Three-dimensional echocardiography for left ventricular quantification in heart failure

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Chapter 1

General introduction

Heart failure is an epidemically growing syndrome. Aging of the population, improved survival of patients with acute myocardial infarction, better medical management of left ventricular (LV) dysfunction and reduced mortality from other diseases are amongst the main reasons for the rapid increase in incidence of heart failure. Data suggest that lifetime risk of developing heart failure is about 20%. Despite the major advances that have occurred in our understanding of the pathophysiological abnormalities, pharmacological, device and surgical therapies for this syndrome during the last decade, heart failure remains a major cause of morbidity and mortality worldwide. It still carries a poor prognosis: approximately 50% of heart failure patients are re-hospitalized within 6 months of discharge and one-year mortality after first admission for heart failure is 37%. In the Netherlands, in 2009, 125990 people were diagnosed with congestive heart failure, and the number of hospitalizations for congestive heart failure as a primary or secondary diagnosis was 29366 [1].

The clinical definition of systolic heart failure is based on (echocardiographic) quantitation of LV function. For example, an ejection fraction of ≤ 40% is an indication for medical therapy for heart failure even in the absence of symptoms [1], an ejection fraction of ≤ 35% is an indication for implantation of an implantable cardioverter/defibrillator with or without cardiac resynchronization therapy [2], an end-systolic volume index > 30 ml/m2 implies worse prognosis, especially after myocardial infarction [3].

Dyssynchronous contraction of different segments of the LV due to lack of proper coordination in the intraventricular electrical activation, has emerged as an important factor in the pathogenesis of patients with heart failure. It further impairs LV contractility and may aggravate mitral valve regurgitation. Cardiac resynchronisation therapy (CRT) has been developed aiming at restoring synchrony by pacing of the most delayed segment of the LV, causing all myocardial segments to reach maximal contraction simultaneously.

Demonstrating improved hemodynamics, reduction in mitral valve regurgitation, and enhanced contractility of the LV, as well as improved functional status and lower mortality in heart failure patients, CRT is now an established line of treatment in heart failure [2, 4-8].

Unfortunately, up to 30-40% of patients do not respond to CRT. One of the reasons for this high non response rate may be the non optimum current selection criteria that depend on electrical rather than mechanical dyssynchrony [9]. Several studies have shown a low correlation between QRS duration and LV mechanical dyssynchrony and have suggested that correction of mechanical dyssynchrony is the main mechanism behind benefit from CRT [10,11]. In order to avoid unnecessary pacemaker implantation in patients who subsequently do not respond to this invasive and expensive therapy, a need to establish novel selection criteria focusing on mechanical dyssynchrony that might be a better predictor of response to CRT than QRS width is warranted [11,12].

Both conventional two-dimensional echocardiography and tissue Doppler imaging have been widely investigated in this field with early encouraging results but their legitimacy has been questioned after the publication of the results of the multicenter PROSPECT trial. This study reported modest sensitivity and specificity of the all studied dyssynchrony parameters and concluded that no single echocardiographic measure of dyssynchrony may be recommended to improve patient selection for CRT beyond current guidelines [9,13].

Three-dimensional echocardiography (3DE) has been shown to be more accurate and reliable than two-dimensional echocardiography in LV quantification in comparison to reference techniques such as cardiac magnetic resonance [14,15]. In addition, with the abilities of 3DE to assess all the myocardial segments simultaneously in three dimensions without assumption, 3DE may provide a complete evaluation of intraventricular mechanical dyssynchrony by examining the composite effect of radial, longitudinal and circumferential dyssynchrony for more adequate measurement of LV mechanical dyssynchrony and ultimately, better prediction of response to CRT. Recently, acquisition of a complete 3D dataset can be performed during a single cardiac cycle aimed at reducing artifacts by cardiac translation, respiration and heart rate variability. For these reasons, single beat acquisition is particularly helpful in patients with heart rhythm irregularities where 3DE was previously difficult to impossible [16,17].

Concurrently, the use of 3DE gained increasing attention as a growing number of studies showed results supporting it as a potential useful, reproducible, robust technique in assessment of ejection fraction, volumes and dyssynchrony in patients with heart failure and might be useful for prediction of response to CRT [18-24]. Therefore, this thesis addresses the quantitative aspects of 3DE in patients with systolic heart failure and evaluates its diagnostic and prognostic capacities.

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Thesis outline

Assessment of left ventricular (LV) function is crucial in patients with heart failure. The ideal imaging modality for assessment of LV function using LV volumes and ejection fraction should be easily applicable, reproducible, real-time and also three-dimensional (3D). Therefore the present thesis focuses on using 3DE as a relatively new imaging tool for this purpose.

Chapter 2 provides an overview of the current state of the art in three-dimensional echocardiography (3DE). It gives a short overview of the methodology and clinical applications for quantification of LV size, function and dyssynchrony.

Chapter 3 delineates the impact of faulty positioning of the two-dimensional echocardiographic transducer on 3D echocardiographic measurement of LV volumes through misalignment of the image plane. It describes the in-vitro effects of translation (horizontal transducer displacement) and angulation (transducer tilting), on volume measurement of both balloons and human LVs after autopsy. For this purpose 6 water-filled aneurysmatic and non-aneurysmatic balloons of 150, 250 and 350 ml and 3 hearts of different sizes and shapes were suspended upright in a water bath. Angulation and/or translation was performed respectively by tilting the transducer with a mechanical arm in a vertical plane relative to the balloon tip or true apex of the hearts and by shifting the water baths in the same vertical plane. For balloon and LV volume assessment a 3D conical data set was obtained by rotational acquisition. For the 6 balloons translation of 1 to 4 cm yielded volumes of up to 74% of the true volume, and angulation of 10^o to 20^o up to 34% of the true volume. Translation in combination with 10^o angulation yielded volumes up to 64%, but for 20% angulation and translation there was no volume loss. Results were similar for the LVs. Even minor angulation or translation of the transducer yields substantial underestimation of the true volume, but off-axis para-apical views, defined as angulation of 20^o and translation greater than 0,5 cm, obviate volume underestimation. Such views in patients, if clinically obtainable, may be an attractive alternative for conventional apical 3D acquisitions, especially in dilated and aneurysmatic hearts. This enables the operator to improve image quality by trying various transducer positions on the patients' chest without negative effects on LV volume measurement.

Chapter 4 describes the validation of 3DE using the freehand acquisition method for assessment of LV volumes and ejection fraction. It uses magnetic resonance imaging (MRI) as the current gold standard in LV volume measurement. Furthermore, LV volumes by breath-hold versus free-breathing acquisitions were assessed and compared with MRI. From the apical position, a fan-like 3D echocardiographic data set was acquired during free breathing and, thereafter, during multiple breath-holds. In 27 patients, 28 breath-hold and 24 free-breathing 3D echocardiographic data sets were acquired. A subgroup of 17 patients underwent both 3DE and MRI. MRI contours were traced along the outer endocardial contour, including trabeculae, and along the inner endocardial contour, excluding trabeculae from the LV volume. All 28 (100 %) breath-hold and 86 % of free-breathing 3D echocardiographic data sets could be analyzed. Intra-observer variation (bias ± 2 SD) of end-diastolic, end-systolic volume and ejection fraction for breath-hold 3DE was, respectively, 0,3 ± 10,2%, 0,3 ± 14,6% and -0,1 ± 5,8%. For free-breathing 3DE, findings were similar. A significantly better interobserver variability, however, was found for breath-hold 3DE for end-systolic volume and ejection fraction. Comparison of breath-hold 3DE with MRI inner contour showed for end-diastolic volume, end-systolic volume, and ejection fraction, a bias (± 2 SD) of, -13,5 ± 26,9%, -17,7 ± 47,8% and -1,8 ± 11,6%, respectively. Compared with the MRI outer contour, a significantly greater difference was observed, except for ejection fraction. Freehand 3DE is fast and highly reproducible for (serial) LV volume and ejection fraction measurement, and, hence, ideally suited for clinical decision making. Breath-hold 3DE is superior to free-breathing 3DE regarding image quality and reproducibility. Compared with MRI, 3DE underestimates LV volumes, but not ejection fraction, which is mainly explained by differences in endocardial contour tracing by MRI (outer contour) and 3DE (inner contour) of the trabecularized endocardium. Underestimation is reduced when breath-hold 3DE is compared with inner contour analysis of the MRI dataset.

Chapter 5 describes the use of 3DE for accurate evaluation and prediction of LV remodelling in the subacute phase of myocardial infarction as being associated with poor prognosis. For these purpose, 33 acute myocardial infarction patients (21 with anterior infarction) underwent 3DE prospectively at baseline (6 ± 4 days) and at 3, 6 and 12 months after acute myocardial infarction. Remodelling was defined as > 20% increase in end-diastolic volume at 6 or 12 months compared to baseline. At baseline, end-diastolic and end-systolic volumes, but not ejection fraction, were significantly increased in patients with subsequent remodelling (n = 13), compared to patients without subsequent remodelling (n = 20). At 12 months, in patients with remodelling end-diastolic and end-systolic volumes were significantly further increased, and ejection fraction unchanged, whilst in patients without remodelling LV volumes were unchanged and ejection fraction slightly increased. Clinical, electrocardiographic and echocardiographic variables were analysed for predictive values in remodelling. Of these, the 3D sphericity index (end-diastolic volume divided by a spherical volume, of which the LV major end-diastolic long axis is the diameter) was the most predictive variable with a sensitivity, specificity, positive and negative predictive value of, respectively, 100%, 90%, 87% and 100%, for a cut-off value of > 0,25. 3DE may accurately and early differentiate patients with and without LV remodelling on the basis of 3D sphericity index, which is a new and highly predictive variable.

Chapter 6 demonstrates use of 3DE as a promising tool for assessment of LV electromechanical dyssynchrony. A system combining 3DE and semi-automatic endocardial contour detection is described. Eighteen consecutive patients underwent transoesophageal, rotational 3DE for various clinical reasons. A subgroup of 7 patients with a biventricular pacemaker underwent 3DE with the pacemaker switched on and off. Using TomTec 4DLV software, a 3D endocardial surface was reconstructed throughout the cardiac cycle. Subsequently, Matlab software was used to generate color-coded polar maps, displaying regional LV displacement and its timing. At segmental level, intra-observer variability (bias ± 2 SD) of displacement was 0,1 ± 3,0 mm and of timing was -4 ± 130 ms. When only non-apical segments were assessed, intra-observer variability was -1,6 ± 94 ms. The combination of 3DE and semi-automatic endocardial contour detection provides accurate assessment of LV segmental contractility and its timing. This may aid in evaluation of patients eligible for biventricular pacing therapy.

In **Chapter 7**, the effect of using an echocardiographic contrast agent on measurement of LV volumes, and on its reproducibility is investigated. Endocardial contour detection may be difficult in 3DE methods that are based on multiple 2D image planes, because the reconstruction method may cause deterioration of image quality. Individual endocardial trabeculae are not clearly visible necessitating LV volumes to be measured by tracing the innermost endocardial contour. Ultrasound contrast agents aim to improve endocardial definition, but may delineate the outermost endocardial contour by filling up intertrabecular space. Twenty patients with a recent myocardial infarction underwent 3DE using the TomTec Freehand method before and during continuous intravenous contrast infusion. LV volumes were measured off-line using TomTec Echo-Scan software. The use of contrast enhancement increased end-diastolic (110 ± 35 versus 144 ± 53 ml; $p<0,01$) and end-systolic volume measurements (68 ± 31 versus 87 ± 45 ml; $p<0,01$) significantly compared to baseline; the ejection fraction remained unchanged (40 ± 13 vs. 41 ± 14%, p=NS). Reproducibility did not improve significantly, however. Volumes measured by 3DE are significantly larger when ultrasound contrast is used. Possibly, intertrabecular space comprises a substantial part of the LV cavity. In the presence of an adequate apical acoustic window, ultrasound contrast does not improve LV volume measurement reproducibility.

In **Chapter 8**, 3DE combined with semi-automatic endocardial contour detection is presented as a valuable tool to provide additional information on LV dyssynchrony through measurement of timing of contraction of LV segments. The endocardial contour detection system is developed further to integrate regional volume-time curves in LV dyssynchrony assessment. Twelve patients with a biventricular pacemaker underwent transoesophageal, rotational 3DE, with the pacemaker switched off and on. Offline, using TomTec 4DLV analysis™ software featuring semi-automatic contour detection, a 3D endocardial surface was reconstructed throughout the cardiac cycle and segmental volume-time curves were generated. By integrating areas under volume-time-curves of segments showing systolic relaxation or diastolic contraction, segmental contractility was combined with timing of contraction in a parameter we named time-volume loss. Reproducibility was assessed in a group of 20 patients with and without cardiac abnormalities. Biventricular pacing resulted in a significant decrease in pre-systolic time-volume loss (from 6914 ± 4171 to 2872 ± 2326 ml*ms, p=0,002) but not in post-systolic time-volume loss. Reproducibility was reasonable. This method enables accurate assessment of LV dyssynchrony.

In **Chapter 9**, in a different patient group underwent CRT using real-time 3DE volume-time curve analysis demonstrated superiority in prediction of response to biventricular pacing over methods based on timing alone. Twenty-eight patients underwent real-time 3DE before pacemaker implantation and after eight months follow-up. Off-line, data were analysed using TomTec Research-Arena software featuring semi-automated endocardial contour detection. Predictive values of response to biventricular pacing of baseline echocardiographic parameters were calculated 1) by integrating area under segmental time-volume-curves 2) by measuring delay between contraction of the earliest and latest segment (L-E) and 3) by calculating the standard deviation of time to minimal segmental volume (SDI) in a 17-segment model. Response to biventricular pacing was defined as ≥10% decrease in LV end-systolic volume at follow-up. Baseline Pre-STV had a higher sensitivity than SDI for prediction of response (94 vs. 67%, respectively), with equal specificity (78%) and a higher area under ROC curve. In contrast, L-E had a sensitivity of 83% and a specificity of 56%. Using 3DE, methods that combine segmental time-to-contraction with segmental contractility might improve LV dyssynchrony assessment more accurately compared to traditional methods based on segmental time-to-contraction alone.