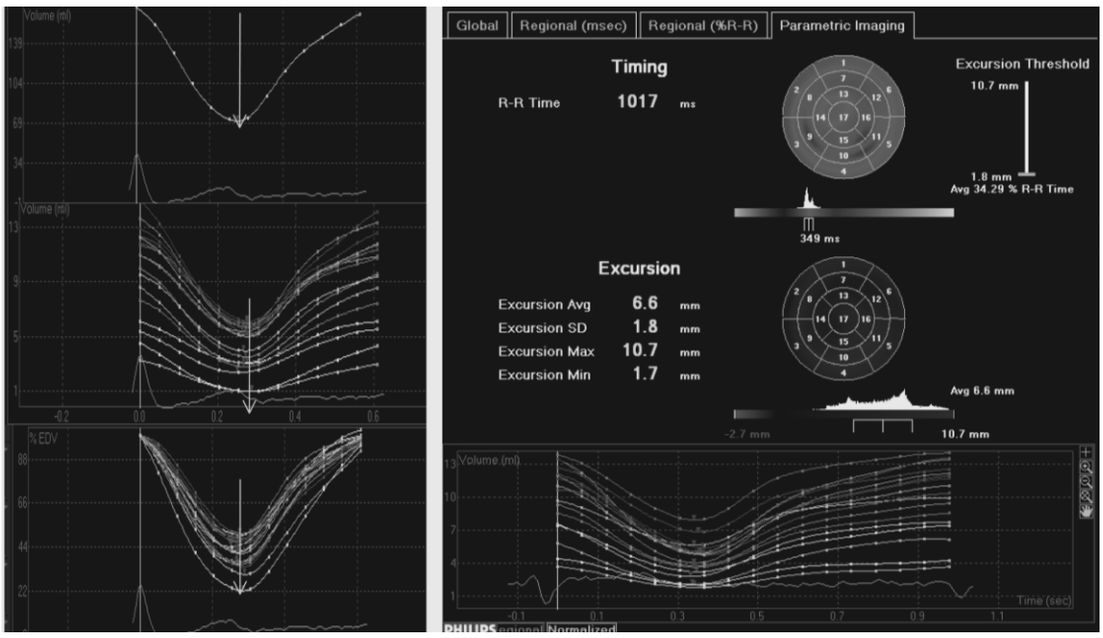


Figure 2. Display of a parametric real-time three-dimensional imaging map from a healthy volunteer. The left panel displays 3 time-volume curves: global time-volume curve (upper), regional time volume curves from the standard 17 left ventricular segments (mid) and the same regional time-volume curves, which are displayed in relative values to the R-R interval on the electrocardiogram. The arrows in the left panel refer to the time-to-minimum systolic volume. In the right panel the parametric bull's eye display of timing map (upper) and radial excursion map (lower). For full color image see the end of this book.

Reproducibility of RT3DE measurements

The inter-observer agreement between the two blinded independent observers for the definition of the territory of latest activation from RT3DE parametric imaging was 0.87 (95% CI 0.74- 0.99) by kappa analysis.

Concordance between radiographic and echocardiographic lead position

As seen in Figure 3, a bull's eye segmentation based on the American Heart Association standard myocardial segmentation was used to display RT3DE parametric color maps of LV activation. Since septal territories are not feasible for pacing; potential concordant LV segments were referred as anterior, antero-lateral, lateral, postero-lateral and posterior. The lead position in the lateral radiographic view was determined as mentioned before. The primary investigator (OIIS) analyzed the degree of concordance between LV latest activation and LV lead implantation sites. Data of suggested pacing sites (most delayed) from RT3DE and actually paced sites from radiographic images were compared. The degree of pacing-RT3DE concordance was classified as concordant (same territory), intermediate (adjacent territories) and discordant (apart by >1 territory).

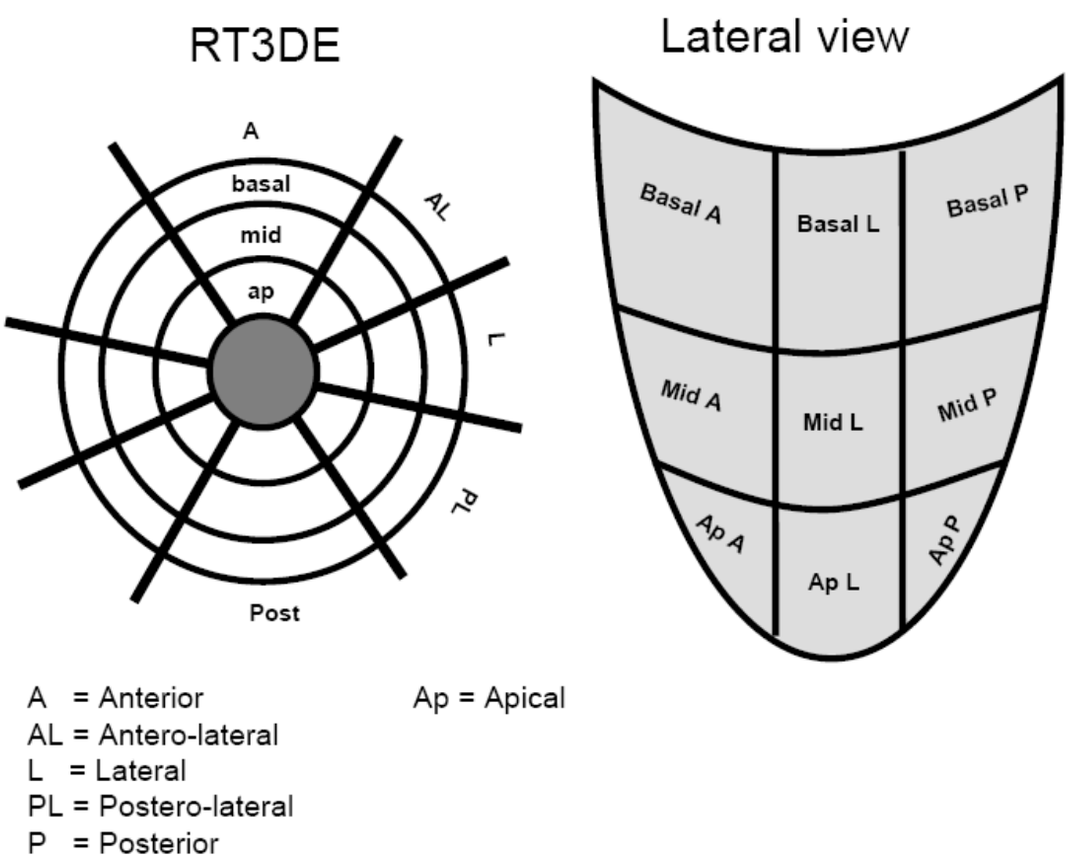


Figure3. Anatomical segmentation of the bull's eye from the real-time three-dimensional imaging map (left) and from lateral radiographic film to the right

STATISTICAL ANALYSES

All statistics were performed using the Statistical Package of Social Sciences (SPSS 12.0.2) for Windows (Chicago, IL, USA). Descriptive statistics for nominal data were expressed in absolute numbers and percentages. After checking for normality, mean values and standard deviations were calculated for normally distributed continuous variables. Baseline values were compared by the unpaired *t* test or the *Mann–Whitney U* test, if appropriate. The *Chi-square* test was used for the comparison of categorical variables. A value of $P < 0.05$ was considered significant.

RESULTS

Patient characteristics

The study included 56 patients (mean age 61 ± 14 years, 55% men). Twenty-seven patients (48%) had ischemic HF and 29 patients (52%) had non-ischemic HF.

Procedural characteristics

LV lead position

Transvenous implantation of the CRT devices was successful in 54 patients (96%). In the remaining 2 patients (4%) surgical placement of the LV lead was performed. The coronary sinus venous tributaries used were: postero-lateral branch in 29 patients (52%), lateral branch in 8 patients (14%), antero-lateral branch in 14 patients (25%) and posterior branch in 3 patients (5%), and surgical implantation at lateral position in 2 patients (4%). The LV lead tip on radiography was in a posterolateral territory in 30 patients (54%), lateral territory in 17 patients (30%), posterior territory in 4 patients (7%), antero-lateral territory in 4 patients (7%) and anterior territory in one patient (2%). The LV lead tip was seen in the basal LV territories in 38 patients (68%), mid LV territories in 14 patients (25%) and apical LV territories in 4 patients (7%). Inter-observer agreement for the definition of the position of LV lead tip on radiography was 0.93 (95% CI 0.84 - 1.0) by kappa analysis.

Echocardiographic (RT3DE) characteristics

The average time for acquisition of a single full-volume RT3DE dataset was 2 minutes and the time for analysis of the RT3DE datasets ranged from 4 to 10 minutes. From the analyzed datasets the following variables were calculated: (i) the extent of mechanical dyssynchrony calculated as the maximum dispersion in Tmsv between any of the 16 myocardial segments, the systolic dyssynchrony index (SDI), which is defined as the standard deviation of Tmsv of the 16-myocardial segments as a percentage from the cardiac cycle, and (iii) the site of latest mechanical activation on color maps.

Table 1. Baseline Clinical, Electrocardiographic, and Echocardiographic Characteristics

Parameter	Concordant (n = 25)	Intermediate (n = 14)	Discordant (n = 17)
Clinical data			
Age, (years)	61 ± 14	60 ± 12	61 ± 13
Male gender, n (%)	15 (60)	8 (57)	8 (47)
NYHA class, n (%)			
I	0 (0)	0 (0)	0 (0)
II	0 (0)	0 (0)	0 (0)
III	25 (100)	14 (100)	17 (100)
IV	0 (0)	0 (0)	0 (0)
6MWD, (meters)	227 ± 52	224 ± 39	221 ± 49
QRS duration, (ms)	169 ± 29	167 ± 27	171 ± 29
Ischemic HF etiology, n (%)	12 (48)	6 (43)	9 (53)
Medications, n (%)			
Amiodarone	8 (32)	4 (29)	6 (35)
Beta-blockers	19 (76)	11 (79)	13 (76)
ACE-inhibitors	22 (88)	12 (86)	14 (82)
Diuretics	23 (92)	12 (86)	15 (88)
Digitalis	7 (28)	4 (29)	6 (35)
Echocardiographic data			
LV-EDV, (ml)	258 ± 119	253 ± 125	248 ± 129
LV-ESV, (ml)	214 ± 102	212 ± 100	207 ± 98
LV-EF, (%)	18 ± 6	18 ± 7	18 ± 7
LV-mass, (g)	244 ± 54	247 ± 63	242 ± 68
MR grade, n (%)	2.7 ± 1.7	2.6 ± 1.7	2.7 ± 1.9
MPI	0.95 ± 0.19	0.97 ± 0.22	0.95 ± 0.24
Dispersion max, (ms)	258 ± 108	248 ± 117	252 ± 122
SDI, (%)	15.9 ± 5.9	14.3 ± 6.2	12.1 ± 7.1

P values were not significant for all comparisons between the three groups. 6MWD = six-minute walk distance; ACE = angiotensin converting enzyme; HF = heart failure; LV-EDV = left ventricular end-diastolic volume; LV-EF = left ventricular ejection fraction; LV-ESV = left ventricular end-systolic volume; MPI = myocardial performance index; MR = mitral valve regurgitation; NYHA = New York Heart Association; RT3DE = real-time three-dimensional echocardiography

RT3DE left ventricular dyssynchrony

Pre-implantation

Assessment of the patients has normal synchronicity before CRT. Five patients (9%) had mild dyssynchrony, SDI <6%, and a mild heterogeneous contraction map without a well-defined single site of latest mechanical activation. In these patients the site of latest LV mechanical activation was not assessed from the color maps but was defined from the maximum dispersion between earliest and latest activated segments. The site of latest LV mechanical activation was the lateral territory in 15 patients (27%),

posterolateral territory in 16 patients (29%), posterior territory in 13 patients (23%), antero-lateral territory in 7 patients (13%) and in more than one territory in 5 patients (8%).

Post implantation

At 3 to 6 months after CRT, LV mechanical contraction patterns were altered in all patients. In the 5 patients, without pre-implantation significant dyssynchrony, worsened LV activation patterns were seen evidenced by an increasing SDI from 5.2 ± 3.5% to 10.1 ± 3.2% (P<0.001) and more heterogeneous color maps. The site of earliest LV mechanical activation after CRT was seen at or adjacent to the territory of LV lead in all patients as a light-to-dark blue area in the contraction map. Figure 4 shows the changes in mechanical activation sequence in a dyssynchronous HF patient becoming more synchronous after CRT.

Table 2. Three-to-six-month outcome after cardiac resynchronization therapy

Parameter	Concordant (n = 25)	Intermediate (n = 14)	Discordant (n = 17)
Responders, n (%)	21 (76)	8 (57)	3 (18)
NYHA class, n			
I	6 (24)	3 (21)	1 (6)
II	15 (60)	5 (36)	5 (29)
III	4 (16)‡	6 (43)	10 (59)
IV	0 (0)	0 (0)	1 (6)
Δ 6MWD, (%)	41‡	35†	21
Δ QRS duration, (%)	-20	-17	-15
Echocardiographic outcome			
Δ LV-EDV, (%)	-32‡	-24†	-11
Δ LV-ESV, (%)	-39‡	-27†	-12
Δ LV-EF, (%)	60‡	46#	13
Δ MR grade, n (%)	-49‡	-34†	-23
Δ MPI	-53‡	-44†	-22
Dispersion max, (ms)	112 ± 102	138 ± 117	205 ± 155
SDI, (%)	7.9 ± 4.7	9.1 ± 7.1	13.7 ± 8.2

Abbreviations as in Table 1
*All P values between concordant and intermediate patients were not significant
†P <0.05; # P <0.01 ‡ P <0.001 for concordant and intermediate versus discordant.

Effects of concordance on LV mechanical dyssynchrony

The mean maximum dispersion in Tmsv between any two of the 16 myocardial segments was 255 ± 114 ms. There was no significant difference between the 3 pacing-RT3DE concordance groups regarding baseline dyssynchrony on RT3DE (Table 1). After 3-6 months of CRT, SDI was reduced in concordant (15.9

± 5.9% vs. 7.9 ± 4.7%, P <0.001) and intermediate (14.3 ± 6.2% vs. 9.1 ± 7.1%, P <0.05) but not in discordant patients (12.1 ± 7.1% vs. 13.7 ± 8.2%).

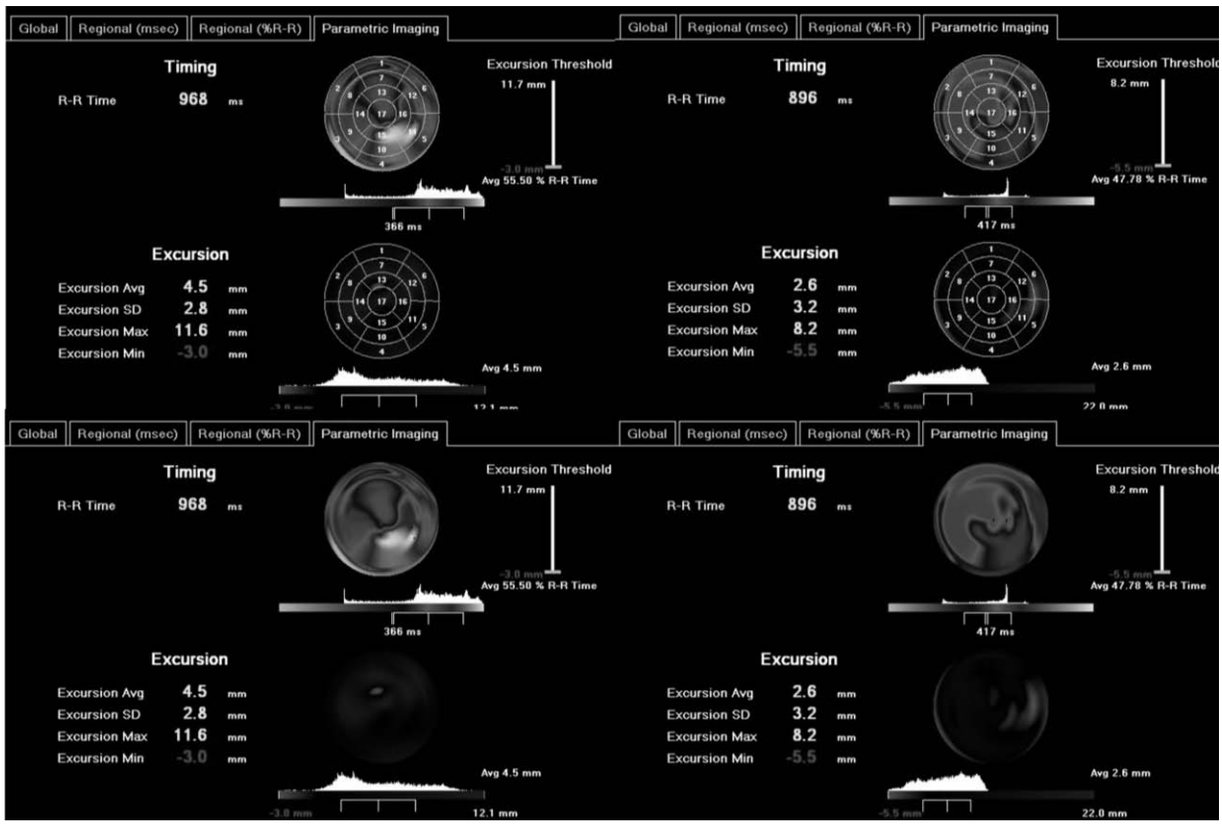


Figure 4. Real-time three-dimensional echocardiography parametric images from a heart failure patient with the standard myocardial segmentations before resynchronization therapy (left upper panel), without segmentation (left lower panel) and after resynchronization therapy with (right upper panel) and without myocardial segmentations. Note the reversal of myocardial activation pattern in the most delayed (yellow-red) postero-lateral and posterior segments to earlier (blue) contraction after therapy. For full color image see the end of this book.

Effects of concordance on clinical outcome and reverse LV remodeling

At 3 to 6 months of CRT, 38 (68%) patients were clinical responders and 32 patients (57%) were echocardiographic responders. Improvements in the 6MWD by 41%, 34, and 21%were seen in concordant, intermediate and discordant patients, respectively (for concordant and intermediate versus discordant patients P <0.001). Reductions in LV-EDV (versus discordant P<0.05) by 32%, 24% and 11% and LV-ESV by 39%, 27% and 12% and improvement in LV-EF (versus discordant P <0.001) by 60%, 46% and 30% were seen, respectively in the 3 groups (for concordant and intermediate versus discordant patients P <0.001, Table 2).

DISCUSSION

The major findings of this study are the following: (1) RT3DE can be used to identify the site of latest LV mechanical activation before CRT, (2) semi-automated endocardial border analysis of RT3DE datasets allow for a reproducible assessment of myocardial contraction sequence in a relatively short time, and (3) patients who have their LV lead implanted at or adjacent to the suggested site of most delayed LV activation on RT3DE (concordant) have a greater chance to benefit from CRT as compared to discordant patients.

RT3DE parametric imaging of LV contraction

The degree of LV mechanical dyssynchrony has been investigated in HF patients using different echocardiographic techniques.[3, 18-21] In all these studies the extent of mechanical dyssynchrony was assessed from cardiac motion in one or two dimensions. Moreover, Doppler based techniques have several technical and physiological limitations related to translational motion and angle dependency and the limited number of myocardial segments studied. In contrast to RT3DE these techniques do also not allow simultaneous assessment of all regional LV contractions. Recently, the RT3DE-derived SDI has been shown to predict reverse LV remodeling after CRT.[22] The software used for analysis of LV function from RT3DE datasets generates time-volume curves that display LV volume changes over time. The full volume RT3DE methodology used in the current study requires only a single acquisition and allows calculation of the LV mechanical activation pattern in less than 10 minutes. Current ultrasound systems allow even online analysis, which may be faster and more practical. Recent advances in transducer technology and software have significantly improved spatial resolution allowing better LV endocardial border definition (a prerequisite for accurate volume analysis) and assessment of the temporal course of LV activation. In the current study, 3D parametric imaging was shown to be a relatively simple, reproducible and easily interpretable technique for the assessment of the temporal course of LV activation.

Position of LV lead in cardiac resynchronization therapy

CRT is an accepted intervention in end-stage HF patients.[11, 23] Unfortunately, in about 30% of patients no clinical benefit is seen.[23] To decrease the percentage of CRT non-responders, initial efforts were focused on detection of baseline dyssynchrony.[24, 25] However, it is well known that still a number of patients with echocardiographically do not respond to CRT.[2-4] Butter et al. was the first to demonstrate that improvement in LV mechanical performance is related to the pacing site.[26, 27] The site of latest LV electrical activation in experimental electrophysiological studies using 3D mapping systems have varied considerably in HF patients with left bundle branch block.[28] In the "real world" the pacing lead is usually implanted "midlateral" [3, 4, 20, 26, 27, 29, 30] and this position gives in most patients indeed a satisfactory result.[3, 4, 26] However, to achieve optimal results in patients with LV dyssynchrony pacing of the last activated LV wall seems essential. Echocardiography may have an important role in identification of this wall and thus in optimal LV pacing. In most echocardiographic studies tissue Doppler imaging [3, 20, 31, 32] or 2D strain imaging[6, 33, 34] was used for identification of the latest activated LV

site. These techniques have inherent limitations.[13] Multiple wall acquisition are necessary and true and simultaneous 3D information on mechanical activation is not given. In the present study, we used color maps representing LV contractility based on RT3DE volumetric analysis of all myocardial segments. LV pacing at the suggested site of latest mechanical activation on RT3DE parametric imaging was associated with better outcome after CRT. Our data emphasizes the role of LV lead position in improving results of CRT that may be guided by RT3DE.

Study limitations

Being an imaging tool RT3DE has the limitation of echocardiography. Therefore, patients with poor echocardiographic window are difficult to image. In patients with end-stage HF the heart may be severely dilated and it may be difficult to encompass the whole LV volume within the image sector. However, in the current study we used an ultrasound machine that allowed for appropriate full-volume acquisition in almost all patients. The third potential limitation is the relatively low temporal resolution of 30-40 ms compared to other echocardiographic modalities such as Doppler imaging. The temporal resolution may be improved in the near future by first-harmonic Fourier transformation in which discrete temporal data points re transformed into a continuous curve.

CONCLUSIONS

RT3DE parametric imaging provides a relatively simple, reproducible technique to identify the site of latest mechanical LV activation. Because pacing at this suggested site is associated with a favorable response to CRT RT3DE may be used for guiding CRT device implantation.

REFERENCES

1. McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, Page RL, Hlatky MA, Rowe BH: **Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review**. *Jama* 2007, **297**(22):2502-2514.
2. Blanc JJ, Etienne Y, Gilard M, Mansourati J, Munier S, Boschat J, Benditt DG, Lurie KG: **Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study**. *Circulation* 1997, **96**(10):3273-3277.
3. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M: **Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing**. *J Am Coll Cardiol* 2002, **39**(3):489-499.
4. Macias A, Gavira JJ, Alegria E, Azcarate PM, Barba J, Garcia-Bolao I: **[Effect of the left ventricular pacing site on echocardiographic parameters of ventricular dyssynchrony in patients receiving cardiac resynchronization therapy]**. *Rev Esp Cardiol* 2004, **57**(2):138-145.
5. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, Klein H, Kramer A, Ding J, Salo R *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.
6. Becker M, Kramann R, Franke A, Breithardt OA, Heussen N, Knackstedt C, Stellbrink C, Schauerte P, Kelm M, Hoffmann R: **Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodelling. A circumferential strain analysis based on 2D echocardiography**. *Eur Heart J* 2007, **28**(10):1211-1220.
7. Soliman OII, Krenning BJ, Geleijnse ML, Nemes A, van Geuns R-J, Baks T, Anwar AM, Galema TW, Vletter WB, Cate FJT: **A Comparison between QLAB and TomTec Full Volume Reconstruction for Real Time Three-Dimensional Echocardiographic Quantification of Left Ventricular Volumes**. *Echocardiography* 2007 **24**(9):967-974.
8. Soliman OI, Krenning BJ, Geleijnse ML, Nemes A, Bosch JG, van Geuns RJ, Kirschbaum SW, Anwar AM, Galema TW, Vletter WB *et al*: **Quantification of Left Ventricular Volumes and Function in Patients with Cardiomyopathies by Real-time Three-dimensional Echocardiography: A Head-to-Head Comparison Between Two Different Semiautomated Endocardial Border Detection Algorithms**. *J Am Soc Echocardiogr* 2007.
9. Jaochim Nesser H, Sugeng L, Corsi C, Weinert L, Niel J, Ebner C, Steringer-Mascherbauer R, Schmidt F, Schummers G, Lang RM *et al*: **Volumetric analysis of regional left ventricular function with real-time three-dimensional echocardiography: validation by magnetic resonance and clinical utility testing**. *Heart* 2007, **93**(5):572-578.
10. Hunt SA: **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)**. *J Am Coll Cardiol* 2005, **46**(6):e1-82.
11. Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A *et al*: **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**(11):1115-1140.
12. Soliman OI, Theuns DA, Cate FJ, Anwar AM, Nemes A, Vletter WB, Jordaens LJ, Geleijnse ML: **Baseline Predictors of Cardiac Events after Cardiac Resynchronization Therapy in Patients with Heart Failure Secondary to Ischemic or Non-Ischemic Etiology**. *Am J Cardiol* 2007, **100**(3):464-469.
13. Soliman OI, Theuns DA, Geleijnse ML, Anwar AM, Nemes A, Caliskan K, Vletter WB, Jordaens LJ, Cate FJ: **Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy**. *Europace* 2007, **9**(2):113-118.
14. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davidson TW, Davis JL, Douglas PS, Gillam LD *et al*: **ACC/AHA guidelines for the clinical application of echocardiography: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography**. *J Am Coll Cardiol* 1997, **29**(4):862-879.
15. 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**(2):167-184.
16. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP, Jr.: **Color Doppler assessment of mitral regurgitation with orthogonal planes**. *Circulation* 1987, **75**(1):175-183.
17. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS: **Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association**. *Circulation* 2002, **105**(4):539-542.
18. Pitzalis MV, Iacoviello M, Romito R, Massari F, Rizzon B, Luzzi G, Guida P, Andriani A, Mastropasqua F, Rizzon P: **Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony**. *J Am Coll Cardiol* 2002, **40**(9):1615-1622.
19. Breithardt OA, Stellbrink C, Herbots L, Claus P, Sinha AM, Bijnens B, Hanrath P, Sutherland GR: **Cardiac resynchronization therapy can reverse abnormal myocardial strain distribution in patients with heart failure and left bundle branch block**. *J Am Coll Cardiol* 2003, **42**(3):486-494.
20. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, 3rd: **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**(7):960-968.
21. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR *et al*: **Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure**. *Circulation* 2002, **105**(4):438-445.

22. 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**(7):992-1000.
23. Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, Kass DA, Powe NR: **Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials**. *Jama* 2003, **289**(6):730-740.
24. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP: **Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy**. *Am J Cardiol* 2003, **91**(6):684-688.
25. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ: **Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy**. *J Am Coll Cardiol* 2004, **44**(9):1834-1840.
26. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, Huvelle E, Spinelli J: **Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients**. *Circulation* 2001, **104**(25):3026-3029.
27. Butter C, Auricchio A, Stellbrink C, Schlegl M, Fleck E, Horsch W, Huvelle E, Ding J, Kramer A: **Should stimulation site be tailored in the individual heart failure patient?** *Am J Cardiol* 2000, **86**(9A):144K-151K.
28. Auricchio A, Fantoni C, Regoli F, Carbucicchio C, Goette A, Geller C, Kloss M, Klein H: **Characterization of left ventricular activation in patients with heart failure and left bundle-branch block**. *Circulation* 2004, **109**(9):1133-1139.
29. Gasparini M, Mantica M, Galimberti P, Bocciolone M, Genovese L, Mangiavacchi M, Marchesina UL, Faletra F, Klersy C, Coates R *et al*: **Is the left ventricular lateral wall the best lead implantation site for cardiac resynchronization therapy?** *Pacing Clin Electrophysiol* 2003, **26**(1 Pt 2):162-168.
30. Rovner A, de Las Fuentes L, Faddis MN, Gleva MJ, Davila-Roman VG, Waggoner AD: **Relation of left ventricular lead placement in cardiac resynchronization therapy to left ventricular reverse remodeling and to diastolic dyssynchrony**. *Am J Cardiol* 2007, **99**(2):239-241.
31. Lane RE, Chow AW, Mayet J, Francis DP, Peters NS, Schilling RJ, Davies DW: **The interaction of interventricular pacing intervals and left ventricular lead position during temporary biventricular pacing: evaluated by tissue Doppler imaging**. *Heart* 2007.
32. Murphy RT, Sigurdsson G, Mulamalla S, Agler D, Popovic ZB, Starling RC, Wilkoff BL, Thomas JD, Grimm RA: **Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy**. *Am J Cardiol* 2006, **97**(11):1615-1621.
33. Becker M, Franke A, Breithardt OE, Kaminski T, Kramann R, Knackstedt C, Stellbrink C, Hanrath P, Schauerte P, Hoffmann R: **Impact of Left Ventricular Lead Position on the Efficacy of Cardiac Resynchronization Therapy. A Two-Dimensional Strain Echocardiography Study**. *Heart* 2007.
34. Bedi M, Suffoletro M, Tanabe M, Gorcsan J, Saba S: **Effect of concordance between sites of left ventricular pacing and dyssynchrony on acute electrocardiographic and echocardiographic parameters in patients with heart failure undergoing cardiac resynchronization therapy**. *Clin Cardiol* 2006, **29**(11):498-502.

Chapter 10

The ischemic etiology of heart failure in diabetics limits the echocardiographic response to cardiac resynchronization therapy

Osama I.I. Soliman[1,2], Bas M. van Dalen[1], Dominic A.M.J. Theuns[1], Folkert J. ten Cate[1]

Attila Nemes[1], Luc J. Jordaens[1], Marcel L. Geleijnse[1]

From the [1]Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt

Submitted for publication

ABSTRACT

Aim of the study: To evaluate reverse volumetric left ventricular (LV) remodeling after cardiac resynchronization therapy (CRT) in heart failure (HF) patients with versus without diabetes mellitus (DM).

Methods: The study comprised 130 consecutive HF patients (mean age 61 ± 12 years) who underwent CRT. Thirty patients (23%) had DM (mean Hb1Ac 7.2 ± 3.4%, 13 (43%) on insulin therapy). Echocardiography, including tissue Doppler measurements, was performed before CRT and between 3 and 6 months after CRT. Echocardiographic response was defined as a >15% reduction in LV end-systolic volume.

Results: DM patients had more often hypertension (60% vs. 29%, P <0.05) and ischemic HF etiology (87% vs. 51%, P <0.05), but similar pre-CRT echocardiographic findings. After CRT, DM patients had equal reductions in QRS-duration and lateral-to-septal mechanical delay, but less improvement in LV end-systolic volume, mitral annular tissue velocity, the myocardial performance (or Tei) index, and the E/E' ratio (an indicator of LV filling pressure). Patients without reverse volumetric LV remodeling had more often DM (HR 1.897, P = 0.042) and an ischemic HF etiology (HR 2.308, P = 0.006). An ischemic HF etiology (HR 2.119, P = 0.018) was the only independent predictor of poor reverse volumetric LV remodeling.

Conclusion: Patients with DM and HF have a relatively poor echocardiographic response to CRT due to a high incidence of atherosclerosis.

INTRODUCTION

An important number of heart failure (HF) patients have concomitant diabetes mellitus (DM), which is associated with a worse prognosis.[1] This is most likely due to the different underlying etiology of HF in DM patients, in whom a higher incidence of hypertension, dyslipidemia, and (aggressive) atherosclerosis is seen. Cardiac resynchronization therapy (CRT) has beneficial effects on left ventricular (LV) performance, HF admissions and mortality in patients with end-stage HF.[2] Patients with DM who undergo CRT still have a worse prognosis.[3, 4] This may be due to the (unchanged) aggressive etiology of HF in DM patients and to a limited effect of CRT on reverse volumetric LV remodeling in these patients. Some authors have suggested that the relative effects of CRT are similar in patients with and without DM.[3, 4] This seems controversial since HF patients with DM have a high incidence of atherosclerosis and this is a well-known negative predictor for reverse volumetric LV remodeling.[5, 6] Therefore, we investigated in detail echocardiographic changes after CRT in HF patients with and without DM.

METHODS

Study Population

One-hundred and thirty consecutive HF patients referred for an implantable cardiac defibrillator and CRT were enrolled into the study according to the following criteria: (1) New York Heart Association (NYHA) functional class ≥III despite optimal drug therapy, (2) impaired LV ejection fraction (LV-EF <35%), and (3) wide QRS complex >120 msec. Patients with acute coronary syndromes or coronary revascularization within 6 months before CRT were excluded. A written informed consent was obtained from all patients and the institutional review board approved the study.

Study Protocol

Before CRT, echocardiography, including TDI assessment of mitral annular velocity, was done. Patients were scheduled for regular clinical follow-up and the CRT device was interrogated to ensure that biventricular pacing was being maintained, at least every three months. Three to six months after CRT implantation, echocardiography was repeated. A patient was considered an echocardiographic responder when a >15% reduction in LV end-systolic volume (ESV) was noted and a clinical responder when an improvement of >1 NYHA class plus improvement in the 6-minute walk distance ≥25% was noted.

Device implantation

As previously described [5, 7], device implantation was performed preferably with a single left pectoral incision, a left cephalic vein cut down and a left subclavian puncture. The defibrillation lead was positioned in the right ventricular apex. Transvenous implantation of the CRT device was successful in 125 patients (96%). The LV pacing lead was placed in a tributary of the coronary sinus. A postero-lateral branch was used in 86 patients (66%), a lateral branch in 23 patients (18%), and an antero-lateral branch in 16 patients (12%) of patients. In the remaining 5 patients the LV lead was surgically implanted. Adequate pacing and sensing properties of all leads, and diaphragmatic stimulation with the LV pacing lead were tested. The lowest effective defibrillation energy was assessed and a safety margin of ≥10 J was used. Devices used were InSync 7272, 7279, and 7298 (Medtronic Inc, Minneapolis, MN, USA), Renewal II (Guidant Inc, St Paul, MN, USA), and Epic HF V-339 and Atlas HF V-341 (St Jude Medical, Sylmar, CA, USA). For all patients, ICD programming was intended to avoid inappropriate therapy and tailored according to the clinical presentation.

Echocardiography

All patients were examined using a Sonos 7500 ultrasound system (Philips, Best, The Netherlands) with a S3 transducer according to the recommendations of the American Society of Echocardiography.[8, 9] LV end-diastolic volumes (LV-EDV), LV-ESV, and LV-EF (by modified bi-plane Simpson rule) were calculated from the apical 4-chamber and 2-chamber views. The degree of mitral regurgitation (grade I-IV) was assessed as the mid-systolic jet area relative to left atrial area in the apical 4-chamber view.[10] From the mitral inflow peak early (E) velocity was measured.

Tissue Doppler Imaging

TDI was applied by placing the sample volume at the side of the medial and lateral mitral annulus in an apical 4-chamber view.[11] Gain and filter settings were adjusted as needed to eliminate background noises and to allow for a clear tissue signal. To acquire the highest tissue velocities the angle between the Doppler beam and the longitudinal motion of the investigated structure was adjusted to a minimal level. The velocity and timing of the mitral annulus systolic wave (Sm) and early diastolic wave (E') were recorded end-expiratory at a sweep speed of 100 mm/s and measured using electronic calipers with EnConcert software (Philips, Best, The Netherlands). Septal-to-lateral mechanical delay was measured form the onset of Sm. The Tei index, defined as isovolumic contraction time plus isovolumic relaxation time divided by LV ejection time, and the dimensionless mitral E/E' ratio were calculated as previously described.[5, 7, 11, 12] For each patient, the average of three measurements was calculated.

STATISTICAL ANALYSES

All statistics were performed using SPSS (12.0.2) for Windows (Chicago, IL, USA). Descriptive data were computed as a mean value ± SD. Baseline and 3-months continuous variables (and changes) were

compared by an unpaired *t* test or a *Mann–Whitney U* test, if appropriate. The *Chi-square* test was used for the comparison of categorical or dichotomous variables. A value of P <0.05 was considered significant. Each variable was evaluated by using Cox proportional hazard analysis for the study endpoint echocardiographic volumetric non-response to CRT. Univariable Cox regression analysis identified baseline clinical and echocardiographic variables that were significantly associated with echocardiographic volumetric non-response. Significantly associated variables were then integrated into a multivariable analysis using Cox proportional hazards modelling using a forward stepwise selection algorithm. The proportional hazards assumptions were then validated in the final model for each categorical variable through visual inspection of log–log curves. For continuous variables, the linearity assumption was checked graphically for all variables using the Martingale residuals. There were no signs of violation of the assumptions.

RESULTS

Baseline demographics

Mean age of the patients was 61 ± 11 years and 96 were men (74%). One hundred and twenty-five patients (96%) were in NYHA class III, 5 patients were in NYHA class IV. Thirty patients (23%) had DM, 13 of these 30 patients (43%) were treated with insulin. In the DM patients Hb1Ac was 7.2 ± 3.4%. DM patients had more often hypertension (60% vs. 29%, P <0.05) and an ischemic HF etiology (87% vs. 51%, P <0.05) (Figure 1). There were no significant differences in baseline echocardiographic findings between patients with and without DM. All pertinent baseline clinical and echocardiographic data are shown in Table 1.

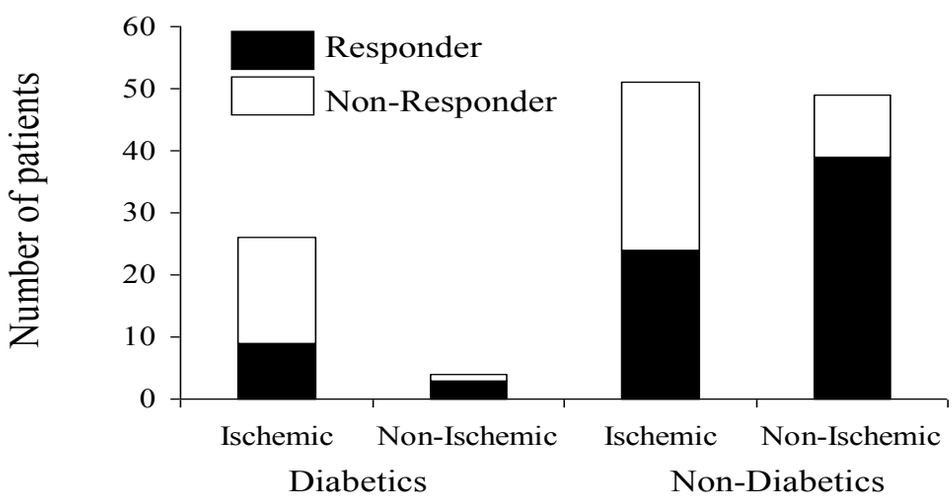


Figure 1. Numbers of diabetic and non-diabetic patients with and without an ischemic etiology. In black the number of patients with an echocardiographic left ventricular volumetric response.

Table 1. Characteristics of the study population according to the presence or absence of diabetes.

	Non-diabetics (n = 100)			Diabetics (n = 30)		
	Baseline	**3-6 months**	**Change**	**Baseline**	**3-6 months**	**Change**
Clinical data						
Age, (years)	61 ± 13	-		60 ± 10	-	
Men, n (%)	74 (74)	-		22 (73)	-	
NYHA class	3.0 ± 0.1	1.8 ± 0.8	-1.2 ± 0.2	3.1 ± 0.3	2.2 ± 1.0	-0.9 ± 0.8‡
NYHA class I/II/III/IV,	0/0/98/2	41/40/15/4		0/0/27/3	8/12/6/4	
6MWD, (meters)	289 ± 97	384 ± 106***	96 ± 134	263 ± 93	308 ± 115*	43 ± 129‡
QRS duration, (msec)	174 ± 28	126 ± 21***	-56 ± 26	166 ± 26	125 ± 24***	-44 ± 35
Ischemic etiology, n (%)	51 (51)	-		26 (87)*	-	
Hypertension, n (%)	29 (29)	-		18 (60)†	-	
Cardiac medication						
Amiodarone, n (%)	42 (42)	38 (38)	-4%	12 (40)	10 (36)	-4%
Beta-blockers, n (%)	79 (79)	72 (72)	-3%	21 (70)	18 (60)	-3%
ACE-inhibitors, n (%)	92 (91)	88 (88)	-3%	27 (90)	25 (83)	-7%
Diuretics, n (%)	88 (88)	76 (76)	-12%	28 (93)	25 (83)	-10%
Digitalis, n (%)	33 (33)	26 (26)	-7%	9 (30)	7 (23)	-7%
Statins, n (%)	53 (53)	48 (48)	-4%	26 (87)	26 (87)	0
Anti-diabetic medication						
Insulin, n (%)	-	-		13 (42)	13 (42)	0
Oral anti-diabetics, n (%)	-	-		17 (58)	17 (58)	0
Biochemical testing						
Serum glucose,	5.2 ± 1.3	4.8 ± 1.3	-0.4 ± 0.4	7.7 ± 2.7	6.7 ± 3.0**	-1.2 ± 1.1‡
HbA1c, (%)	-	-		7.2 ± 3.4	5.9 ± 3.3**	-1.5 ± 0.8
Echocardiographic data						
LV-EDV, (ml)	257 ± 108	233 ± 116***	-25 ± 37	226 ± 33	213 ± 86*	-10 ± 22‡
LV-ESV, (ml)	209 ± 97	172 ± 87***	-38 ± 37	183 ± 71	159 ± 65***	-18 ± 24‡
LV-EF, (%)	19 ± 6	29 ± 8***	10 ± 8	19 ± 5	26 ± 9***	8 ± 8
MR, grade	3.2 ± 1.7	2.2 ± 1.1***	-1.2 ± 1.0	3.1 ± 1.4	2.4 ± 1.5***	-0.7 ± 1.3†
LSD, (msec)	77 ± 48	30 ± 22 ***	-44 ± 15	70 ± 44	27 ± 20***	-43 ± 16
Sm, (cm/s)	4.1 ± 2.4	5.5 ± 2.3***	1.5 ± 1.1	4.0 ± 1.9	4.7 ± 1.8	0.7 ± 0.9†
MPI index	0.92 ± 0.22	0.55 ± 0.32***	-0.36 ± 0.26	0.89 ± 0.12	0.65 ± 0.30**	-0.23 ± 0.31†
E/E' ratio	15.1 ± 6.3	9.1 ± 5.2***	-6.3 ± 3.3	18.0 ± 9.2†	13.3 ± 6.2*‡	-5.1 ± 4.4

Values are mean ± SD or n (%). 6MWD = Six-minute walk distance; LV-EDV = Left ventricular end-diastolic volume; LV-EF = Left ventricular ejection fraction; LV-ESV = Left ventricular end-systolic volume; LSD = Lateral-to-septal delay; MR = Mitral regurgitation; NYHA = New York Heart Association; Sm = peak systolic mitral annular velocity.
*P <0.05; ** P <0.01; *** P <0.001 versus baseline; †P <0.05; ‡P <0.001 versus non-diabetics

Three to six months' follow-up data

LV dyssynchrony data

Patients with and without DM had a comparable decrease in QRS duration (44 ± 35 vs. 56 ± 26 msec, P = NS) and lateral-to-septal mechanical delay, defined as time-to-onset of Sm (43 ± 16 vs. 44 ± 15 msec, P = NS).

Clinical data

At 3 to 6-months follow-up, patients with DM had significantly less improvements in NYHA class (0.9 ± 0.8 in patients without DM vs. 1.2 ± 0.2 in patients with DM, P <0.001) and 6-minute walk distance (43 ± 129 vs. 96 ± 134 msec, P <0.001). Fifteen DM patients (50%) were clinical responders versus 72 patients (72%) without DM (P <0.05).

Echocardiographic data

Patients with DM had less reduction in LV-EDV (10 ± 22 vs. 25 ± 37 ml (P <0.001), LV-ESV (18 ± 24 vs. 38 ± 37 ml (P <0.001), and mitral regurgitation grade (0.7 ± 1.3 vs. 1.2 ± 1.0, P <0.05). Twelve DM patients (40%) were echocardiographic responders versus 63 patients (63%) without DM (P <0.05).

Tissue Doppler data

Patients with DM had less improvement in mitral annular systolic velocity (0.7 ± 0.9 vs. 1.5 ± 1.1 cm/sec, P <0.05), the myocardial performance (or Tei) index (0.23 ± 0.31 vs. 0.36 ± 0.26, P <0.05), and the E/E' ratio (5.1 ± 4.4 vs. 6.3 ± 3.3, P <0.05).

Insulin-dependent versus insulin-independent DM patients

As seen in Table 2, patients with insulin-dependent DM tended to have less reverse volumetric LV remodeling.

Univariable and multivariable prediction of echocardiographic responders

As seen in Table 3, patients without reverse volumetric LV remodeling had more often DM (HR 1.897, P = 0.042), higher E/E' ratios (HR 1.843, P = 0.033), and ischemic HF etiology (HR 2.308, P = 0.006). Ischemic HF etiology (HR 2.119, P = 0.018) was the only independent predictor of poor reverse volumetric LV remodeling.

Table 2. Echocardiographic characteristics of insulin-dependent and insulin-independent diabetics.

	Insulin-dependent DM (n = 13)			Insulin-Independent DM (n = 17)		
	Baseline	3-6 months	Change	Baseline	3-6 months	Change
Echocardiographic data						
LV-EDV, (ml)	224 ± 42	217 ± 89	-7 ± 26	227 ± 35	213 ± 85	-13 ± 24
LV-ESV, (ml)	182 ± 74	167 ± 75	-15 ± 28	185 ± 71	161 ± 65	-23 ± 24
LV-EF, (%)	18 ± 5	23 ± 9	5 ± 8	19 ± 5	25 ± 9	6 ± 8
MR, grade	3.0 ± 1.4	2.5 ± 1.5	-0.5 ± 1.4	3.2 ± 1.4	2.3 ± 1.5	-0.8 ± 1.3
LSD, (msec)	71 ± 44	29 ± 20**	-42 ± 18	70 ± 44	26 ± 20**	-44 ± 16
Sm, (cm/s)	4.0 ± 1.9	4.6 ± 1.8	0.6 ± 0.9	4.1 ± 1.9	4.8 ± 1.9	0.9 ± 0.9
MPI index	0.92 ± 0.15	0.66 ± 0.33**	-0.25 ± 0.31	0.89 ± 0.12	0.63 ± 0.30**	-0.29 ± 0.33
E/E′ ratio	19.3 ± 10.2	14.3 ± 7.2	-4.9 ± 4.4	17.5 ± 9.2	12.3 ± 6.2*	-5.3 ± 4.4

Abbreviations as in Table 1.

Table 3. Predictors of Echocardiographic Non-Responders After Cardiac Resynchronization Therapy.

Variable	**HR (95% CI)**	**P-value**
Univariable analysis		
Diabetes	1.879 (1.120 - 3.150)	0.042
Ischemic etiology	2.308 (1.562 - 4.288)	0.006
E/E′ ratio	1.843 (1.052 - 3.229)	0.033
Hypertension	1.255 (0.952 - 1.001)	0.212
LSD, (msec)	0.996 (0.990 - 1.845)	0.146
LV-EDV, (ml)	0.997 (0.993 - 1.001	0.106
LV-ESV, (ml)	0.995 (0.0993 - 1.008)	0.123
LV-EF, (%)	0.977 (0.932 - 1.008)	0.433
Multivariable analysis		
Ischemic etiology	2.119 (1.512 - 4.122)	0.018
E/E′ ratio	1.322 (0.982 - 3.101)	0.095
Diabetes	1.402 (0.861 - 2.712)	0.102

Abbreviations as in Table 1. HR = hazard ratio

DISCUSSION

HF is a frequent and often fatal complication in DM patients.[13] In selected HF patients, CRT has beneficial effects on LV performance, HF admissions and mortality.[2] Still, patients with HF and DM (and in particular insulin-treated DM patients) who undergo CRT seem to have a worse prognosis. [3, 4] This may be due to a limited effect of CRT on reverse LV volumetric remodeling in these patients. However, in two previously published CRT series, DM patients had similar LV dimensional and functional changes compared to patients without DM.[3, 4] This seems controversial since DM patients have a very high incidence of atherosclerosis as underlying etiology of HF.[3, 4] In several studies an ischemic etiology was identified as a negative predictor for reverse volumetric LV remodeling.[5, 6, 14] This may be due to the progressive character of coronary artery disease and the presence of scar tissue not-responsive to pacing.[15] In agreement with results published by others, [3, 4] DM patients with HF referred for CRT in our study had more often an ischemic HF etiology. Importantly, and in contrast to previously published data [3, 4], our DM patients (and in particular insulin-treated DM patients) were characterized by less reverse volumetric LV remodeling. This was not due to inadequate pacing since QRS-duration and lateral-to-septal mechanical delay were improved to a similar extent in patients with and without DM. Nevertheless, patients with DM had less volumetric changes and less improvement in mitral annular tissue velocity, the myocardial performance (or Tei) index, and the E/E' ratio (an indicator of LV filling pressure). At multivariate analysis, ischemic HF etiology was the only independent predictor of reverse volumetric LV remodeling. Since DM patients with HF had more often an ischemic HF etiology this may explain why DM patients profit less from CRT. DM patients and non-diabetic patients without an ischemic HF etiology had a similar probability of echocardiographic response, although the absolute number of such patients was quite small, and thus limiting this conclusion.

CONCLUSION

Patients with DM and HF have a relatively poor echocardiographic volumetric response to CRT due to the high incidence of atherosclerosis as HF etiology.

REFERENCES

1. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB: **Predictors of mortality and morbidity in patients with chronic heart failure**. *Eur Heart J* 2006, **27**(1):65-75.
2. Rivero-Ayerza M, Theuns DA, Garcia-Garcia HM, Boersma E, Simoons M, Jordaens LJ: **Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials**. *Eur Heart J* 2006, **27**(22):2682-2688.
3. Kies P, Bax JJ, Molhoek SG, Bleeker GB, Boersma E, Steendijk P, van der Wall EE, Schalij MJ: **Comparison of effectiveness of cardiac resynchronization therapy in patients with versus without diabetes mellitus**. *Am J Cardiol* 2005, **96**(1):108-111.
4. Hoppe UC, Freemantle N, Cleland JG, Marijianowski M, Erdmann E: **Effect of cardiac resynchronization on morbidity and mortality of diabetic patients with severe heart failure**. *Diabetes Care* 2007, **30**(3):722-724.
5. Soliman OI, Theuns DA, Ten Cate FJ, Anwar AM, Nemes A, Vletter WB, Jordaens LJ, Geleijnse ML: **Baseline predictors of cardiac events after cardiac resynchronization therapy in patients with heart failure secondary to ischemic or nonischemic etiology**. *Am J Cardiol* 2007, **100**(3):464-469.
6. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E: **Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE)**. *Circulation* 2006, **113**(2):266-272.
7. Soliman OI, Theuns DA, Geleijnse ML, Anwar AM, Nemes A, Caliskan K, Vletter WB, Jordaens LJ, Cate FJ: **Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy**. *Europace* 2007, **9**(2):113-118.
8. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR *et al*: **ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography)**. *J Am Coll Cardiol* 2003, **42**(5):954-970.
9. 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**(2):167-184.
10. Helmcke F, Nanda NC, Hsiung MC, Soto B, Adey CK, Goyal RG, Gatewood RP, Jr.: **Color Doppler assessment of mitral regurgitation with orthogonal planes**. *Circulation* 1987, **75**(1):175-183.
11. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA: **Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures**. *J Am Coll Cardiol* 1997, **30**(6):1527-1533.
12. Tei C: **New non-invasive index for combined systolic and diastolic ventricular function**. *J Cardiol* 1995, **26**(2):135-136.
13. Bell DS: **Heart failure: the frequent, forgotten, and often fatal complication of diabetes**. *Diabetes Care* 2003, **26**(8):2433-2441.
14. Mangiavacchi M, Gasparini M, Faletra F, Klersy C, Morenghi E, Galimberti P, Genovese L, Regoli F, De Chiara F, Bragato R *et al*: **Clinical predictors of marked improvement in left ventricular performance after cardiac resynchronization therapy in patients with chronic heart failure**. *Am Heart J* 2006, **151**(2):477 e471-477 e476.
15. Bleeker GB, Kaandorp TA, Lamb HJ, Boersma E, Steendijk P, de Roos A, 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**(7):969-976.

Part IV

Summary, conclusions and future perspectives

Includes chapter 11

Chapter 11

Summary, conclusions and future perspectives

Osama I.I. Soliman MD, MSc., FESC.

Department of Cardiology, Thoraxcenter,

Erasmus Medical Center, Rotterdam, The Netherlands

SUMMARY

The aim of this thesis was to investigate the potential application of echocardiography for an efficient management of heart failure (HF) patients. The thesis is presented in four parts as follows: part I (introduction), part II (assessment of global left ventricular systolic function), part III (assessment of cardiac resynchronization therapy), and part IV (summary and conclusion).

The general introduction (**Chapter 1**) of this thesis provides an overview of HF management using cardiac resynchronization therapy (CRT). HF constitutes an increasing and prevalent health burden worldwide. Echocardiography is a versatile non-invasive imaging modality that can be used for an efficient management of HF by proper diagnosis and guiding therapeutic interventions. Accurate assessment of left ventricular (LV) volumes and ejection fraction (LV-EF) would have important prognostic implications. CRT is a technique in which atrio-biventricular pacing is used to improve clinical and echocardiographic outcome for selected HF patients. The rationale behind CRT is the restoration of atrio-ventricular, inter-ventricular and intra-ventricular synchrony by stimulation of the delayed ventricular sites. It results in effective LV filling and emptying, reducing ventricular size improving ventricular geometry and most importantly improves survival. However, these impressive results of CRT are not seen in ~30% of patients. There are several unresolved and potentially other undetected reasons behind the high percentage of CRT failure. The echocardiography may improve the efficacy of CRT by reducing the non –response rate. The potential fields of echocardiography are: proper selection of candidates; optimization of atrio- and inter-ventricular pacing; guiding lead placement and proper detection of the response to CRT by accurate assessment of atrial and ventricular structure and function. These fields are mostly the topics of this thesis.

Accurate assessment of LV volume and systolic function forms a routine part of daily echocardiographic practice. However, the geometric assumptions in motion-mode (1D) and two-dimensional (2D) echocardiography as well as the poor inter and intra-observer variability limits these techniques. The developments of real-time three-dimensional echocardiography (RT3DE) with the matrix transducer technology allows for acquisition of full volumetric data of the LV with relatively acceptable endocardial border delineation.

In **part II,** accurate assessment of LV volumes and function were investigated using RT3DE. Several online and off-line RT3DE software programs for LV volume quantification by RT3DE are available. These programs use a wide spectrum of endocardial contour tracing and volume generation models, ranging from manual to fully automated algorithms. Patients with HF have a distorted LV geometry, which theoretically may impose difficulty in accurate LV quantification.

In **Chapter 2**, the accuracy and inter-observer variability of two different semi-automated border detection RT3DE analysis programs in 53 patients with HF were tested against cardiac magnetic resonance imaging for assessment of LV volumes from full-volume RT3DE datasets. The multiplane interpolation

algorithm determines a geometric model for the LV through manual definition of the mitral annulus, aortic valve and apex, and semi-automated border detection in various oblique sagittal (or long-axis) and coronal (or frontal) planes. Then it calculates 3D LV volume by interpolating the 2D image planes in rotational spline. The newer full volume reconstruction algorithm necessitates manual tracing of endocardial borders in 3 planes of LV at end-systole and end-diastole for initialization of the algorithm. Based on these 6 initial contours, a spatio-temporal spline interpolation model (like a pulsating balloon) is created by rotational and temporal interpolation of these contours. According to the initial balloons, the algorithm starts to detect the endocardial border continuously in the entire dataset (without large gaps due to interpolation as in the first method), like deforming the balloon in the LV until it best fits the walls in each frame. We found that the full volume method more accurately estimates LV volumes in patients with HF.

In **Chapter 3**, we investigated two commercially available software programs in our echocardiography laboratory at Erasmus Medical Center in 41 HF patients against cardiac magnetic resonance imaging for assessment of LV volumes and function. The two tested software systems use the full volume reconstruction algorithm for generation of LV volume model. The two techniques differ significantly in the extent of manual operator input needed during endocardial border tracing necessary for generation of LV volume model. LV volume derived from both techniques correlated well with magnetic resonance imaging with acceptable inter- and intra-observer agreement. However, the more the automated software provided faster but less accurate volume calculation in patients with severely distorted LV.

In **part III**, the effectiveness of CRT in HF patients who were implanted at Erasmus University Medical Center in accordance e to the guidelines was described. All included patients met the standard criteria for CRT implantation in the guidelines as drug refractory HF defined as New York Heart Association (NYHA) functional class III or IV with QRS duration >120 msec and severely depressed LV ejection fraction <35% with sinus rhythm. All the CRT registry patients were implanted with CRT-D, a combined CRT and implantable-cardioverter defibrillator (ICD).

In **Chapter** 4, reverse LV remodeling after long-term CRT was investigated in 74 consecutive HF patients. Data from 66 patients who were alive and completed clinical and echocardiographic evaluation were analyzed at baseline and at 12 months after CRT. Echocardiographic responders was defined as those who have >15% reduction in LV end-systolic volume. Fifty patients (76%) were echocardiographic responders at 12 months after CRT. LV volumetric and structural reverse remodeling was seen as early of 3 months and become more evident at 12-month follow-up. Volumetric LV reverse remodeling was seen as reductions in LV end-diastolic volume (LV-EDV) from 260 ± 113 ml to 248 ± 120 ml ($P < 0.05$) at 3 months and to 217 ± 110 ml at 12 months after CRT ($P < 0.01$) and LV end-systolic volume (LV-ESV) decreased from 214 ± 97 ml to 179 ± 88 ml and to 158 ± 86 ml, respectively (all $P < 0.01$). LV ejection fraction (LV-EF) increased from 18% ± 4% to 28% ± 7% ($P < 0.001$) and to 27 ± 7%, respectively. Structural remodeling was

shown by a reduction in LV mass from 242 ± 52 g to 222 ± 45 g and to 206 ± 50 g (all P <0.01), and improvement in sphericity indices. Volumetric responders had a marked reduction in LV mass from 240 ± 50 to 210 ± 38 and to 186 ± 37 g, respectively (all P <0.01). In contrast, non-responders showed an increase in LV mass (from 248 ± 59 g to 258 ± 54 g and to 269 ± 60 g, respectively, all P <0.05). Likewise, in echocardiographic responders only, regression of asymmetric hypertrophy of the lateral wall was noted. The results show that CRT results not only in volumetric improvement but also in true structural LV reverse remodeling, evidenced by progressive reduction in LV mass and restoration of regional wall symmetry.

In **Chapter 5**, Clinical parameters, left atrial and LV dimensions and volumes were examined in 83 consecutive patients with HF at baseline and after 3 to 6 months of CRT. The presence of AF was determined by use of ECG's, monitoring, and stored electrograms of the defibrillator. NYHA class, six-minute walk distance (6MWD), and LV-EF improved significantly. LV-EDV and LV-ESV decreased from 228 ± 84 to 206± 86 ml, and from 181 ± 66 to 146 ± 66 ml, respectively (p < 0.001). Significant reduction in mitral regurgitation was observed. Left atrial diameter and volume decreased from 46 ±7 to 42 ±7 mm and from 67 ±21 to 57 ± 19 ml, respectively (p < 0.001). At baseline 35% of patients had a history of AF. During the follow-up, 28% of patients had documented episodes of AF. The results of the study show that three months of CRT resulted in significant left atrial and LV reverse remodeling. Despite the remodeling effects, the proportion of patients with AF was not significantly reduced. The results emphasize previous finding in some major randomized trials and can be explained in the context of essential differences between the “less” left atrial and “more amenable” LV structure to reverse remodeling.

The topic of chapters 6 to 8 was the search for predictors, at baseline and early after device implantation, of the clinical and echocardiographic long-term outcomes of CRT.

In **Chapter 6**, the predictive value of baseline dyssynchrony for CRT outcome is studied. The lateral-to-septal delay (LSD) is a common and important issue in the pathophysiology of HF in patients with a left bundle branch block. The study comprised 60 HF patients, in whom pre-implantation longitudinal velocities from the basal septal and lateral LV segments in the apical 4-chamber view were recorded by spectral pulsed-wave tissue Doppler imaging (TDI). LSD was calculated from the onset of Q-wave in the surface electrocardiogram to the onset (time-to-onset) and peak (time-to-peak) of systolic velocity wave on TDI tracing. A literature-related cut-off value of ≥60 msec was used to define the baseline dyssynchrony. The study end-points were clinical and echocardiographic outcomes at 12-months after CRT. Clinical response was defined as improvement of >1NYHA functional class plus >25% increase in the 6MWD and echocardiographic response was defined as a ≥15% reduction in LV-ESV. At 12-months after CRT, 50 patients (83%) were clinically responders and 47 patients (78%) were echocardiographic responders. Both (time-to-onset) and peak (time-to-peak) LSD failed to predict clinical or echocardiographic CRT outcome. In addition, there were no significant differences between

"synchronous" and "dyssynchronous" patient populations at baseline or follow-up in either clinical or echocardiographic variables. If CRT had only been offered to patients with time-to-onset LSD as an index of dyssynchrony, 16 patients (80%) who have demonstrated reverse LV remodeling and 17 patients (85%) who clinically benefited from CRT would have been denied CRT. Similar results were found for time-to-peak LSD. The reasons behind these negative results can broadly be divided into technical and physiological factors related to TDI. LV dyssynchrony is a complex three-dimensional issue that comprises electromechanical coupling, the pattern of electrical LV activation, the distribution of myocardial fibers, and the torsion forces on the cardiac fibers. Although the short time for acquisition and analysis of a two-segment velocity model is very practical, optimal LV dyssynchrony analysis should include at least more segments and most appropriate three-dimensional analysis of all myocardial segments. Moreover, Doppler-based measurements are prone to angle dependency and translational cardiac movements which is not uncommon in patients with severe HF. Also, in these patients it might be difficult to define peak of velocity waves. Finally, it should be noticed that although timing of LV muscle displacement is important, the extent of (miss) timed muscle displacement is not measured by Doppler and may be a crucial factor (a small dyssynchronous muscle area may not necessarily have a great impact on LV function).

The topic of **Chapter 7** was the search for pre-implantation independent predictors of CRT failure. The primary composite end-point was combination of cardiovascular mortality and unplanned hospitalization for HF. Seventy-four consecutive HF patients were included. All patients underwent standard two-dimensional echocardiography including recordings of the lateral and medial mitral annular Doppler velocity profiles before and 3-months after CRT. Patients were categorized according to the presence or absence of the study endpoint. Several pre-implantation clinical and echocardiographic characteristics were evaluated between patients without and those with study endpoint. Previously important prognostic parameters from published literature, such as the NYHA class, six-minute walk distance, HF aetiology, and diabetes, were included. TDI derived parameters included the lateral and septal mitral annular derived ratios of peak early mitral inflow filling to peak early mitral annular diastolic wave (E/E'). Univariable Cox-regression analysis was performed for significantly different variables between patient groups. Univariable predictors were included into multivariable Cox-regression model to separate independent predictors of study endpoint. During a median follow-up period of 720 days (range 210 to 1020 days), 21 patients (28%) had events (8 deaths, and hospitalization for HF in the remaining 13). These patients had more often an ischemic etiology ($P < 0.05$), diabetes ($P < 0.05$), and restrictive filling ($P < 0.001$), less often LV dyssynchrony ($P < 0.05$), and higher septal and lateral E/E' ratios (both $P < 0.001$). In a multivariable analysis only the lateral E/E' ratio remained an independent predictor of study endpoint. Furthermore, subgroup analysis was conducted according to HF etiology. After 3 months CRT, the tissue Doppler-derived systolic mitral annular systolic and diastolic velocities improved significantly in non-ischemic patients both for the septal and lateral side. In contrast, in ischemic patients no significant improvements were seen. There were significant improvements in the Doppler-derived septal and lateral E/E' ratios in both ischemic and non-ischemic patients. However, the improvement in lateral E/E' ratio

was significantly less and the absolute 3-months E/E' ratios were worse in ischemic patients. The results of the study showed that, the baseline lateral E/E' ratio is an independent predictor for cardiac events in HF patients treated with CRT. Previous finding in published literature suggest that the Doppler derived E/E' ratio provide an estimate for LV filling pressure. The worse clinical outcome in ischemic patients may be due to failure of improvement in systolic and diastolic mitral annular velocities after CRT reflecting less pronounced improvement in LV filling pressures, evidenced by this E/E' ratio.

In **Chapter** 8, the evolution of clinical and echocardiographic parameters early of 3-months after CRT was examined along with pre-implantation values for prediction of composite study endpoint of combine cardiovascular mortality and hospitalization for HF. The 3-months follow-up data after CRT were included in uni- and multivariable models to identify independent predictors who will retain significant in multivariable model of Cox-regression analysis. The baseline, 3-months values and changes in these values were included. From the baseline data univariable Cox-regressions analysis revealed that diabetes (hazard ratio (HR) 3.703, P <0.01), early-to-late LV filling (E/A) ratio (HR 3.492, P <0.001), and E/E' ratio (HR 1.130, P <0.001), the 3-months E/A ratio (HR 2.988, P <0.005), the 3-months E/E' ratio (HR 1.170, P <0.001), the 3-months LV-EF (HR 0.835, P <0.01), the 3-months deceleration time (HR 0.977, P <0.05), and the 3-months Tei index (HR 15.784, P <0.001) were predictors for cardiac events. After multivariable analysis only diabetes (HR 5.544, P <0.05), the 3-months E/E' ratio (HR 1.229, P <0.001), and the 3-months change in Tei index (HR 32.174, P <0.001) were independent predictors for cardiac events. Patients with a persistent high E/E' ratio at 3-months after CRT had suffered 88% cardiac event rate. The results show that the Tei index and E/E' ratio are independent predictors of cardiac events after CRT. The cut-off values for the prediction of cardiac events which were generated from receiver-operating characteristic curves were: E/E' ratio >18 at baseline, E/E' >13 at 3-months and Tei index >0.60 at 3-months follow-up have the highest area under the curve. The results can be interpreted as failure of CRT to improve LV filling pressure or LV ejection time as early of 3-months after CRT is associated with worse prognosis.

In **Chapter 9**, the temporal course of LV contraction was evaluated by novel technique based on RT3DE. Therefore, the potential target site for LV pacing can be identified from RT3DE as the site of most delayed mechanical activation (3D-suggested). The rationale behind the study was (i) to define the site with the latest LV mechanical activation and (ii) to examine the impact of placement of LV lead at the 3D-suggested pacing sites. The study included 56 consecutive HF patients underwent RT3DE full volume acquisition of LV before and after CRT. Semi-automated endocardial border detection algorithm generated time-volume curves from the RT3DE datasets using a dedicated software program. The software program allows for assessment of the temporal course of the LV contraction from one full cardiac cycle and displays the mechanical events on a bull's eye color map based on the American Heart Association standard myocardial segmentation. At peak contraction LV volume reaches the minimum (Tmsv). The Tmsv on the global time-volume curve is used as the reference point for myocardial contraction map. Normal distribution of Tmsv was defined from 30 healthy volunteers without apparent cardiac problems as ± 35

msec. The 3D-suggested pacing sites were defined in all patients by two independent observers. Since, septal territories were not feasible for pacing; potential 3D-suggested pacing sites on the bull's eye display were referred as anterior, anterolateral, lateral, posterolateral and posterior. Two independent observers from radiographic images in two views determined the exact position of LV pacing lead (actual paced site). Inter-observer agreement for the definition of 3D-suggested pacing sites was 0.87 (95% CI 0.74- 0.99) and 0.93 (95% CI 0.84- 1.01) for actual paced sites by kappa analysis. Data of 3D-suggested pacing sites and actual paced sites were matched. The degree of concordance was classified as concordant (same territory), intermediate (adjacent territories) and discordant (remote territories). The baseline characteristics of the three groups were comparable. At 3-6 months follow-up, LV reverse remodeling was evident mainly in concordant patients, less in intermediate patients and minimal in discordant patients as follows: reduction in LV-EDV by 32%, 24% and 11% and LV-ESV by 39%, 27% and 12% and improvement in LV-EF by 60%, 46% and 30% was seen respectively, in the 3 groups (all P <0.001). LV mass reduction was seen as 15%, 10% in concordant and intermediate but not in the discordant group (P <0.001). The results emphasize the role of LV lead placement for successful CRT. Also it suggests the use of RT3DE parametric imaging before CRT implantation for optimal LV lead placement.

In **Chapter 10,** the effect of diabetes on LV reverse remodeling after CRT is studied in 130 consecutive HF patients with versus without diabetes mellitus (DM). Thirty patients (23%) had DM (mean Hb1Ac) 7.2 ± 3.4%, 13 (43%) on insulin therapy). DM patients had more often hypertension (60% vs. 29%, P <0.05) and ischemic HF etiology (87% vs. 51%, P <0.05), but similar pre-CRT echocardiographic findings. After CRT, DM patients had equal reductions in QRS-duration and dyssynchrony, but less improvements in LV-ESV, mitral annular tissue velocity, the myocardial performance (or Tei) index, and the E/E' ratio (an indicator of LV filling pressure). Patients without reverse volumetric LV remodeling had more often DM (HR 1.897, P = 0.042) and an ischemic HF etiology (HR 2.308, P = 0.006). An ischemic HF etiology (HR 2.119, P = 0.018) was the only independent predictor of poor reverse volumetric LV remodeling. The results show that patients with DM and HF have a relatively poor echocardiographic response to CRT due to a high incidence of atherosclerosis.

CONCLUSIONS

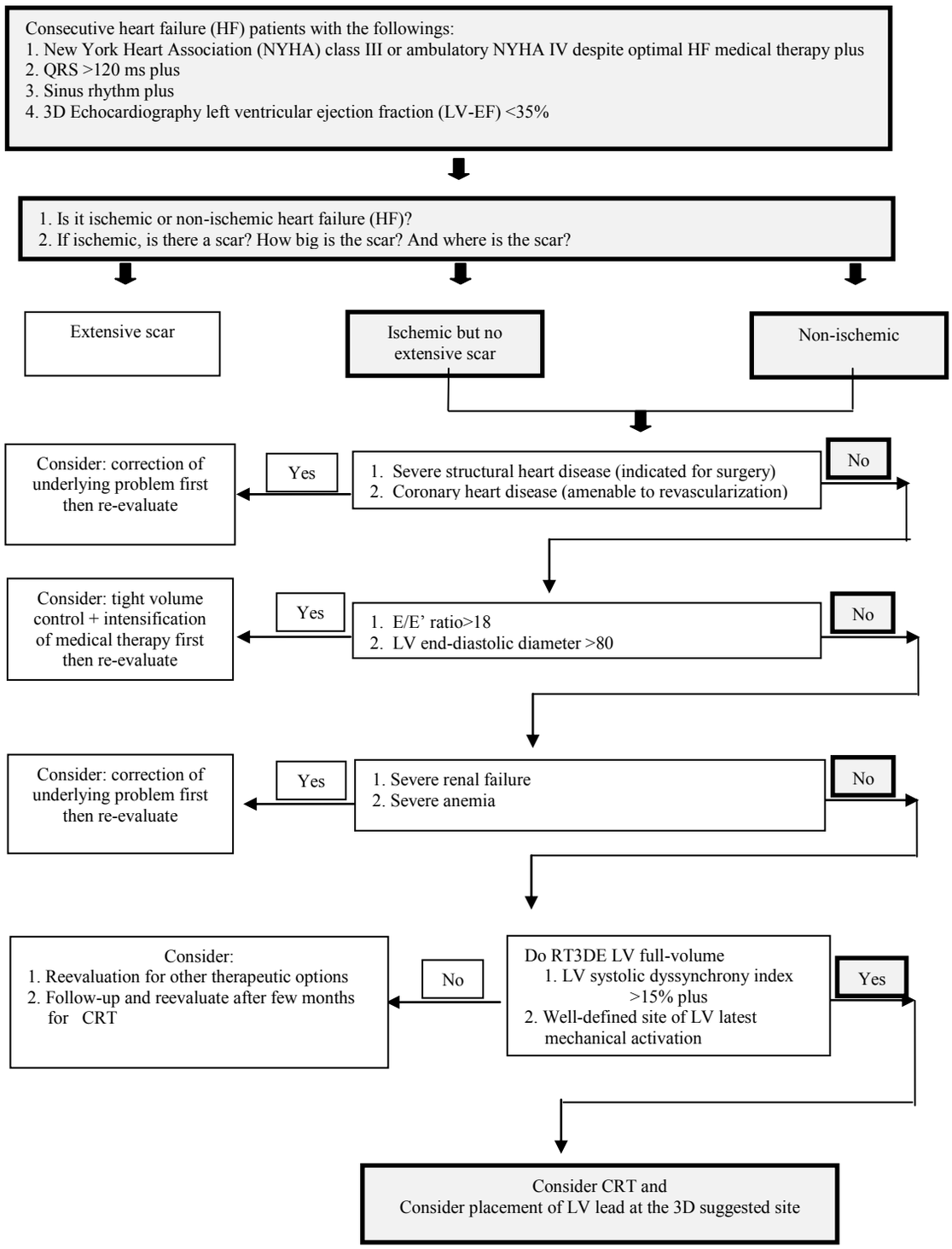
The advances in echocardiography with introduction of full-matrix transducer allow for acquisition of full volumetric RT3DE data from the LV as a function of time. Analysis of these data using "appropriate" algorithm provides accurate assessment of LV volume and function. CRT using atrio-biventricular pacing is an effective therapy for patients with a drug refractory severe HF, very low LV-EF <35%, dyssynchrony (QRS duration >120 msec) and sinus rhythm. It results in improvement of the NYHA functional class and the exercise capacity. Moreover, it results in reverse LV remodeling manifested by reductions in LV volume and LV mass and to less extent reductions of left atrial volume. However, these impressive results are not seen in significant proportion of patients defined as "non-responders". In these non-responders HF pathology progresses and may necessitate hospitalization and may eventually die. The TDI-derived

lateral-to-septal delay does not provide enough evidence to be used as selection criteria for CRT implantation. Pre-implantation and persistent high (early after CRT) LV filling pressures as estimated from the ration between Doppler peak early LV filling to peak early mitral early diastolic velocity (E/E') are associated with worse outcome. Likewise, failure of CRT to improve LV ejection time and hence myocardial performance index or Tei index is associated with a worse outcome. RT3DE parametric imaging may be used for selection of optimal LV lead placement to reduce non-response rate. The ischemic etiology in HF patients may limit the response to CRT due to common associated vascular complications in diabetics.

FUTURE PERSPECTIVES

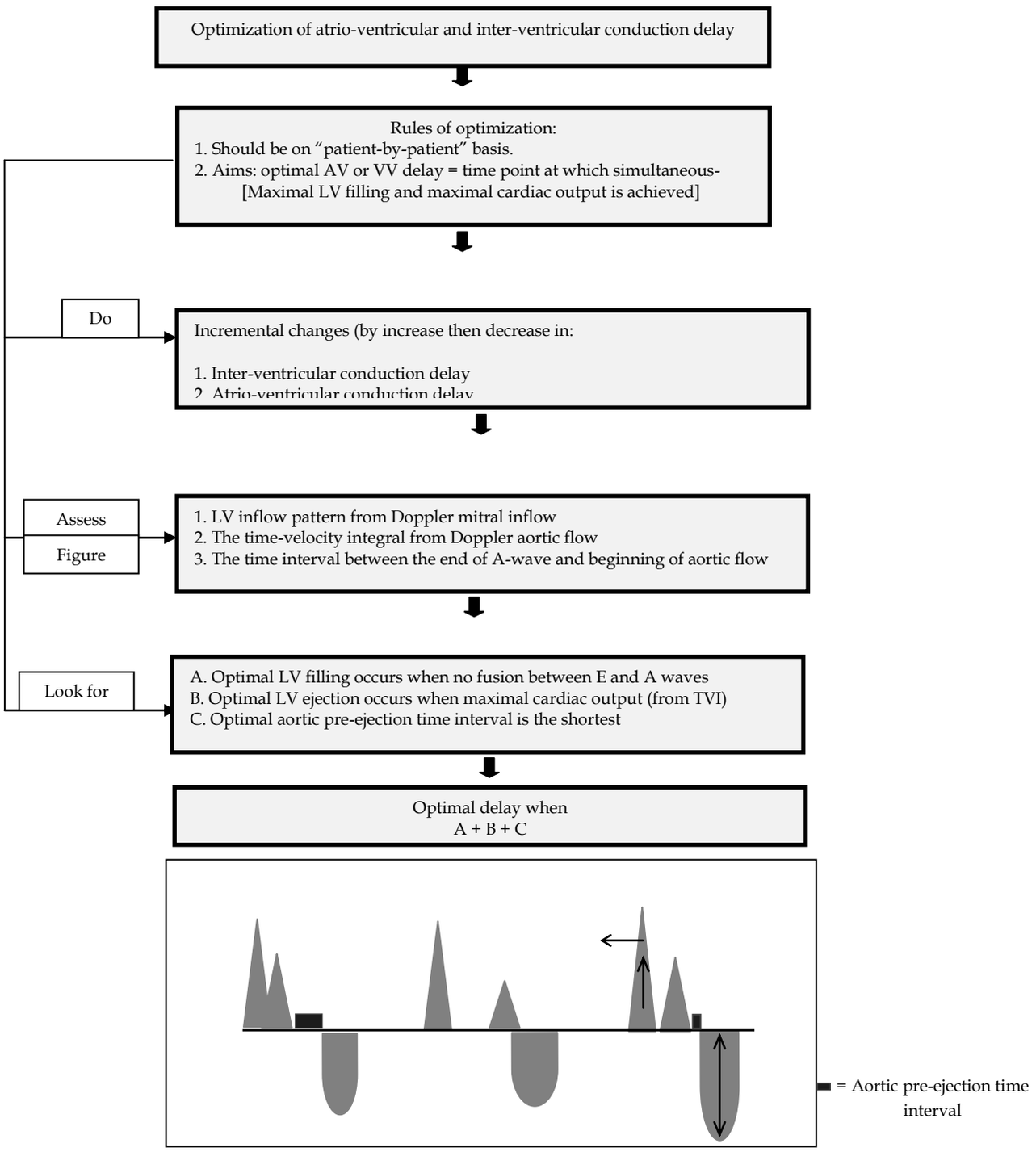
Optimal use of CRT with internal cardiovertor defibrillators for treatment of HF patients requires sound and integrated consideration of pre- and post-implantation and technical issues during lead implantation. The concept of baseline mechanical dyssynchrony should be addressed in the context that cardiac contractility has longitudinal, circumferential and radial dimensions with also rotational movement between myocardial segments with an important contribution to myocardial performance. Thinking in one dimension will not allow for proper assessment of "true" and "significant" dyssynchrony. The use of RT3DE and possibly 3D speckle tracking echocardiography could help in assessment of dyssynchrony. Patients with a huge LV, extensive scar and irreversible restrictive LV filling are beyond the "point of no return" and these significant issues should be considered before sending patients for CRT. Several variables that were identified in observational studies should be addressed in larger randomized trials to confirm these results. Despite no enough evidence in published literature for CRT in patients with mild HF or narrow QRS complex, research should be extended beyond current CRT. Finally, the effective use of non-invasive imaging should be used, as an integrated approach to collectively address pre-, during and post-implantation issues would probably maximize the CRT benefit for HF patients. A protocol based on evidence from published literature and suggested measures (based on our experience at the Erasmus University Medical Center) that could be undertaken to optimize the response to CRT is displayed as a flow chart (appendix 1 to 3).

Appendix 1: Before implantation



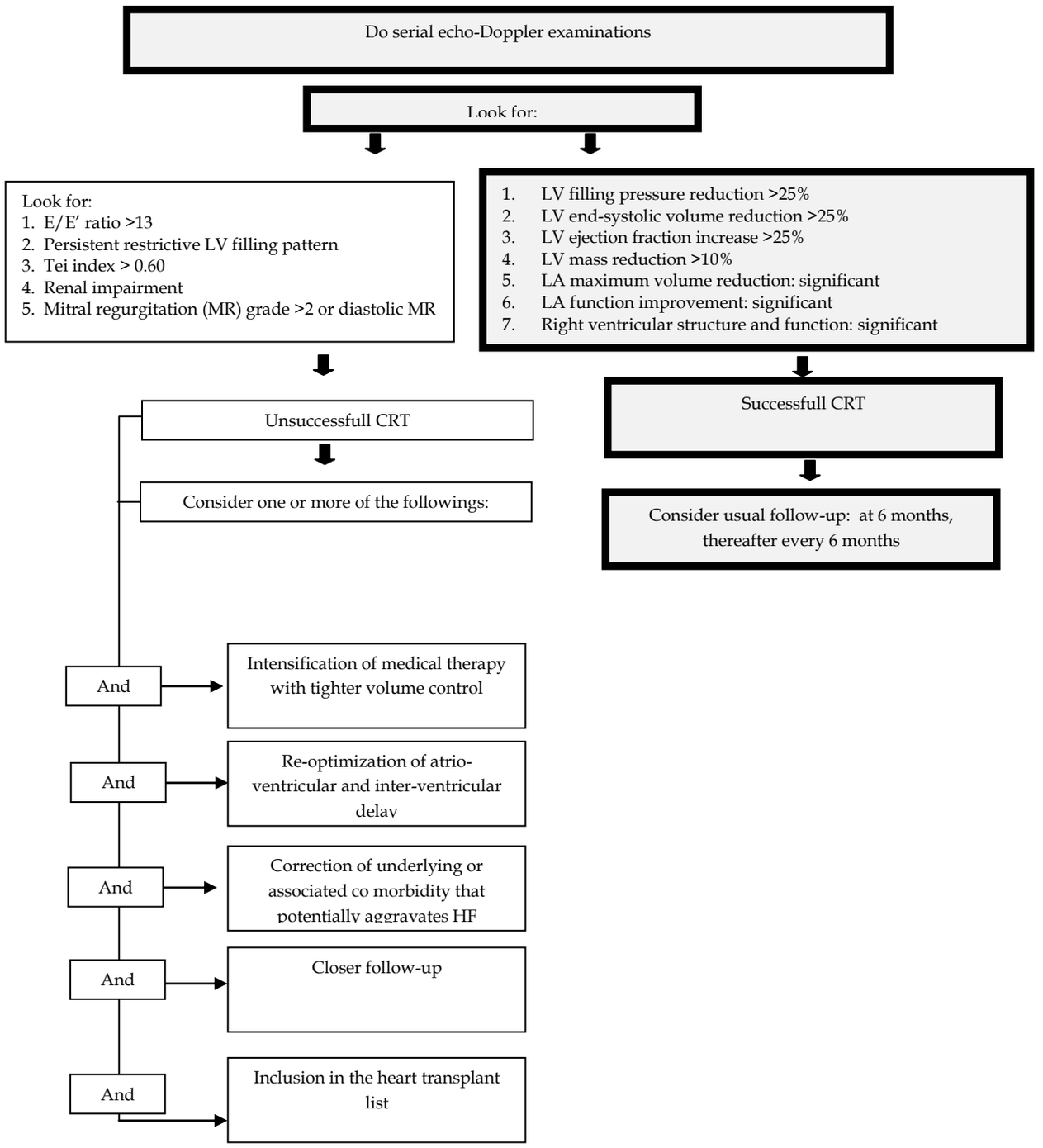
Appendix 1: Flow chart displays suggested protocol for optimization of patient selection for cardiac resynchronization imaging using echocardiography.

After implantation: from the second day



Appendix 2: Flow chart displays suggested protocol for use of echocardiography after cardiac resynchronization imaging for: optimization of atrio- and inter-ventricular pacing delay and follow-up for detection of response.

After implantation: From the 3-months visit after CRT



Appendix 3: Flow chart displays suggested protocol for follow-up of HF patients after CRT implantation.

Hoofstuk 11

Samenvatting, conclusie en toekomstperspectief

Folkert J. ten Cate MD, PhD, FESC., FACC.;
Osama I.I. Soliman MD, MSc., FESC.,
Afdeling Cardiologie, Thoraxcentrum,
Erasmus Medisch Centrum, Rotterdam, Nederland

SAMENVATTING

Het doel van dit proefschrift is om de potentiële toepassingen van echocardiografie te onderzoeken om behandeling van hartfalen te kunnen verbeteren.

In **hoofdstuk 1** (deel I) van dit proefschrift wordt een overzicht gegeven van de behandeling van hartfalen met behulp van cardiale resynchronisatie therapie (CRT). Hartfalen is een belangrijk en toenemend probleem voor de gezondheidszorg wereldwijd. Echocardiografie is een handzame niet invasieve beeldvormende techniek wat in potentie een meer efficiënte behandeling van hartfalen mogelijk kan maken door verbeterde diagnose en indicatiestellingen. Accurate beoordeling van LV volume en ejectiefractie kunnen belangrijke prognostische implicaties hebben. CRT is een techniek waarbij atrio-biventriculair pacing wordt gebruikt om de klinische en echocardiografische parameters voor geselecteerde patiënten te verbeteren. De achtergrond achter deze CRT techniek is om atrio-ventriculaire, inter-ventriculaire en intra-ventriculaire synchronie te herstellen door stimulatie van ventriculaire wanden waar een late contractie optreedt. Dit resulteert in een verbeterde LV vulling en lediging, vermindert de grootte van de LV, verbetert de vorm van het ventrikel en het meest belangrijke, verbetert de overleving.

Echter, deze indrukwekkende resultaten van CRT worden niet gezien in ongeveer 30% van de patiënten. Er zijn een aantal nog niet opgeloste en potentieel andere redenen waarom dit percentage zo hoog is. Echocardiografie zou de efficiëntie van CRT door het verminderen van de patiënten die niet op CRT reageren kunnen verbeteren. Potentieel toepassingsgebied van echocardiografie kan dan zijn verbeterde selectie van de kandidaten, optimalisering van atrio- en inter-ventriculaire pacing, optimale plaatsing van de pacemakerelektrodes en een goede detectie van het resultaat van CRT. Deze onderwerpen vormen de basis van dit proefschrift.
Accurate beoordeling van LV volume en systolische functie is een routine echocardiografische toepassing. Echter, geometrische aannames van de echocardiografie, zowel in M-mode als 2D-echo tezamen met matige intra-observer en inter-observer variabiliteit hebben deze technieken gelimiteerd. De ontwikkeling van real-time 3Decho (RT3DE) met de matrix transducer technologie stelt de onderzoeker in staat echte volumetrische data te realiseren.

In het **tweede gedeelte (II)** worden LV volume en functie onderzocht met behulp van RT3DE. Enkele online en offline RT3DE softwareprogramma's voor LV volume kwantificatie zijn beschikbaar. Deze programma's gebruiken de mogelijkheid voor endocardiale border detectie en het genereren van volume modellen, zowel manueel als volautomatisch. Patiënten met hartfalen hebben een verstoorde LV geometrie welke theoretisch kan resulteren in een verminderde accurate LV kwantificatie.

In **Hoofdstuk 2** wordt de accuratesse en inter-observer en intra-observer variabiliteit van twee verschillende programma's onderzocht die gebruik maken van een semi-automatische detectie van de

endocardiale borders in 53 patiënten met hartfalen. De resultaten werden vergeleken met de bevindingen bij cardiale magnetische resonantie. Het algoritme bepaalt een geometrisch model voor de LV door een manuele definitie van de mitraal annulus, aortaklep en apex van de linker kamer, waarbij een automatische border detectieprogramma in verschillende sagittale en coronale vlakken kan worden gereconstrueerd. Daarna wordt de 3D LV volume berekend door een interpolatie van deze 2D vlakken. Dit wordt herhaald in zowel eind- systole en eind-diastole. Gebaseerd op deze contouren wordt een model gecreëerd van het volume in tijd en ruimte. Deze methode bepaalt zeer accuraat de LV in patiënten met hartfalen.

In **hoofdstuk 3** worden twee commercieel verkrijgbare softwareprogramma's onderzocht in 41 hartfalen patiënten met behulp van echocardiografie. De resultaten werden vergeleken met MRI voor LV volume en functie. De 2 programma's verschillen in behoorlijke mate in hoeverre manuele correctie toegepast moet worden. Beide programma's tonen een goede correlatie met magnetische resonantie met aanvaardbare inter- en intra-observer beoordeling. Echter het automatische softwareprogramma is sneller maar minder accuraat in de beoordeling van LV volumes.

In **deel III** wordt de effectiviteit van CRT in hartfalen patiënten beschreven. Alle patiënten voldeden aan de standaard criteria voor CRT implantatie zoals in de richtlijnen vermeld, namelijk hartfalen niet reagerend op medicinale therapie, functionele klasse III of IV, QRS duur >120 msec en een ejectiefractie van < 35% in sinusritme.

In **Hoofdstuk 4** wordt de LV, zowel wat betreft volume als structuur, bestudeerd in 74 patiënten met hartfalen die een CRT hadden gekregen tezamen met een ICD. Er waren data beschikbaar van 66 patiënten, zowel bij het begin van het onderzoek als 12 maanden later. De echocardiografische responders werden gedefinieerd als diegene die een vermindering van de LV eind-systolische volume hebben van >15%. Vijftig patiënten waren responders na 12 maanden. Deze veranderingen werden eigenlijk al gezien na 3 maanden. Maar waren meer uitgesproken na 12 maanden. De LV eind-diastolische volume veranderde van 260 ± 113 ml naar 248 ± 120 ml op 3 maanden en verbeterde verder naar 217 ± 110 ml op 12 maanden ($P<0.01$). Het eind-systolische volume verminderde van 214 ± 97 ml naar 179 ± 88ml en verbeterde verder naar 158 ± 86 mm op 12 maanden. Deze veranderingen werden ook gezien in de LV-ejectie fractie welke veranderde van 18 ± 4% naar 27 ± 7% op 12 maanden. LV massa veranderde van 242 ± 52 gr. naar 222 ± 45gr., en verminderde verder naar 206 ± 50gr. op 12 maanden. Diegene bij wie een volumetrisch reductie werd gevonden hadden ook een forse reductie in de LV massa. Dit in tegenstelling tot diegene die geen veranderde volume aantoonde welke een toename van LV massa lieten zien. Wij concludeerden dus dat in echocardiografische responders een regressie van de hypertrophie van de laterale wand werd gezien, maar dat er ook structurele verandering van de LV optrad.

In **hoofdstuk 5** worden linker atrium en LV dimensie en volumes bestudeerd in 83 patiënten met hartfalen vòòr en 3 en 6 maanden na CRT. Validiteit, 6 minuten loopafstand en LV ejectiefractie verbeterden significant. LV eind-diastolisch volume en LV eind-systolische volume verminderden respectievelijk van 220 ± 84 naar 206 ± 86 ml en van 181 ± 66 ml naar 146 ± 66 ml. Bovendien werd een significante vermindering van de mitraalinsufficientie gevonden en een afname van de atriale diameters en volumes. Interessant is te vermelden dat 35% de patiënten atriumfibrilleren hadden bij het begin van de studie en dat dit niet verbeterde na CRT.

In hoofdstuk 6 t/m 8 wordt beschreven of voorspellers bestaan zowel bij het begin van de studie als na implantatie die bepaald kunnen worden uit de klinische en echocardiografische parameters na CRT.

In **hoofdstuk 6** wordt de voorspellende waarde van dissynchronie van CRT bepaald. De vertraging in contractie tussen de laterale en septale wand wordt algemeen gevonden in patiënten met hartfalen en in patiënten met linker bundeltakblok. In al deze patiënten werd ook TDI bepaald. De uitkomst van de studie waren klinische en echocardiografiche parameters na 12 maanden CRT. Klinische verbetering werd gedefinieerd als verbetering van validiteit van een functioneel klasse tezamen met 25% toename van de inspanningstolerantie zoals gemeten met de 6 minuten looptest. Een echocardiografische respons was gedefinieerd als meer dan 15% reductie in het LV eind-systolische volume. Op 12 maanden waren 50 patiënten klinische responders en 47 patiënten echocardiografische responders. TDI was niet in staat deze voorspelling te doen, bovendien konden wij geen verschil vinden tussen zogenaamde synchrone en dissynchrone patiënten voor populaties als we TDI als inclusie criteria hadden genomen. Dit betekent in de praktijk dat 16 patiënten die goed reageerden op CRT en klinisch voordeel daarvan hadden geen CRT hadden gekregen op basis van de TDI criteria. De conclusie is dat LV dissynchrone een ingewikkeld 3-dimentioneel fenomeen is waarbij TDI te beperkt is om dit complexe fenomeen in beeld te brengen.

In **Hoofdstuk 7** zochten wij naar onafhankelijke factoren die CRT-falen zouden kunnen bepalen. Eindpunt was een combinatie van cardiovasculaire mortaliteit en niet verwachte hospitalisatie voor hartfalen. Vierenzeventig patiënten met hartfalen werden bestudeerd. Alle patiënten kregen 2-dimentioneel echo met TDI van laterale en mediale annulus van de mitralisklep, voor en 3 maanden na CRT. Validiteit, 6 minuten loopafstand werden ook bepaald. Er werd een univariabele cox-regressie analyse uitgevoerd. Bovendien wordt een multivariabele cox-regressie model bestudeerd om separaat onafhankelijke voorspellers te bepalen. Eenentwintig patiënten hadden events (8 overleden; hospitalisatie voor hartfalen voor de overige 13 patiënten) Deze patiënten hadden vaker ischemie als oorzaak, suikerziekte en restrictieve vullingspatroon en minder vaak dissynchronie van de LV en hogere septale en laterale E/E ratio's, welke als enige overbleef in de miltivariabele analyse. Als onafhankelijke voorspeller werd ook gezien dat 3 maanden na implantatie van CRT de TDI parameters in de patiënten die geen ischemie vertoonden verbeterden. Dit in tegenstelling tot de patiënten met een ischemische etiologie. Wij toonden

aan dat de basale laterale E/E ratio's met behulp van TDI een onafhankelijke voorspeller is voor cardiale events in patiënten met hartfalen die behandeld werden met CRT.

In **hoofdstuk 8** wordt de evolutie beschreven van klinische en echocardiografische parameters 3 maanden na CRT en vergeleken met waarden voor de implantatie voor de voorspelling van een gecombineerd eindpunt voor cardiovasculaire mortaliteit en hospitalisatie. De 3 maanden follow-up data na CRT werden bepaald in een uni- en multivariabele modellen om onafhankelijke voorspellers aan te tonen. De baseline, 3 maanden waarden en veranderingen in deze waarden werden geincludeerd. Van de baseline data werd middels een univariabele cox-regressie analyse aangetoond dat diabetes, de vroege en late LV vulling (E/A-ratio, E/E- ratio, de 3 maanden E/A ratio, de 3 maanden E/E-ratio, de 3 maanden LV ejectiefractie en de 3 maanden deceleratie tijd en de 3 maanden Tei index) voorspellers waren voor cardiale events. Na multivariabele analyse bleef alleen diabetes, 3 maanden E/E-ratio en 3 maanden Tei index over. Patiënten met een persisterende hoge E/E-ratio 3 maanden na implantatie hadden een 88% cardiale event rate. De resultaten tonen aan dat da Tei index en de E/E ratio onafhankelijke voorspellers zijn voor cardiale gebeurtenissen na CRT. De ROC-curvers toonden een cut-off waarden aan van E/E-ratio >18 bij baseline, E/E-ratio > 13 op 3 maanden en Tei index > 0.60 op 3 maanden. De resultaten kunnen worden geïnterpreteerd als falen van CRT als na 3 maanden LV vullingsdrukken of LV ejectietijd niet verbeterd, en zijn geassocieerd met een ernstige prognose.

In **hoofdstuk 9** worden de temporele veranderingen van de LV contractie geëvalueerd middels een nieuwe techniek gebaseerd op RT3DE. Het doel van de studie was om de plaats van de laatste mechanische activatie aan te tonen en de invloed van deze plaats bij de actuele plaatsing van de LV lead. Er werden 56 patiënten met hartfalen bestudeerd middels 3D en volledige volume acquisitie voor en na CRT. Middels het softwareprogramma kunnen wij een precieze bepaling doen van het temporele veranderingen van de LV contractie gedurende de hartcyclus en de resultaten werden gepresenteerd in zogenaamde bull's eye kleurenmap middels de standaard myocardiale segmentatie. Het tijdstip waarop de globale tijdvolume curve minimaal was, werd gebruikt als referentiepunt voor de myocardiale contractiebepaling. Normale verdeling van deze tijdsveranderingen werd gedefinieerd uit de studie bij 30 vrijwilligers als ± 35msec. De gesuggereerde 3D pacing plaats van de pacingleads werden bepaald in alle patiënten door 2 onafhankelijke onderzoekers. Potentiële 3D pacing plaatsen werden gedefinieerd als anterior, anterolateraal, lateraal, posterolateraal en posterior. De exacte positie van de LV pacing lead welke actueel werd gebruikt door de onderzoeker werd middels radiografie aangetoond. Inter-observer overeenstemming voor de definitie van 3D pacingplaats was 0.87 en 0.93 voor de actuele plaats van pacing. De mate van overeenstemming van tussen de gesuggereerde pacingplaats en de actuele pacingplaats werd gedefinieerd als concordant (hetzelfde gebied) intermediair (dichtstbijzijnde gebied) en discordant (afwijken gebied). Op 3 tot 6 maanden follow-up werd een goede verandering van de LV aangetoond in patiënten met concordante pacingplaatsing, minder in intermediair en minimaal in discordante plaatsing. Dit gold zowel voor de reductie in LV en diastolisch volume, verbetering van LV

ejectiefractie en reductie in LV mass. Onze resultaten benadrukken de rol van het goede pacemaker lead voor een succesvolle CRT. Bovendien suggereert het gebruik van RT3DE parametrisch imaging voordat de CRT wordt gedaan om een optimale plaats van LV lead te vinden.

In **Hoofdstuk 10** werden de effecten van suikerziekte op de linkerkamer remodeling bij CRT aangetoond in 130 patiënten met hartfalen. Dertig patiënten hadden diabetes mellitus en gebruikten insuline. De diabetes mellitus patiënten hadden meer hypertensie en ischemish etiologie voor hartfalen, maar dezelfde pre-CRT echoardiografische bevindingen. Na CRT hadden patiënten met suikerziekte dezelfde reductie in QRS-duur en dissynchronie maar verminderde verbetering in de LV eind-systolische volume, mitralis annulus snelheid, Tei-index en E/E- ratio. De patiënten hadden ook vaker ischemie. Ischemische etiologie was de enige onafhankelijke voorspeller voor een verminderde verbetering van een LV volume. Deze resultaten tonen aan dat patiënten met suikerziekte en hartfalen een minder goede prognose hebben op CRT, waarschijnlijk ten gevolge van atherosclerose.

CONCLUSIE

De verbeteringen in echocardiografietechniek voor bepaling van RT3D volume kunnen toegeschreven worden aan de ontwikkeling van de matrix transducer. Indien het goede algoritme wordt gebruikt, worden LV volume en functie accuraat bepaald. CRT is een atrio-biventriculaire pacing methode die effectief is in patiënten met hartfalen, lage ejectiefractie en dissynchronie. Wij hebben aangetoond dat een remodeling van de LV aanwezig is door reductie van de LV volume en LV massa een ook wel vermindering van het LA volume. Echter er bestaat een significant deel van de patiënt waarbij de CRT methode niet effectief is. TDI is geen goede parameter om selectiecriteria voor CRT implantatie vast te stellen. Hoge vullingsdruk bepaald als de E/E-ratio voorspelde een minder goede resultaat na CRT. Ook de Tei-index is een goede parameter om uitkomst te voorspellen. Ischemie als oorzaak voor CRT kan een oorzaak zijn van verminderde effectiviteit, ook als diabetes optreed.

TOEKOMSTPERSPECTIEF

Optimaal gebruik van CRT met een ICD voor behandeling van hartfalen patiënten vereist een geïntegreerde analyse van pre- en postimplantatie en technische factoren. Mechanische dissynchronie is een resultaat van abnormale cardiale contractiliteit zowel in longitudinaal, circumferentieel en radiale dimensies met ook rotatie van het hart. Dit is de reden dat TDI niet nuttig is voor de voorspelling van een succesvolle CRT. In onze studie denken we dat real-time 3D en waarschijnlijk in de toekomst 3D-Speckle waarbij rotatie van het hart bestudeert wordt, een verbeterde bepaling van dissynchronie kan laten zien. Ook patiënten met een heel groot hart, forse aanwezigheid van littekenweefsel en hoge vullingsdrukken met restrictie zullen geen goede kandidaten zijn voor deze therapie. Meer patiënten zullen in de toekomst eventueel mogelijk in gerandomiseerde onderzoeken worden bestudeerd. Ook patiënten met een niet verbreed QRS-comples en hartfalen zullen met behulp van real-time 3D moeten bestudeerd worden om een eventuele voorspelling te doen van het succes. Wij stellen in figuren 1a en 1b een flow diagram voor, voor de indicatie van CRT met behulp van echocardiografie. Ook wordt een protocol voorgesteld met behulp van echocardiografie na synchronisatie therapie om atrioventriculeren en intraventriculair pacing te optimaliseren.

Acknowledgments

ACKNOWLEDGMENTS

I am greatly indebted to the staff of the Cardiology department at the Thoraxcenter who helped me a lot during my stay as a guest researcher, which was resulted in this thesis. It is very important step in pursuing my career and scientific achievements.

First of all, I would like to express my gratitude and thank to **Prof.dr. Maarten L. Simoons,** the head of cardiology department for being my promotor, for allowing me to stay at the Thoraxcenter and for his invaluable and critical comments that led to the thesis in its present form.

Second, but not less important I would like to thank very much **Prof.dr. Luc J.L.M. Jordaens,** the chief of Electrophysiology laboratory for being my promotor. His suggestions and critics have been an indispensible part in preparation of all manuscripts addressing the topic of cardiac resynchronization therapy that finally led to this thesis.

Third, but not less important I would like to thank very much **Dr. Folkert J. ten Cate,** the head of Echocardiography laboratory for being my copromotor. He is the reason for being at the Thoraxcenter by accepting to supervise me during my fellowship period. He taught me the secrets of contrast echocardiography and hypertrophic cardiomyopathy. His ideas about three-dimensional echocardiography as well as the use of echocardiography for cardiac resynchronization therapy had become true research topics, therefore become published articles and finally led to this thesis. I would like to thank him very much for his continuous support, for believing in me and so many other great things. He is not only a great scientist but also a great man.

I would like to express my gratitude to **Dr. Marcel L. Geleijnse** for every minute, he spent with me reviewing every patient, writing manuscripts, and performing statistical analysis of the data and chapters of this book. His ideas about several aspects in cardiac resynchronization therapy and cardiomyopathy patients have led to several studies that finally led to several published articles. It is of notion that without his support this thesis would not be completed.

Next, I infinitely thank my friends **Dr. Dominic A.M.J. Theuns** and **Dr. Bas M. van Dalen** for being my paranymphs**.**

I would like to deeply thank **Mr. Wim B. Vletter** and **Mrs. Jackie McGhie** the distinguished and highly experienced sonographers with a great scientific background. Dear Jackie and Wim I deeply thank you for your help in data acquisition and analysis and their invaluable suggestions to complete this project. You certainly made a great contribution to this book.

I would like to thank **Mr**. **René Frowijn** the computer Admin for his great and invaluable help for solving all technical problems, managing all aspects related to hardware and software, workstations and ultrasound machines that was essential part of the research till this book comes true. Dear René I deeply thank you for your friendship and patience in listening to the complaints, managing to send "hundreds" of patients' data to the EnConcert and other so many great help. You certainly have an essential contribution for the 'construction' of this book.

I would like to thank **Mrs**. **Kitty Oosterman** and **Mrs. Annet Louw** for their invaluable help for preparation of bureaucratic issues related to the thesis. Dear Kitty and Annet thank you for your great help.

I would like to thank all staff of the Echocardiography laboratory and Electrophysiology laboratory at the Thoraxcenter: particularly **Linda** de Jonge, **Anne-Marie** Duthler, **Ellen** Wiegers, **Marianne** Blüm, **Debbie** van Dongen and **Dieny** de Viet.

The Thoraxcenter is a really unique international scientific community. During may stay in Rotterdam, as well the scientific unique experience I had the opportunity to meet a lot of colleagues and friends: Ashraf M. Anwar (Egypt), Attila Nemes (Hungary), Michele Michels (the Netherlands), Tjebbe W. Galema (the Netherlands), Boudewijn J. Krenning (the Netherlands), Annemien E. van den Bosch (the Netherlands), Marjolein Kamphuis-Menses (the Netherlands), Willem P.M.H.I.A. Gielen (the Netherlands), Sharon W. Kirschbaum (the Netherlands), Sing C. Yap (the Netherlands), Yusuf Karamermer (the Netherlands), Andy Wijono (Indonesia), Kadir Caliskan (the Netherlands), Caroline Veltman (the Netherlands), Robert-Jan van Geuns (the Netherlands), Timo Baks (the Netherlands), Remco G.M. Timmermans (the Netherlands), René F.M. de Coo (the Netherlands), J.H.P. Wilson (the Netherlands), Nadine A.M.E. van der Beek (the Netherlands), Bob Meijboom (the Netherlands), Liesbeth Spruit (the Netherlands), Maximo J. Rivero Ayerza (Argentine), Ron T. van Domburg (the Netherlands), Fesile Basar (the Netherlands).

So many others… I would like also to thank all the others fellows, staff members, assistants and people I had the great pleasure to meet and I worked with during my stay at the Thoraxcenter.

Special thank to Hans, Ester, and Gerard the engineers from the department of Experimental Echocardiography at the 23rd floor for great help in explaining many issues related physics of ultrasound.

Coming back to Egypt, I am particular indebted to **Prof.dr. Safwat Al-Hawary** the present head of the department, **Prof.dr. Ahmed K. Metawea** the main supervisor of my Egyptian research project, **Prof.dr. Aly M. Al-Amin**, **Prof.dr. Mohammed Al-Amin, Dr. Youssef FM Nosir** and all staff members of the cardiology department at Al-Azhar Faculty of Medicine, Cairo, Egypt for their support and encouragement during my fellowship period at the Thoraxcenter that led to this thesis.

Finally, but not the last I would like to hearty thank my parents to whom I owe my existence and to my lovely brothers and sister for their continuous support, love and devotion. To my family, you are always the best thing I ever have and you gave me the best things I have had in my life.

Osama S.S. Soliman

Curriculum vitae and list of publications

Curriculum Vitae

Osama I.I. Soliman MD, MSc., FESC.

Personal data

Date of birth	02-01-1974
Place of birth	Ashmun (Monofia) Egypt
Nationality	Egyptian
Current residency	Wijnkade 9, 3011VZ, Rotterdam, The Netherlands
Address for correspondences	
The Netherlands	
Address	Department of Cardiology, Thoraxcenter, Erasmus MC, Ba 302, 's-Gravendijkwal 230, 3015CE, Rotterdam, The Netherlands
Phone	+(31) 10 46 35 994
Fax	+(31) 10 46 35 498
E-mail	o.soliman@erasmusmc.nl
Egypt	
Address	7 Alkadam Alshareef, El-Mesaha, Haram, Giza, Egypt.
Phone	+ (20) 2 58 77 077
Fax	+ (20) 2 511 1776
E-mail	o.i.soliman@gmail.com

Pre-doctoral education

1989-1996 (M.B.B.Ch., *magna cum laude*)	Faculty of Medicine, Al-Azhar University, Cairo, Egypt
1998-2001 (MSc. Cardiology and Internal Medicine, *cum laude*)	Faculty of Medicine, Al-Azhar University, Cairo, Egypt
October 2000 MSc Thesis	Intravascular ultrasound versus quantitative coronary angiography for the assessment of immediate results of coronary artery stenting
F.E.S.C.-2007	Fellowship of the European Society of Cardiology

Post graduate training

1996-1997	House Officer: Al-Azhar University Hospitals, Cairo, Egypt
1998-2001	Resident of Cardiology: Al-Azhar University Hospitals, Cairo, Egypt
2001-2005	Assistant Lecturer of Cardiology: Al-Azhar University Hospitals, Cairo, Egypt
2005- present	Research Fellow in Cardiovascular Diseases: Thoraxcenter, Erasmus MC (Erasmus University), Rotterdam, The Netherlands
Since 2005	PhD Fellow: Thoraxcenter, Erasmus MC (Erasmus University), Rotterdam, The Netherlands

Scientific awards

*Certificate for the second place in national ranking in general secondary certificate, Egypt (May 1990)
*Certificate for the best achievement for medical students in "Biochemistry", Al-Azhar Faculty of Medicine, Cairo , Egypt (June 1992)
*Certificate for the best achievement for medical students in "Histology and Cell Biology", Al-Azhar Faculty of Medicine, Cairo , Egypt (July 1992)
*Certificate for the best achievement for medical students in "Cell Biology", from the Egyptian Society of Cell Biology, Cairo , Egypt (November 1992)
*Prize for the first rank in Deans list for medical students in basic medical sciences (second year medical students) Al-Azhar Faculty of Medicine, Cairo, Egypt (June 1992)

*Prize for the first rank in Deans list for medical students in basic medical sciences (third year medical students) Al-Azhar Faculty of Medicine, Cairo, Egypt (June 1993)
*Prize for the first rank in Deans list for medical students in clinical medical sciences (fourth year medical students) Al-Azhar Faculty of Medicine, Cairo, Egypt (June 1994)
*Prize for the first rank in Deans list for medical students (M.B.B.Ch. degree) Al-Azhar Faculty of Medicine, Cairo, Egypt (December 1996)
*Prize for the first rank in M.B.B.Ch. degree from the Egyptian Medical Syndicate (national graduation ceremony), Cairo, Egypt (April 1997)
*Two-years international fellowship grant (nominated for highly ranked young researchers) from the Egyptian Ministry of Higher Education, Cairo, Egypt (2005)
*Centificate for the Young Investigator Award Finalist in Euroecho 2007, Lisbon, Portugal from the European Association of Echocardiography (selected in July 2007- to be recieved Dec 2007)

Membership

Egyptian Society of Cardiology	2001-present
European Association of Echocardiography	2007
American Society of Echocardiography	2007

Fellowship

European Society of Cardiology	2007

Attendance

Egyptian Society of Cardiology	Since 1998
American Society of Cardiology	2006, 2007
American Society of Echocardiography	2006, 2007
European Society of Cardiology	2006, 2007
European Society of Echocardiography	2006, 2007
Dutch Society of Cardiology	2006
Cardiovascular Medicine Rotterdam	2005, 2006, 2007
Rotterdam Contrast Symposium	2005, 2006, 2007
Rotterdam Echo Course	2006, 2007

Academic duties

Editorial	Peer reviewer for: Heart European Journal of Clinical Investigation Journal of Am Society of Echocardiography Journal of Clinical Ultrasound European Journal of Echocardiography
Publications in peer review journals	
Original articles and abstracts	72
Reviews	4
Invited reviews	2

PUBLICATIONS IN PEER REVIEW JOURNALS

1. **O.I.I. Soliman**, D.A.M.J. Theuns, M.L. Geleijnse, A.M. Anwar, A. Nemes, W.B. Vletter, L.J. Jordaens, and F.J. ten Cate: Spectral pulsed-wave tissue Doppler imaging lateral-to-septal delay fails to predict clinical or echocardiographic outcome after cardiac resynchronization therapy. *Europace.* 2007 Feb; 9(2): 113-8. Epub 2007 Jan 11.

2. **O.I.I. Soliman**, D.A.M.J. Theuns, F.J. ten Cate, A.M. Anwar, A. Nemes, W.B. Vletter, L.J. Jordaens, and M.L. Geleijnse. Baseline predictors of cardiac events after cardiac resynchronization therapy in patients with heart failure secondary to ischemic or non-ischemic etiology. *Am J Cardiol.* 2007 Aug: 100 (4): 464-469. 1.

3. **O.I.I. Soliman,** M.L. Geleijnse, D.A.M.J. Theuns, A. Nemes, W.B. Vletter, Bas M. van Dalen, A.K Motawea, L.J. Jordaens, and F.J. ten Cate,. Reverse of left ventricular volumetric and structural remodeling in heart failure patients treated with cardiac resynchronization therapy. *Am J Cardiol.* (Accepted for publication).

4. **O.I.I. Soliman,** B. J. Krenning, M. L. Geleijnse, A. Nemes, R-Jan van Geuns, S.W. Kirschbaum, A. M. Anwar, T. W. Galema, W.B. Vletter, and F. J. ten Cate. Quantification of left ventricular volumes and function in patients with cardiomyopathies by real-time three-dimensional echocardiography: a head-to-head comparison between two different semi-automated endocardial border detection algorithms. *J Am Soc Echocardiogr*. 2007 Jun 11; [Epub ahead of print]

5. **O.I.I. Soliman**, B. J. Krenning, M. L. Geleijnse, A. Nemes, R-Jan van Geuns, T. Baks, A. M. Anwar, T. W. Galema, W.B. Vletter, and F. J. ten Cate. A comparison between QLAB and TomTec full volume reconstruction for real-time three-dimensional echocardiographic quantification of left ventricular volumes. *Echocardiography* 2007 Oct; 24 (9) 967- 974

6. **O.I.I. Soliman**, P. Knaapen, M. L. Geleijnse, P. A. Dijkmans, A. M. Anwar, A. Nemes, M. Michels, W. B. Vletter, A. A. Lammertsma and F. J. ten Cate. Assessment of intra- and extra-vascular mechanisms of myocardial perfusion abnormalities in obstructive hypertrophic cardiomyopathy by myocardial contrast echocardiography. *Heart.* 2007 May 8; [Epub ahead of print]

7. **O.I.I. Soliman**, M.L. Geleijnse, F. Meijboom, A. Nemes, O. Kamp, P. Nihoyannopoulos, N. Masani, S. Feinstein and Folkert J. ten Cate. The use of contrast echocardiography for the detection of cardiac shunts. *Eur J Echocardiogr.* 2007 Jun;8(3):S2-12. Epub 2007 Apr 25.

8. **O.I.I. Soliman**, R.G.M. Timmermans, A. Nemes, W.B. Vletter , J.H.P. Wilson, Folkert J ten Cate, and M.L. Geleijnse. Cardiac abnormalities in adults with the attenuated form of mucopolysaccharidosis type I. *J Inherit Metab Dis.* 2007 Jun 14; [Epub ahead of print]

9. **O.I.I. Soliman**, D.A.M.J. Theuns, F.J. ten Cate, A.M. Anwar, A. Nemes, W.B. Vletter, L.J. Jordaens, M.L. Geleijnse. Predictors of cardiac events after cardiac resynchronization therapy by tissue Doppler derived parameters. *J Card Fail.* 2007 (in press)

10. **O.I.I. Soliman**, M.L. Geleijnse, Folkert J ten Cate. Femoral vein versus brachial approach during contrast administration for the detection of cardiac shunts. *Eur J Echocardiogr.* (in press) (Reply to a letter to the editor).

11. T.C.G. Vydt, R.F.M. de Coo, **O.I.I. Soliman,** F.J. ten Cate, R.J.M. van Geuns, W.B. Vletter, K.Schoonderwoerd, B.J. van den Bosch, B.J.M. Smeets, M.L. Geleijnse: Cardiac involvement in adults with m.3243A>G MELAS gene mutation. *Am J Cardiol.* 2007 Jan 15;99(2):264-9. Epub 2006 Nov 29.

12. A. Nemes, M.L. Geleijnse, B. Krenning, **O.I.I. Soliman,** A.M. Anwar, W.B. Vletter, F.J. ten Cate: Usefulness of ultrasound contrast agent to improve image quality during real-time three-dimensional stress echocardiography. *Am J Cardiol.* 2007 Jan 15;99(2):275-8. Epub 2006 Nov 27.

13. M.L Geleijnse, B.J. Krenning**, O.I.I. Soliman**, A. Nemes, T.W. Galema, F.J. ten Cate: Dobutamine stress echocardiography For the detection of coronary artery disease in women. *Am J Cardiol.* 2007 Mar 1;99(5):714-7. Epub 2007 Jan 11.

14. A. Nemes, T.W. Galema, M.L. Geleijnse, **O.I.I. Soliman,** S.-C. Yap, A.M. Anwar, F.J. ten Cate: Aortic valve replacement for aortic stenosis is associated with improved aortic distensibility at long-term follow-up. *Am Heart J.* 2007 Jan; 153(1): 147-51.

15. A.M. Anwar, M.L. Geleijnse, **O.I.I. Soliman**, J.S. McGhie, A. Nemes, F.J. ten Cate. Evaluation of rheumatic tricuspid valve stenosis by real-time three-dimensional echocardiography. *Heart.* 2007 Mar; 93(3): 363-4.

16. B.J. Krenning, S.W. Kirschbaum, **O.I.I. Soliman**, A.Nemes, R-Jan van Geuns, W.B. Vletter, F.J. ten Cate, J. Roelandt, and M.L. Geleijnse,. Comparison of contrast agent–enhanced versus non–contrast agent–enhanced real-time three-dimensional echocardiography for analysis of left ventricular systolic function. *Am J Cardiol.* (in press)

17. A.M. Anwar, M.L. Geleijnse, **O.I.I. Soliman**, A. Nemes, F.J. ten Cate. Left atrial Frank Starling law assessed by real-time three-dimensional echocardiographic left atrial volume changes. *Heart.* 2007 May 13; [Epub ahead of print]

18. A. Nemes, M.L. Geleijnse, **O.I.I. Soliman**, W.B. Vletter, F.J. ten Cate: Real-time three-dimensional echocardiography for regional evaluation of aortic stiffness. *Eur J Echocardiogr.* 2007 Mar;8(2):161-2. Epub 2006 Apr 5.

19. A. Nemes, M.L. Geleijnse, R.J. van Geuns, K. Caliskan, M. Michels, **O.I.I. Soliman**, J.S. McGhie, F.J. ten Cate. Evaluation of pericardial hydatid cysts by different echocardiographic imaging modalities. *Int J Cardiovasc Imaging.* 2006 Oct; 22(5):647-51. Epub 2006 Apr 20.

20. A. Nemes, **O.I.I. Soliman,** M.L. Geleijnse, A.M. Anwar, N.A.M.E. van der Beek, P.A. van Doorn, H. Gavallér, É. Csajbók, F.J. ten Cate: Increased aortic stiffness in glycogenosis type 2 (Pompe's disease). *Int J Cardiol.* 2006 Nov 2; [Epub ahead of print]

21. A. Nemes, M.L. Geleijnse, **O.I.I. Soliman,** F.J. ten Cate. Predictive value of combination of coronary flow reserve with aortic distensibility indices. *Eur Heart J.* 2006 Nov;27(21):2607-8.

22. A. Nemes, K. Caliskan, M.L. Geleijnse, **O.I.I. Soliman,** A.M. Anwar, F.J. ten Cate: Alterations in aortic elasticity in noncompaction cardiomyopathy. *Int J Cardiovasc Imaging.* 2007 Mar 3; [Epub ahead of print]

23. A.M. Anwar, **O.I.I. Soliman**, M.L. Geleijnse, M. Michels, W.B Vletter, A. Nemes, F. J ten Cate. Assessment of left atrial ejection force in hypertrophic cardiomyopathy using real-time three-dimensional echocardiography. *J Am Soc Echocardiogr.* 2007 Jun; 20(6): 744-8.

24. A.M. Anwar, **O.I.I. Soliman**, A.Nemes, T. Germans, B. J. Krenning, M.L Geleijnse, A.C. Van Rossum, F. J ten Cate Assessment of mitral annulus size and function by real-time three dimensional echocardiography in cardiomyopathy: comparison with magnetic resonance imaging. *J Am Soc Echocardiogr.* 2007 Aug; 20 (8): 941-948; 2007 Jun 5; [Epub ahead of print]

25. A.M. Anwar, M.L. Geleijnse, **O.I.I. Soliman**, J.S. McGhie, A. Nemes, F.J. Ten Cate: Evaluation of normal tricuspid anulus by real-time three-dimensional echocardiography. *Int J Cardiovasc Imaging.* 2006 (in press)

26. A.M. Anwar, **O.I.I. Soliman**, A. Nemes, R-Jan van Geuns, M.L. Geleijnse, F.J. Ten Cate: Value of assessment of tricuspid annulus: real-time three-dimensional echocardiography and magnetic resonance imaging. *Int J Cardiovasc Imaging.* 2007 Feb 13; [Epub ahead of print]

27. A.M. Anwar, M.L. Geleijnse MD, **O.I.I. Soliman**, J.S. McGhie, R. Frowijn, A. Nemes, A. E. van den Bosch, T. W. Galema, F.J. Ten Cate: Assessment of normal tricuspid valve anatomy in adults by real-time three-dimensional echocardiography. *Int J Cardiovasc Imaging.* 2007 Feb 23; [Epub ahead of print]

28. A.M. Anwar, **O.I.I. Soliman**, F.J. Ten Cate, A. Nemes, J.S. McGhie, R-Jan van Geuns, B. J. Krenning, T. W. Galema, M.L. Geleijnse: True mitral annulus diameter is underestimated by two-dimensional echocardiography as evidenced by real-time three-dimensional echocardiography and magnetic resonance imaging. *Int J Cardiovasc Imaging.* 2006 Dec 13; [Epub ahead of print]

29. A.M. Anwar, **O.I.I. Soliman**, A.E. van den Bosch, J.S. McGhie, M.L. Geleijnse, F.J. ten Cate, F.J. Meijboom. Assessment of pulmonary valve and right ventricular outflow tract with real-time three-dimensional echocardiography. *Int J Cardiovasc Imaging.* 2007 Apr;23(2):167-75. Epub 2006 Sep 8.

30. A.M. Anwar, **O.I.I. Soliman**, A. Nemes, M.L. Geleijnse, F.J. Ten Cate: An Integrated approach to determine left atrial volume, mass and function in hypertrophic cardiomyopathy by two-dimensional echocardiography. *Int J Cardiovasc Imaging.* 2007 May 31; [Epub ahead of print]

31. A.M. Anwar, **O.I.I. Soliman**, ML Geleijnse, A Nemes, WB Vletter , FJ ten Cate. Assessment of left atrial volume and function by real-time three-dimensional echocardiography. *Int J Cardiol.* 2007 Apr 16; [Epub ahead of print]

32. M.L Geleijnse, B.J. Krenning, A. Nemes MD, **O.I.I. Soliman**, T.W. Galema, F.J. ten Cate: Diagnostic value of dobutamine stress echocardiography in patients with normal wall motion at rest. *Echocardiography.* 2007 May; 24(5):553-7.

33. A. Nemes, T. Forster , ML Geleijnse, V. Kutyifa, K. Neu, **O.I.I. Soliman,** F.J. ten Cate, M. Csanady. The additional prognostic power of diabetes mellitus on coronary flow reserve in patients with suspected coronary artery disease. *Diabetes Res Clin Pract.* 2007 Apr 10; [Epub ahead of print]

34. A. Nemes, ML Geleijnse, B.J. Krenning, W.B. Vletter, **O.I.I. Soliman,** F.J. ten Cate. Role of parasternal data acquisition during contrast enhanced real-time three-dimensional echocardiography. *Echocardiography* (in press)

35. A. Nemes, R.G.M. Timmermans, M.L. Geleijnse, J.H. Paul Wilson, **O.I.I. Soliman,** B.J. Krenning ,F.J. ten Cate The mild form of mucopolysaccharidosis type I (Scheie syndrome) is associated wit increased ascending aortic stiffness. *Heart Vessels* (in press)

36. A. Nemes, M.L. Geleijnse, T. Forster, **O.I.I. Soliman**, F. J. ten Cate, M. Csanády. Echocardiographic evaluation and clinical implications of aortic stiffness and coronary flow reserve and their relation. *Clinical Cardiology* (in press)

37. A. Nemes T. Forster, M.L. Geleijnse, V. Kutyifa, K. Neu, **O.I.I. Soliman,** F.J. ten Cate, M. Csanady. Prognostic role of aortic atherosclerosis and coronary flow reserve in patients with suspected coronary artery disease. *International Journal of Cardiology.* (in press)

38. A. Nemes, A.M. Anwar, K. Caliskan, **O.I.I. Soliman,** B.M. van Dalen, M.L. Geleijnse, F.J. ten Cate: Evaluation of left atrial systolic function in non-compaction cardiomyopathy by real-time three-dimensional echocardiography. *Int J Cardiovasc Imaging.* (in press)

ABSTRACTS

39. **OII. Soliman**, DAMJ. Theuns, ML. Geleijnse, FJ. ten Cate: Tissue Doppler imaging for cardiac resynchronization therapy are the current Guidelines sufficient? (*ACC*-2006) *J Am Coll Cardiol.* 2006; 47: Supplement A102

40. **OII. Soliman**, P. Knaapen, ML. Geleijnse, AM. Anwar, A. Nemes, WB Vletter, FJ. ten Cate: Adenosine myocardial contrast echocardiography versus positron emission tomography in assessment of microvascular dysfunction in hypertrophic cardiomyopathy patients. (*ASE*-2006) *J Am Society Echocardiography.* 2006: 19 (5) 668

41. AM. Anwar, **OII. Soliman**, J. McGhie, ML. Geleijnse, A. Nemes, FJ. ten Cate: Left atrial volume and function assessed by real-time three-dimensional transthoracic echocardiography. (*ASE*-2006) *J Am Society Echocardiography.* 2006; 19 (5) 609

42. AM. Anwar, **OII. Soliman**, J. McGhie, ML. Geleijnse, A. Nemes, FJ. ten Cate: Starling law and left atrium: real time three dimensional echocardiographic study. (*ASE*-2006) *J Am Society Echocardiography.* 2006; 19 (5) 631

43. AM. Anwar, **OII. Soliman,** ML. Geleijnse, FJ. ten Cate: Effects of Cardiac Resynchronization Therapy on Cardiac Remodeling. (*AHFS*-2006) *J Card Fai.* 12 (6): Supplement 1: S65

44. **OII. Soliman**, ML. Geleijnse, AM. Anwar, A. Nemes, WB. Vletter, FJ. ten Cate: Reproducibility of real-time three dimensional echocardiographic quantification of left ventricular volume using two commercially available software systems. (*ESC*-2006) *Eur Heart J.* 2006; 27 Supplement 1:858

45. **OII. Soliman**, P. Knaapen, ML. Geleijnse, AM. Anwar, A. Nemes1, FJ. ten Cate: Adenosine myocardial contrast echocardiography versus positron emission tomography in assessment of microvascular dysfunction in hypertrophic cardiomyopathy patients. (*ESC*-2006) *Eur Heart J.* 2006; 27 Supplement 1:847

46. A. Anwar, **O.I.I. Soliman**, M.L. Geleijnse, J. Mcghie, A. Nemes, FJ. ten Cate: Assessment of tricuspid valve annulus size and shape with real-time three-dimensional echocardiography. (*ESC*-2006) *Eur Heart J.* 2006; 27 Supplement 1:707

47. A. Nemes, ML. Geleijnse, WB. Vletter, **OII. Soliman** AM. Anwar, B. Krenning, FJ. ten Cate: The use of an ultrasound contrast agent is mandatory during real-time 3D stress echocardiography. (*ESC*-2006) *Eur Heart J.* 2006; 27 Supplement 1:714

48. **OII. Soliman**, M L. Geleijnse, A M. Anwar, A. Nemes, W B. Vletter, F J. ten Cate: Regional left ventricular systolic function in dilated cardiomyopathy: A real-time three dimensional echocardiographic study. **(***Euroecho*-2006**)** *Eur J Echocardiogr.* 7; Supplement 1:S97

49. **OII. Soliman,** M L. Geleijnse, A M. Anwar, A. Nemes, W B. Vletter, F J. ten Cate: Regional left ventricular systolic function in hypertrophic cardiomyopathy evaluated by real-time three dimensional echocardiography. **(***Euroecho*-2006**)** *Eur J Echocardiogr.* 7; Supplement 1:S213

50. **OII. Soliman,** ML. Geleijnse, AM. Anwar, A. Nemes, WB. Vletter, FJ. ten Cate: Early echocardiographic predictors of long-term outcome after cardiac resynchronization therapy by combined systolic and diastolic parameters (Role of Tei index and E/e ratio). **(***Euroecho*-2006**)** *Eur J Echocardiogr.* 7; Supplement 1:S8

51. AM. Anwar, **OII. Soliman,** A. Nemes, ML. Geleijnse, W B. Vletter, FJ. ten Cate: Assessment of left atrial function: A real-time 3-D Echocardiography study. **(***Euroecho*-2006**)** *Eur J Echocardiogr.* 7; Supplement 1:S97-S98

52. A. Nemes, T.W. Galema, M.L. Geleijnse, **O.I.I. Soliman**, A.M. Anwar, S.C. Yap and F.J. ten Cate: Aortic valve replacement for aortic stenosis is associated with improved aortic distensibility at long-term follow-up. **(***Euroecho*-2006**)** *Eur J Echocardiogr.* 7; Supplement 1:S116

53. A. Nemes, M.L. Geleijnse, N. A.M.E. Van DerBeek, P.A. Van Doorn, **O.I.I. Soliman**, E. Csajbok, H. Gavaller and F.J. ten Cate: Increased aortic stiffness in glycogenosis type 2 (Pompe's disease). **(***Euroecho*-2006**)** *Eur J Echocardiogr.* 7; Supplement 1:S112

54. **O.I.I. Soliman**, T.C.G. Vydt, R.F.M. de Coo, F.J. ten Cate, R.J.M. van Geuns, W.B. Vletter, K. Schoonderwoerd, B.J. van den Bosch, B.J.M. Smeets, M.L. Geleijnse: Cardiac Involvement in Adults with m.3243A>G MELAS Gene Mutation**, (***European Meeting of Cardiovascular Research Nice, France* 2006**)** *Hypertension.* 2006; 48: 761

55. **OII. Soliman**, ML. Geleijnse, DAMJ. Theuns, A. Nemes, WB. Vletter, LJ. Jordaens, FJ. ten Cate: Effect of left ventricular pacing site and outcome after cardiac resynchronization therapy using novel real-time three-dimensional echocardiography to define site of latest activation. (*ASE*-2007- Highlights session) *J Am Society Echocardiography.* 2007; 20 (5) 558

56. **OII. Soliman,** BJ. Krenning, ML. Geleijnse, A. Nemes, AM. Anwar, R-J. Van Geuns, SW. Kirschbaum, WB. Vletter1, TW. Galema, FJ. ten Cate: Accuracy of endocardial border tracking algorithms for real-time three-dimensional echocardiographic quantification of left ventricular volumes. (*ESC*-2007) *Eur Heart J*. 2007: 28 Supplement 1: 488

57. **OII. Soliman,** ML. Geleijnse, DAMJ. Theuns, A. Nemes, WB. Vletter, LJ. Jordaens, YFM. Nosir, FJ. ten Cate: Effect of left ventricular pacing site and outcome after cardiac resynchronization therapy using novel real-time three dimensional echocardiography to define site of latest activation. (*ESC*-2007) *Eur Heart J*. 2007; 28 Supplement1: 290

58. **OII. Soliman,** ML. Geleijnse, DAMJ. Theuns, A. Nemes, WB. Vletter, LJ. Jordaens, AK. Motawea, FJ. ten Cate: A novel parametric imaging of mechanical dyssynchrony and mechanical-electrical activation sequence by real-time three-dimensional echocardiography. (*ESC*-2007) *Eur Heart J*. 2007; 28 Supplement1: 490

59. **OII. Soliman,** DAMJ. Theuns, ML. Geleijnse, A. Nemes, WB. Vletter, LJ. Jordaens, AM. Al-Amin, FJ. ten Cate: Echocardiographic parameters of cardiac mechanical dyssynchrony and outcome after cardiac resynchronization therapy: a prospective comparative study. (*ESC*-2007) *Eur Heart J*. 2007; 28 Supplement1: 637

60. CE. Veltman, **OI. Soliman**, E. Meliga, ML. Geleijnse, PC. Smits, FJ. ten Cate, AH. Balk, PW. Serruys, RT. Van Domburg, W.J. Van Der Giessen: Four-year follow-up of patients with ischaemic cardiomyopathy treated with skeletal myoblasts. (*ESC*-2007) *Eur Heart J*. 2007; 28 Supplement1: 442

61. M. Michels, YM. Hoedemaekers, MJ. Kofflard, **OII. Soliman**, D. Dooijes, D. Majoor-Krakauer, FJ. ten Cate: The yield of cardiac screening and risk stratification for sudden cardiac death in asymptomatic hypertrophic cardiomyopathy mutation carriers. (*ESC*-2007) *Eur Heart J*. 2007; 28 Supplement1: 473

62. A. Nemes, K. Caliskan, ML. Geleijnse, **OII. Soliman**, WB. Vletter, FJ. ten Cate: Reduced regional systolic function is not confined to the non-compacted segments in non-compaction cardiomyopathy.(*ESC*-2007) *Eur Heart J*.2007; 28 Supplement1: 555

63. D.AMJ. Theuns, **OII. Soliman,** M. Rivero-Ayerza, E.R. Jessurun, ML Geleijnse, FJ. ten Cate, LJ Jordaens: Effects of cardiac resynchronization therapy on left atrial size and incidence of atrial fibrillation in heart failure patients with implantable defibrillators. (*Annual meeting of Heart Rhythm Society, Denver, USA 2007) Heart Rhythm* 2007: 4 (5); S378-S402

64. **OII. Soliman**, RMG. Timmermans, A. Nemes, WB. Vletter, JHP. Wilson, FJ. Ten Cate, ML. Geleijnse. Cardiac involvement in adults with the attenuated form of mucopolysaccharidosis Type I: *(Euroecho*-2007*) Eur J Echocardiogr.* (Accepted for presentation)

65. **OII. Soliman**, ML. Geleijnse, M. Michels, P. Dijkmans, A. Nemes, BM. Van Dalen, FJ. ten Cate. Improvement of microvascular dysfunction after successful alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: *(Euroecho*-2007*) Eur J Echocardiogr.* (Accepted for presentation)

66. **OII. Soliman**, DAMJ. Theuns, FJ. ten Cate, BM. Van Dalen, WB. Vletter, LJ. Jordaens, ML. Geleijnse. Prognostic value of structural left ventricular reverse remodeling after cardiac resynchronization therapy: *(Euroecho*-2007*) Eur J Echocardiogr.* (Accepted for presentation)

67. **OII. Soliman**, SW. Kirschbaum, ML. Geleijnse, A. Nemes, BM. Van Dalen, WB. Vletter, BJ. Krenning, DAMJ. Theuns, LJ. Jordaens, FJ. ten Cate. Three-dimensional echocardiographic parametric quantification of regional left ventricular function: validation and clinical application in cardiac resynchronization therapy: *(Euroecho*-2007*) Eur J Echocardiogr.* (Accepted for presentation- Young Investigator Award Finalist)

68. N.A.M.E. van der Beek, **O.I.I. Soliman**, M.L. Geleijnse, M.A. Kroos, A.J.J. Reuser, W.B. Vletter, A.T. van der Ploeg, P.A. van Doorn. Cardiologic evaluation in adults with Pompe disease shows no signs of cardiomyopathy. **(***World Muscle Society 12th Meeting, Taormina, Italy* 2007**)** *Neuromuscular Disorders.* 2007; Supplement?.

69. A. Nemes, R.G.M. Timmermans, W.B. Vletter, **O.I.I. Soliman,** M.L. Geleijnse, J.H.P. Wilson, Folkert J ten Cate. Vascular alterations in mucopolysaccharidosis type I. *(Euroecho*-2007*) Eur J Echocardiogr.* (Accepted for presentation)

70. A. Nemes, K. Caliskan, ML. Geleijnse, **OII. Soliman**, WB. Vletter, FJ. ten Cate: Left atrial systolic function in non-compaction cardiomyopathy. *(Euroecho*-2007*) Eur J Echocardiogr.* (Accepted for presentation)

71. **OII. Soliman**, SW. Kirschbaum, ML. Geleijnse, A. Nemes, BJ. Krenning, BM. Van Dalen, WB. Vletter, Robert-Jan van Geuns, Aly M. Al-Amin, FJ. ten Cate. Usefulness of Three-Dimensional Echocardiographic Parametric Quantification of Regional Left Ventricular Function: a Feasibility Study: *(AHA-2007) Circulation Oct 7, 2007, Volume 116, Issue15 Supplement.* (Accepted for presentation)

72. **OII. Soliman**, DAMJ. Theuns, ML. Geleijnse, A. Nemes, BM. Van dalen, Willem P.M.H.I.A. Gielen, WB. Vletter, LJ. Jordaens, Aly M. Al-Amin, FJ. ten Cate. Echocardiographic Predictors of Left Ventricular Reverse Remodeling after Cardiac Resynchronization Therapy: a prospective Comparative Study. *(AHA-2007) Circulation Oct 7, 2007, Volume 116, Issue15 Supplement.* (Accepted for presentation)