KTH Technology
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Assessment of Left Ventricular Function and Hemodynamics using Three-dimensional Echocardiography

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Doctoral Thesis

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ABSTRACT

Left ventricular (LV) volumes and ejection fraction (EF) are important predictors of cardiac morbidity and mortality. LV volumes provide valuable prognostic information which is particularly useful in the selection of therapy or determination of the optimal time for surgery. Two-dimensional (2D) echocardiography is the most widely used non-invasive method for assessment of cardiac function, 2D echocardiography has however several limitations in measuring LV volumes and EF since the formulas for quantifications are based on geometrical assumptions. Three-dimensional (3D) echocardiography has been available for almost two decades, although the use of this modality has not gained wide spread acceptance. 3D echocardiography can overcome the above mentioned limitation in LV volume and EF evaluation since it is not based on geometrical assumption. 3D echocardiography has been shown in several studies to be more accurate and reproducible with low inter- and intraobserver variability in comparison to 2D echocardiography regarding the measurements of LV volumes and EF.

The overall aim of the thesis was to evaluate the feasibility and accuracy of 3D echocardiography based-methods in the clinical context.

In **Study I** the feasibility of 3D echocardiography was investigated for determination of LV volumes and EF using parasternal, apical and subcostal approaches. The study demonstrated that the apical 3D echocardiography view offers superior visualization.

S**tudy II** tested the possibility of creating flow-volume loops to differentiate patients with valvular abnormalities from normal subjects. There were significant differences in the pattern from flow-volume loops clearly separating the groups.

In **Study III** the visual estimation, “eyeballing” of EF was evaluated with two- and tri-plane echocardiography in comparison to quantitative 3D echocardiography. The study confirmed that an experienced echocardiographer can, with a high level of agreement estimate EF both with two- and tri-plane echocardiography.

Study IV exposed the high accuracy of stroke volume and cardiac output determination using a 3D biplane technique by planimetrically tracing the left ventricular outflow tract and indicating that an assumption of circular left ventricular outflow tract is not reliable.

In **Study V**, two 3D echocardiography modalities, single-beat and four-beat ECG-gated 3D echocardiography were evaluated in patients having sinus rhythm and atrial fibrillation. The single-beat technique showed significantly lower inter-and intraobserver variability in LV volumes and EF measurements in patients having atrial fibrillation in comparison to four-beat ECG-gated acquisition due to absence of stitching artifact.

All studies demonstrated good results suggesting 3D echocardiography to be a feasible and accurate method in daily clinical settings.

Keywords: Three-dimensional echocardiography, heart chambers, flow-volume loop, left ventricular ejection fraction, visualization, left ventricular stroke volume, left ventricular outflow tract, and single-heartbeat.

LIST OF PUBLICATIONS

The thesis is based on the five following papers, and will be referred to by their Roman numerals:

I. Ostenfeld E, **Shahgaldi K**, Winter R, Willenheimer R, Holm J. Comparison of different views with three-dimensional echocardiography: apical views offer superior visualization compared with parasternal and subcostal views. *Clin Physiol Funct Imaging. 2008;28:409-16.*

II. **Shahgaldi K**, Söderqvist E, Gudmundsson P, Winter R, Nowak J, Brodin LÅ. Flow-volume loops derived from three-dimensional echocardiography: a novel approach to the assessment of left ventricular hemodynamics. *Cardiovasc Ultrasound. 2008;4:6:13.*

III. **Shahgaldi K,** Gudmundsson P, Manouras A, Brodin LÅ, Winter R. Visually estimated ejection fraction by two dimensional and triplane echocardiography is closely correlated with quantitative ejection fraction by real-time three dimensional echocardiography. *Cardiovasc Ultrasound. 2009;25:7:41.*

IV. **Shahgaldi K,** Manouras A, Brodin LÅ, Winter R. Direct measurement of left ventricular outflow tract area using three-dimensional echocardiography in biplane mode improves accuracy of stroke volume assessment. *Accepted Feb. 2010, Echocardiography.*

V. **Shahgaldi K,** Manouras A, Abrahamsson A, Gudmundsson P, Brodin LÅ, Winter R. Three-dimensional echocardiography using single-heartbeat modality decreases variability in measuring left ventricular volumes and function in comparison to four-beat technique in atrial fibrillation. *Submitted to J Am Soc Echocardiogr April 2010.*

DIVISION OF WORK BETWEEN AUTHORS

I. R. Winter introduced the study idea. Image acquisition and analysis of the patient data was performed by K. Shahgaldi. The preparation of the manuscript was performed by E. Ostenfeld, and J. Holm and R. Willenheimer reviewed and contributed with clinically content to the manuscript. All authors reviewed the final manuscript.

II. L. Å. Brodin and R. Winter initiated the study. R. Winter supervised the study and participated in the interpretation of the results and manuscript preparation. K. Shahgaldi performed measurements, made all data conversions, plots and calculations from ultrasound data, and participated in the preparation of the manuscript. P. Gudmundsson participated in data collection and interpretation of the results. E. Söderqvist participated in data conversion, creation of plots and calculations from ultrasound data. J. Nowak performed statistical analysis and was responsible for final manuscript. All authors read and approved the final manuscript.

III. K. Shahgaldi and P. Gudmundsson initiated the study. R. Winter and L. Å. Brodin supervised the study and participated in the interpretation of the results and manuscript preparation. K. Shahgaldi and P. Gudmundsson performed measurements, made all data conversions, plots and calculations from ultrasound data, and participated in the preparation of the manuscript. K. Shahgaldi and A. Manouras performed statistical analysis and participated in the interpretation of the results. Finally, all authors reviewed and commented on the manuscript.

IV. K. Shahgaldi planned and designed the study. A. Manouras participated in the interpretation of the results. Image acquisition and preparation of the manuscript was performed by K. Shahgaldi. A. Manouras and K. Shahgaldi performed off-line analysis of the patient data. R. Winter critically read the manuscript and contributed with his clinical experience. L. Å. Brodin and R. Winter supervised the study. All authors read and approved the manuscript.

V. R. Winter and K. Shahgaldi introduced the study idea. K. Shahgaldi acquired the ultrasound images. A. Abrahamsson and K. Shahgaldi performed the off-line analysis. A. Manouras helped in the interpretation of the results and statistical analysis. K. Shahgaldi wrote the manuscript, R. Winter and P. Gudmundsson added clinical discussion to the manuscript. L. Å. Brodin reviewed the manuscript. Finally, all authors read and approved the manuscript.

SCIENTIFIC CONTRIBUTIONS NOT INCLUDED

Not included papers to which I have contributed during my work on the present thesis:

Scientific Publication:

I. Manouras A, **Shahgaldi K**, Winter R, Nowak J, Brodin LÅ.
Comparison between color-coded and spectral tissue Doppler measurements of systolic and diastolic myocardial velocities: effect of temporal filtering and offline gain settings. *Eur J Echocardiogr. 2009;10:406-13.*

II. Bjällmark A, Larsson M, **Shahgaldi K**, Lind B, Winter R, Brodin LÅ.
Differences in myocardial velocities during supine and upright exercise stress echocardiography in healthy adults. *Clin Physiol Funct Imaging. 2009;29:216-23.*

III. Manouras A, **Shahgaldi K**, Winter R, Brodin LÅ, Nowak J.
Measurements of left ventricular myocardial longitudinal systolic displacement using spectral and colour tissue Doppler: time for a reassessment? *Cardiovasc Ultrasound. 2009;17:7:12.*

IV. Gudmundsson P, **Shahgaldi K,** Winter R, Dencker M, Kitlinski M, Thorsson O.
Head to head comparisons of two modalities of perfusion Adenosine stress echocardiography with simultaneous SPECT. *Cardiovasc Ultrasound. 2009;20:7:19.*

V. Gudmundsson P, **Shahgaldi K,** Winter R, Dencker M, Kitlinski M, Thorsson O, Ljunggren L, Willenheimer R.
Quantitative detection of myocardial ischemia by stress echocardiography. A comparison with SPECT. *Cardiovasc Ultrasound. 2009;18:7:28*.

VI. Manouras M, Shala A, Nyktaria E, S**hahgaldi K,** Winter R, Vardas P, Brodin LÅ. Nowak N.
Are measurements of systolic myocardial velocities and displacement with colour and spectral Tissue Doppler compatible? *Cardiovasc Ultrasound. 2009;23:7:29.*

VII. Sadigh B, **Shahgaldi K,** Sylvén C, Quintana M, Winter R.
Preconditioning effects of adenosine in patients with severe coronary artery disease but preserved coronary flow reserve. *Coron Artery Dis. 2009;20:354-9.*

VIII. Gudmundsson P, **Shahgaldi K,** Winter R, Dencker M, Kitlinski M, Thorsson O, Ljunggren L, Willenheimer R.
Parametric quantification of myocardial ischemia using real-time perfusion adenosine stress echocardiography images. A comparison with SPECT as reference method. Clin Physiol Funct Imaging. *2010;30:30-42.*

IX. Magnusson M, Jovinge S, **Shahgaldi K,** Israelsson B, Groop L, Melander O.
Brain natriuretic peptide is related to diastolic dysfunction whereas urinary albumin excretion rate is related to left ventricular mass in asymptomatic type 2 diabetes patients. *Cardiovascular Diabetology 2010;18:9:2*

X. Bjällmark A, Lind B, Poelsson M, **Shahgaldi K,** Brodin LÅ, Nowak J.
Ultrasonographic strain imaging is superior to conventional non-invasive measures of vascular stiffness in the detection of age-dependent differences in the mechanical properties of the common carotid artery. *Eur J Echocardiogr 2010;10.*

XI. Sahlén A, **Shahgaldi K**, Aminoff A, Aagaard P, Manouras A, Winter R, Ehrenborg E, Bruanschweig F.
Effects of prolonged exercise on LV mechanical synchrony in experienced long-distance runners and beginners. *Submitted to J Am Soc Echocardiogr 2010.*

XII. Sahlén A, **Shahgaldi K**, Aagaard P, Manouras A, Winter R, Braunschweig F.
Circulatory Response to Brief Supine Exercise in Athletes with and without Troponin T Release during Prolonged Exercise. *Submitted to J Appl Physiol 2010.*

Conference Abstracts:

I. Flow-volume loops from three-dimensional echocardiograph; A novel technique for assessment of left ventricular function and hemodynamics.
Shahgaldi K, Söderqvist E, Gudmundsson P, Winter R, Nowak J, Brodin LÅ.
EuroEcho, Florence 2005.

II. Choice of view in real time 3-dimensional echocardiography.
Ostenfeld E, **Shahgaldi K**, Winter R, Willenheimer R, Holm J.
EuroEcho, Florence 2005.

III. Feasibility of quantitative analysis in real-time myocardial contrast echocardiography in clinical settings compared with coronary flow reserve.
Gudmundsson P, Borgquist R, Winter R, **Shahgaldi K**, Kitlinski K, Willenheimer R.
EuroEcho, Florence 2005.

IV. Flow-volume loops from three-dimensional echocardiograph; A novel technique for assessment of left ventricular function and hemodynamics.
Shahgaldi K, Söderqvist E, Gudmundsson P, Winter R, Nowak J, Brodin LÅ.
ACC, Atlanta 2006.

V. Flow-volume loops from three-dimensional echocardiography; A novel technique for assessment of left ventricular function and hemodynamics.
Shahgaldi K, Söderqvist E, Gudmundsson P, Winter R, Nowak J, Brodin LÅ.
EuroEcho, Prague 2006.

VI. Quantitative detection of myocardial ischemia by stress echocardiography. A comparison with SPECT.
Gudmundsson P, **Shahgaldi K**, Winter R, Dencker M, Kitlinski M, Thorsson O, Ljunggren L, Willenheimer R.
EuroEcho, Lisbon 2007.

VII. Parametric quantification of myocardial ischemia using real-time perfusion adenosine stress echocardiography images.
Gudmundsson P, **Shahgaldi K**, Winter R, Dencker M, Kitlinski M, Thorsson O, Ljunggren L, Willenheimer R.
EuroEcho, Lisbon 2007.

VIII. Color coded Tissue Doppler is more accurate and less sensitive to filtering and gain settings compared to spectral tissue Doppler – A comparison of two commonly used tissue Doppler techniques in the clinical setting.
Manouras A, **Shahgaldi K**, Winter R, Nowak J, Brodin LÅ.
EuroEcho, Lisbon 2007.

IX. Analysis of temporal requirements of speckle tracking myocardial assessment. Comparison with color- spectral- tissue Doppler and M-mode.
Manouras A, **Shahgaldi K**, Winter R, Nowak J, Brodin LÅ.
EuroEcho, Lyon 2008.

X. Echocardiographic findings in senior endurance athletes with exercise-induced biomarker release.
Sahlén A, **Shahgaldi K**, Winter R, Ståhlberg M, Linde C, Braunschweig F.
EuroPRevent, Stockholm 2009.

XI. Feasibility and accuracy of 3D echocardiography for measurements of the right ventricular volumes and function.
Ostenfeld E, **Shahgaldi K**, Carlsson M, Holm J.
EuroEcho, Madrid 2009.

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ABBREVIATIONS

2D	Two-dimensional
3D	Three-dimensional
2ch	Apical two-chamber view
3ch	Apical three-chamber view
4ch	Apical four-chamber view
AF	Atrial fibrillation
AS	Aortic stenosis
BP	Biplane
BPS	Biplane Simpson
CI	Confidence interval
EF	Ejection fraction
4B	Four-beat
LA	Left atrium
LV	Left ventricular
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVOT	Left ventricular outflow tract
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MS	Mitral stenosis
RA	Right atrium
RV	Right ventricular
SB	Single-beat

SD	Standard deviation
SEE	Standard error of estimate
SR	Sinus rhythm
SV	Stroke volume
TP	Tri-plane
VTI	Velocity time integral

1 INTRODUCTION

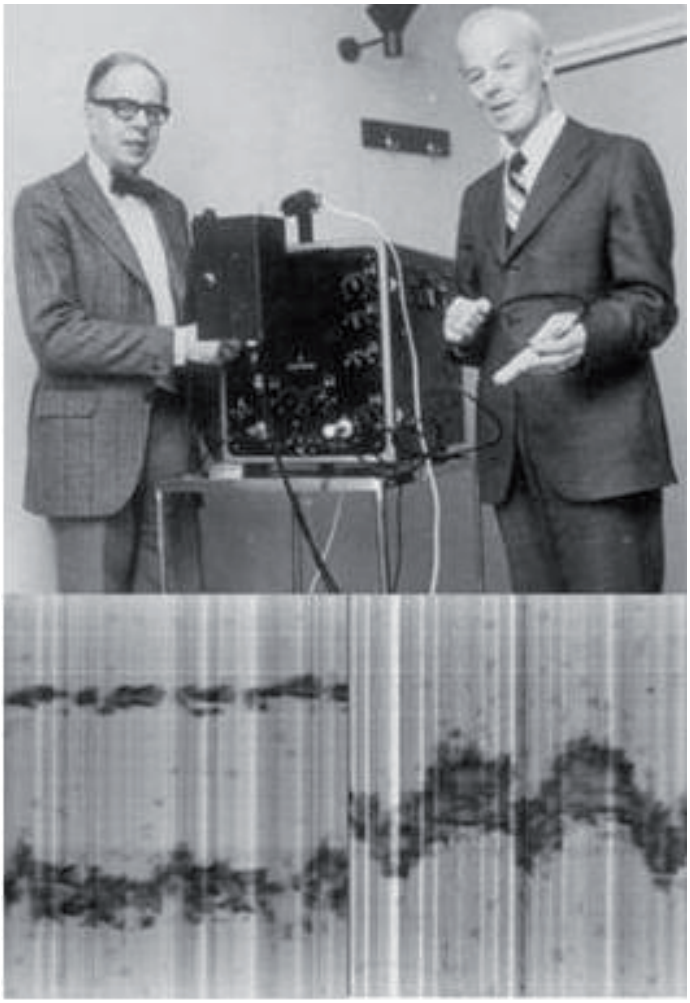

Figure 1.1 Helmuth Hertz (*left*) and Inge Edler (*right*) registering the very first recording of the ultrasound echo of the heart

In 1953, the first ultrasound cardiac examination (echocardiography) in the world was performed in Lund. The pioneers of echocardiography were Professors Inge Edler, cardiologist, and Helmuth Hertz, physicist. They borrowed equipment from the ship-building industry, where ultrasound was used to test construction materials. It soon became apparent that ultrasound could be used for the diagnosis of heart diseases. Cardiac functions and dimensions could be assessed using M-mode (motion-mode, see page 3) and 2D images. In the 1960s the Doppler echocardiography was developed in Lund, utilizing the Doppler frequency shift of measuring the velocity and direction of the blood flow. Doppler echocardiography is an important cornerstone in the non-invasive evaluation of cardiac valves, intra-cardiac pressures and hemodynamics. Today, echocardiography is the most valuable medical imaging technique for the non-invasive assessment of cardiac function and morphology. Indeed, echocardiography is used as the primary imaging tool in the vast majority of cardiac patients, where the need for further investigation with other image modalities is limited. In fact, magnetic resonance imaging (MRI) and computer tomography might provide additive information only in a small number of cases.

1.1 Echocardiography Principles

Ultrasound is high-frequency sound produced when a piezoelectric crystal, built up in a transducer, is electrically stimulated. The sound waves are too high in frequency to be audible

(>20 kHz). They are harmless within the range of clinically used frequencies and intensities. The passage of sound waves depends on the acoustic impedance of body tissues. Sound is directed into the body and is reflected by interfaces between tissues of different acoustic impedance such as myocardium, valves and blood. Blood reflects little sound so it appears relatively black compared with the myocardium which reflects more of the ultrasound signal and therefore appears relatively white. The pericardium and valves are the most echogenic cardiac structures. Ultrasound does not pass through air or bone. Because the heart is surrounded by lung over the majority of its surface and is contained within the bony cage of the thoracic cavity, the ultrasound beam must be aimed through gaps (*acoustic windows*), in order to produce images of the heart.

The majority of the ultrasound waves pass through structures on to other structures lying further from the surface. Reflected sound returns to strike the crystal, deforming it and producing electric signals the amplitude of which corresponds to the degree of deformation. The acquired electrical information is further processed in the ultrasound machine and subsequently displayed in the monitor of the employed instrumentation.

Frequencies of 2-10 MHz are used in diagnostic cardiac ultrasound. The lower the frequency used the deeper the penetration of the emitted sound in the tissue. A disadvantage when employing low frequency transducers is that there is a loss of image detail because the increased wavelength results in reduced resolution.

M-mode was the first clinical application of ultrasound. It provides a one-dimensional moving image of the heart on the vertical axel of a display. M-mode indicate structures in the heart, such as the valves, chambers and walls during systole and diastole versus time. (Figure 1.2)

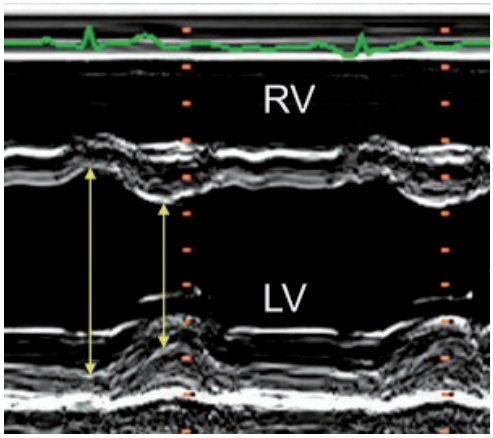

Figure 1.2 M-mode of left- and right ventricular motion in long-axis view. The arrows present the left ventricular end-diastolic dimension (*left*) and left ventricular end-systolic dimension (*right*).

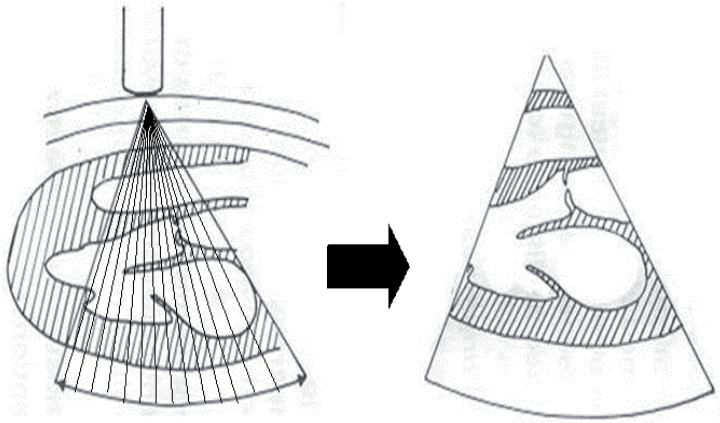

Figure 1.3 The 2D image is constructed by the reflections of the ultrasound beam sweeping within the sector.

2D echocardiography uses the principle of ultrasound reflection to produce images of the heart. 2D echocardiography images are obtained by the ultrasound beam sweeping along the sector, from one side to the other side (Figure 1.3). By adjusting the timing of the individual crystals in a phased-array transducer, the beam can be focused. Beam steering is a fundamental feature of how 2D images are created. The reflection points for each beam are seen in the ultrasound monitor and these points together create the 2D image. 2D echocardiography is capable of displaying slices of the heart, including chambers, atria and valves. Echocardiography has become more popular since the advent of 2D echocardiography, which produces an image of cardiac structure in an anatomical context of a 2D image.

When a source generating waves moves relative to an observer, or when an observer moves relative to a source, there is an apparent shift in frequency. If the distance between the observer and the source is increasing, the frequency apparently decreases, whereas the frequency increases if the distance between the observer and the source is decreasing. This relationship is called Doppler Effect or Doppler Shift which was first described by the Austrian physicist Christian Doppler. (Figure 1.4**)**

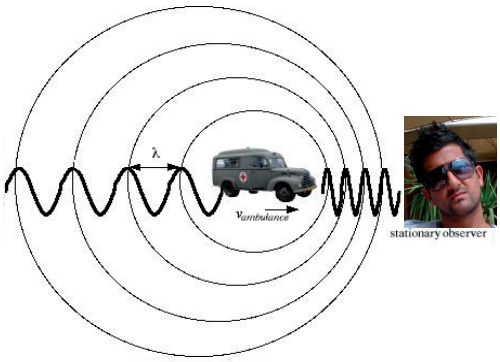

Figure 1.4 The Doppler Effect. When the sound of the siren is moved towards a stationary observer, the sound waves are compressed (shortened wavelength). Conversely, as the siren moves away, the sound wave is extended.

Doppler echocardiography is a method for detecting the direction and velocity of blood. The technique is mainly used in echocardiography for the assessment of cardiac valvular function (insufficiency or stenosis). The Doppler Effect is used to measure the blood velocity and direction (Figure 1.5).

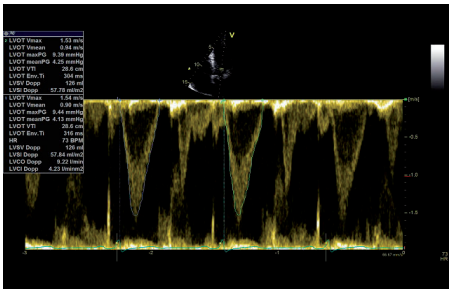

Figure 1.5 Pulsed-wave Doppler recordings performed approximately one cm below the aortic valve.

1.2 The Technology and Principles of Three-dimensional Echocardiography

The heart has a complicated anatomy and is in constant movement. Conventional echocardiography can only provide limited information about the spatial and temporal relationship of cardiac structures during the cardiac cycle. Furthermore, 2D echocardiography requires a difficult processing by the operator to reconstruct an image of the heart based on the interpretation of multiple tomographic slices.

Real-time 3D echocardiography uses a matrix array transducer which consists of 3000-4000 simultaneously active ultrasound crystals [1]. While the transducer is maintained in a fixed orientation, the ultrasonic beam scan steer automatically in multiple directions. The multidirectional ray steering capability enables simultaneous visualization of two or three views of the heart using split screen technology (Figure 1.6). Similar to a linear array, the direction in which the matrix array transmits and receives ultrasound energy is controlled by timing individual transducer elements during transmission and reception of the ultrasound waves. Parallel processing simply refers to doing more than one thing at a time. Following this analogy, the volumetric scanning device uses multiple receive lines for any given transmitted line to create the 3D volume.

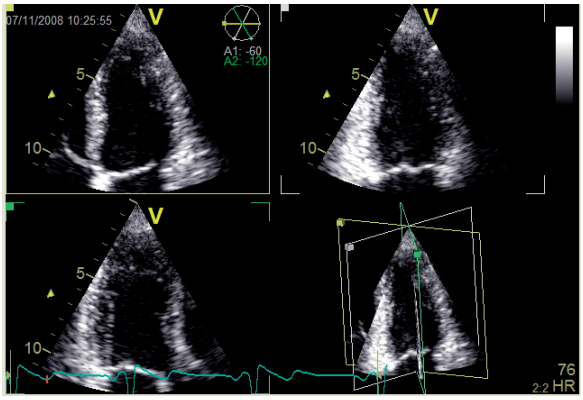

Figure 1.6 Real-time tri-plane echocardiography: 4 – 2 - and 3 chamber views are simultaneously displayed with 4-chamber as the reference view *(top left)*. Interplane angles are set at 60 degrees but can easily be steered to any desired angle on their 3D representation (*bottom right*).

3D echocardiography requires the gathering of volumetric data [2]. In real-time mode, a pyramidal volume of data of approximately 60 x 60° is obtained. In order to acquire larger volume data (90 x 90°) the gathering of sub-volumes of several consecutive cardiac cycles is required. A process commonly referred as "***full volume***" (Figure 1.7). Employing the full volume method it is possible in order to obtain complete imaging of the heart within the data set. The time resolution of such a data set is relatively low ranging from approximately 40-50 ms which corresponds to frame rate of 20-25 volumes/s. Data acquisition using 3D has been shown to be less time consuming [3] compared to 2D echocardiography with the mean time required being roughly 1 ½ minutes after completing the learning curve [4]. A major disadvantage of ECG-gated 3D image acquisition technique is the occurrence of "stitch artifacts" due to irregular

heartbeats, or movement of the patient or transducer during acquisition. Recent technological developments have provided the capability of capturing the entire heart in one cardiac cycle, single-beat (SB). This approach may reduce artifacts and further improve the speed of acquisition. SB 3D echocardiography is a novel imaging concept, which holds promise as a "break-through" technology for 3D echocardiography.

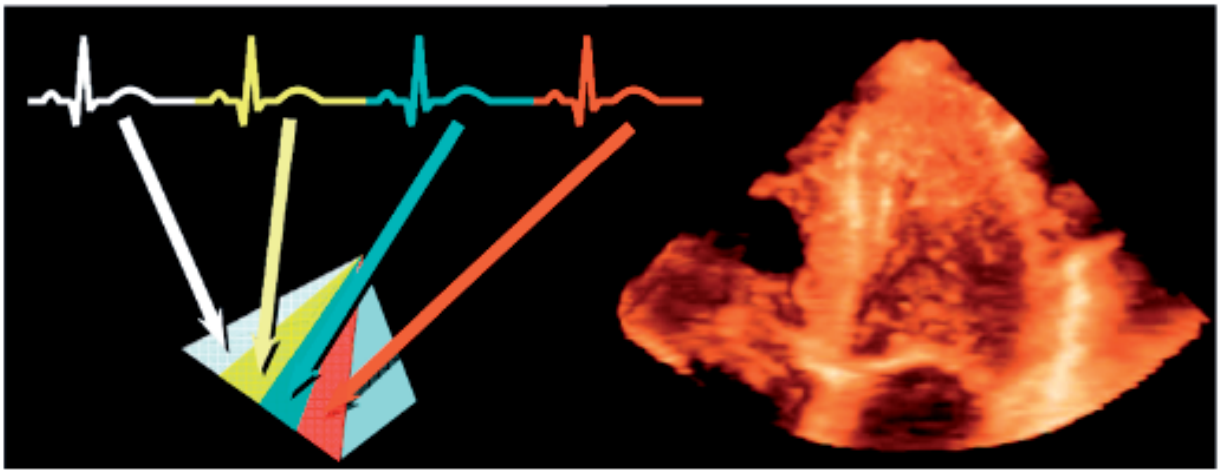

Figure 1.7 A full volume ECG-gated acquisition gathered over 4 cardiac cycles. Reprinted with permission [5].

1.3 Current Limitations of Three-dimensional Echocardiography

Despite the potential of 3D echocardiography to visualize cardiac structures and perform volume calculations this technique has not gained widespread acceptance. This may be related to a number of factors:

- Image quality is both patient and user dependent.
- Image manipulation (cropping) is required to find and display the region of interest.
- Low temporal (20 – 30 frames/sec) and spatial resolution.
- The limited scan size.
- Stitching artifacts, lines that appear during full volume acquisition due to irregular heart beat or inability to hold breath. [6].

2 ASSESSMENT OF CARDIAC FUNCTION AND HEMODYNAMICS

2.1 Cardiac Image Acquisition using Echocardiography

Echocardiography is performed with the patient in the left lateral position. At least three sinus beats of each view should be recorded during quiet respiration or at end expiration. Echocardiography is a common used modality in the clinical practice for determination of cardiac function, valves morphology and hemodynamics. The standardized and commonly used scan planes in echocardiography are the parasternal long- and short-axis view, the apical four-chamber view (4ch), the apical two-chamber view (2ch), the apical three-chamber view (3ch), and the subcostal view (Figure 2.1**)**.

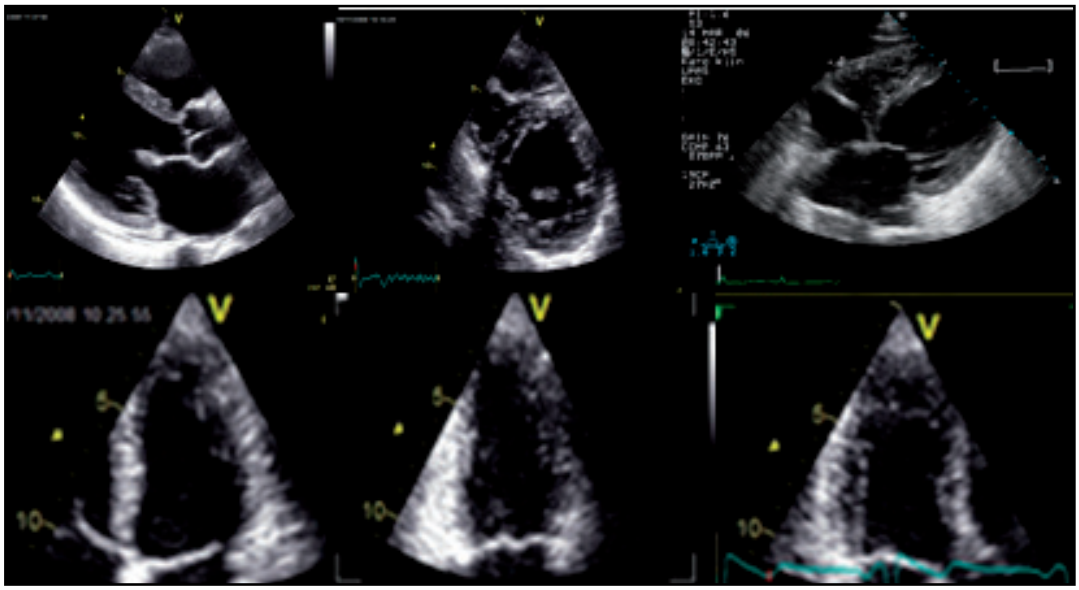

Figure 2.1 Echocardiographic views. From top left: parasternal long-axis view, parasternal short-axis view at the mid level, subcostal view, apical four-chamber view, apical two-chamber view and apical three-chamber view.

Parasternal projection is obtained with the transducer in the third or fourth intercostal space immediately to the left of the sternum. The transducer is angled so that aortic valve, mitral valve and LV are in their long-axis (Figure 2.1 *top left*). The parasternal short-axis view at the papillary level is obtained by angling the probe 90° with respect to the parasternal long-axis of the LV (Figure 2.1 *top middle*). This view among others provides information about the LV in short-axis for determination of radial contraction. The subcostal view is obtained with the transducer moved to a subxyphoid position and directed superiorly and leftward (Figure 2.1 *top right*).

The apical views (figure 2.1 *lower* panel) are gathered by placing the ultrasound transducer apically and rotating the transducer 60° between each plane (Figure 2.2 C).

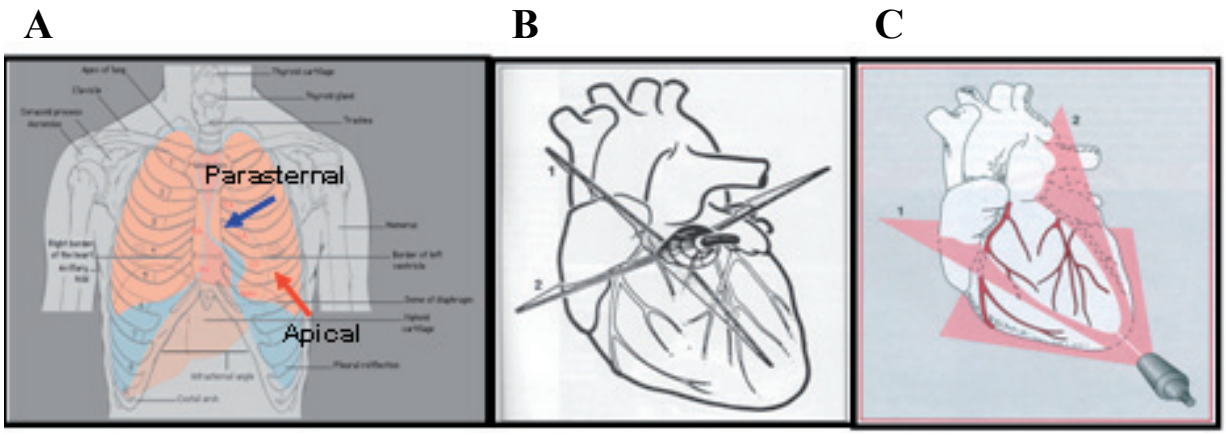

Figure 2.2 (**A**) The position of the transducer to obtain the parasternal and apical views. (**B**) In the parasternal long-axis window the transducer is placed next to the sternum (**1**) and then rotated 90° to obtain the short-axis view (**2**). (**C**) Apical views are achieved by placing the transducer apically and rotating the transducer 60° to obtain the each plane. Reprinted with permission [7]

2.2 The Role of Echocardiography

Measurements of cardiac chamber size, ventricular mass and LV function are the most clinically important and most commonly requested tasks of echocardiography and are important clinical variables with respect to diagnosis, management, and prognosis in patients with cardiac disease [8-10]. Heart chamber volumes provide information of diagnostic and prognostic [11-14]. Echocardiography has become the leading cardiac imaging technique, which due to its portability and flexibility is now used in emergency rooms, operating rooms, and intensive care units. Echocardiography is associated with an extremely low rate of dangerous events and is relatively low-cost. Imaging modalities, like X-ray, scintigraphy or cardiac MRI can sometimes provide better image quality, but the techniques are not nearly as mobile.

At present, the mainstay of echocardiography is 2D imaging. The limitations of 2D echocardiography, especially from the standpoint of LV quantification, are that many of the formulas for calculation of LVEF and volumes are based on assumptions that do not necessarily hold true in the setting of dilated, failing ventricles that become more spherical as the disease process progresses. In addition, one reason that interobserver variability exists in 2D echocardiography interpretations is that individuals interpolate data between 2D images in different ways. After myocardial infarction (MI), increased ventricular volumes have been shown to be associated with increased mortality, poor cardiovascular events, and a poorer prognosis [15]. Accurate assessment of LV volumes adds incremental value to risk assessment and guides further therapy. However, conventional quantitative volumetric measurements by 2D

echocardiography are subject to errors of geometric assumptions that may be more significant after MI, where there are regional wall-motion abnormalities subject to regional remodeling [16, 17]**.** 2D echocardiography has become a routine examination for LV volumes and function assessment but the assumptions about LV geometry remain a limitation. The interpretation of echocardiographic images requires a complex mental integration of multiple image planes for a true understanding of anatomic and pathologic structures. In the past decade, 3D echocardiography has emerged as a more accurate and reproducible approach for LV quantification mainly by avoiding the use of geometric assumptions of the LV shapes [18-20]. The presentation of images in a 3D format more closely resembles reality and could therefore enhance image interpretation. Real-time 3D echocardiography is under rapid expansion both clinically and for research purposes. Several studies have documented the high accuracy of 3D echocardiography in the evaluation of LV volumes and function expressed as EF [21-24] when compared to 2D echocardiography. There are reports about good reproducibility and accuracy of 3D echocardiography for the assessment of LV volumes in broad patient groups, using MRI as reference method [20, 24].

Left atrium (LA) size is a marker of diastolic function and an increase in LA dimension is associated with cardiovascular disease and is a risk factor for atrial fibrillation (AF), stroke and death [11]. Therefore, accurate volume measurement is of great importance, and it can be measured precisely with 3D echocardiography, using MRI as the gold standard [25-29].

In one study, 3D echocardiography showed good accuracy and reproducibility, and also a good correlation with MRI for the evaluation of right atrium (RA) [25].

The assessment of right ventricular (RV) function and dimension is of clinical importance in many cardiac diseases [30-34]. The evaluation of RV by echocardiography is challenging because of its geometry. These limitations have hampered routine clinical assessment of RV function. Because visual assessment of RV function is suboptimal due to subjectivity, quantification of RV has been attempted using a variety of echocardiographic techniques, including 2D imaging, tissue Doppler and strain. 2D echocardiography tends to be inadequate in measuring RV volumes and function due to its anatomy. Many methods have been suggested in the literature to overcome this problem, none are fully reliable [35*,* 36]. 3D echocardiography may overcome these limitations because it does not require standardized image acquisition and reconstructs the entire RV from multiple 2D images without geometric assumptions. 3D echocardiography has been shown to fulfill this potential in vitro [37, 38] and in vivo [39] but there are still few patient data available [40-45].

2.3 Flow-Volume Loops

The most reliable method for the evaluation of LV contractility is the simultaneous, real-time measurement of LV pressure and volume and the analysis of thus created pressure-volume loop diagrams [46]. However, the procedure has the disadvantage of being invasive and is therefore rarely used in clinical practice. Another, non-invasive way to measure LV contractility has been proposed and involves analysis of the relationship between sphygmomanometrically measured systolic blood pressure (substitute of LV end-systolic pressure) and the echocardiographically derived LV end-systolic volume (ESV) index at rest and during exercise [47]. A new non-invasive approach in the assessment of LV function based on the analysis of LV flow-volume relationship in time domain, using estimates of LV volume and flow derived from echocardiographic variables, has been described [48]. The concept of cardiac flow-volume measurement originates from the flow-volume analysis that has been, for a long time generally applied as a clinical measure of lung function and differentiation between obstructive and restrictive disorder. Similarly, the LV flow-volume relationship throughout the cardiac cycle presented as a flow-volume loop can be expected to show different characteristic patterns in different specific hemodynamic situations and to provide thereby useful diagnostic information and therapeutic guidance. The normal systolic flow-volume relationship may be disturbed by aortic stenosis (AS) while the diastolic flow-volume relationship may be affected by mitral stenosis (MS). 3D echocardiography provides the possibility of a direct measurement of LV volumes and the first derivative of LV volume would describe blood flow in and out of the LV. Therefore, by using volume and flow data extracted from the 3D data set acquired throughout the cardiac cycle, LV flow-volume loops can be constructed (Figure 2.3).

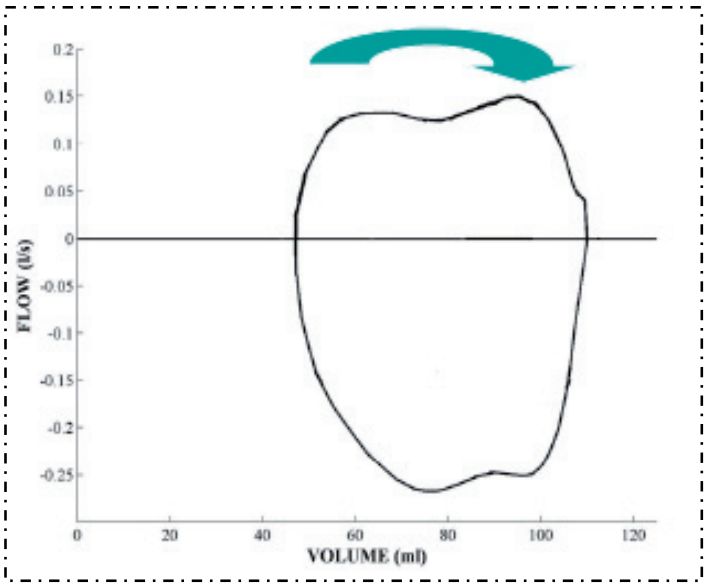

Figure 2.3 Illustration of flow-volume loop in a normal heart where diastole is seen in the upper part of the loop and systole in the lower part. Reprinted with permission [49]

2.4 Left Ventricular Ejection Fraction

The most common echocardiographic method for estimation of cardiac function is the measurement of LVEF, which is the fraction of blood pumped out of a ventricle with each heartbeat. By definition, the volume of blood within a ventricle immediately before a contraction is known as end-diastolic volume (EDV). Similarly, the volume of blood left in the ventricle at the end of the contraction is ESV. The difference between EDV and ESV is the stroke volume (SV), the volume of blood ejected with each beat. EF is the fraction of the EDV that is ejected with each beat, which is SV divided by EDV:

$$\mathbf{EF}\ (\%) = \frac{\boldsymbol{EDV - ESV}}{\boldsymbol{EDV}} = \frac{\mathbf{SV}}{\boldsymbol{EDV}}$$

LVEF is frequently visually estimated; however the LVEF may have significant interobserver variability and is a function of interpreter skill. Therefore, EF should regularly be compared to quantitative measurements using the most common 2D measurement for volume calculation, the biplane method of discs (modified Simpson´s rule). The EDV and ESV are manually traced in four- and two chamber view and the above mentioned formula is used for calculating of EF [50]. LVEF and LV volumes have prognostic value in patients with heart failure [51] and are strong predictors of patient survival after MI, and these data are incremental to LVEF [15]. LVEF measured by echocardiography shows to agree with other image modalities [15, 52].

The accurate estimation of LV systolic function expressed as EF is important for therapeutic decision making in heart failure [53]. EF can be assessed using a selection of modalities including contrast ventriculography [54], MRI [55] and echocardiography [56]. 2D echocardiography has a number of well-known limitations, the two most important perhaps being LV foreshortening and that different projection are not possible to obtain during the same cardiac cycle. The latter is particularly important in patients with variable heart rhythm (i.e. atrial fibrillation). Both these limitations can be overcome using a 3D-array transducer for acquiring the apical four-two-and three chamber views simultaneously in the tri-plane (TP) mode. Quantitative 2D-EF using biplane Simpsons (BPS) rule can be somewhat time-consuming, and the endocardial border tracing is sometimes difficult to perform, especially in patients with poor image quality, since it is performed on still frames. In clinical practice “eyeballing” for the evaluation of LVEF can be done faster and is often easier to perform, especially in patients with poor image quality. Previous studies have demonstrated the value of eyeballing EF [57-61] and one study revealed a good correlation with quantitative 2D echocardiography measurements [57]. However, the studies comparing to radionuclide methods were performed before the introduction of second harmonics and although eyeballing EF measurement has proven to be robust when performed carefully, it is still considered highly subjective and is questioned in both clinical and research settings.

2.5 Left Ventricular Stroke Volume

LVSV is the difference between EDV and ESV. EDV is the filled volume of the ventricle prior to contraction and ESV is the residual volume of blood remaining in the ventricle after ejection. In a typical heart, EDV is about 120 ml of blood and the ESV about 50 ml of blood. The difference in these two volumes, 70 ml, represents the SV. Therefore, any factor that alters either the EDV or the ESV will change SV.

Changes in preload affect SV through the Frank-Starling mechanism. An increase in venous return to the heart increases the filled volume (EDV) of the ventricle, which stretches the muscle fibres thereby increasing their preload. This leads to an increase in the force of ventricular contraction and enables the heart to eject the additional blood that was returned to it. Therefore, an increase in EDV results in an increase in SV (Figure 2.4). On the contrary, a decrease in venous return and EDV leads to a decrease in SV by this mechanism [62].

Afterload is related to the pressure that the ventricle must generate in order to eject blood into the aorta. Changes in afterload affect the ability of the ventricle to eject blood and thereby alter ESV and SV. For example, an increase in afterload (i.e., increased aortic pressure) decreases SV, and causes ESV to increase (Figure 2.4). Conversely, a decrease in afterload increases SV and decreases ESV [63].

Changes in ventricular inotropy (contractility) alter the rate of ventricular pressure development, and thereby affect the rate of ejection. An increase in inotropy will reduce ESV and increase SV. The increased SV causes a secondary reduction in EDV and pressure because there is less ESV to be added to the incoming venous return [64].

$$\uparrow Preload \rightarrow \uparrow SV \rightarrow \uparrow (EDV)$$
$$\uparrow Afterload \rightarrow \downarrow SV \rightarrow \uparrow (ESV)$$
$$\uparrow Inotropy \rightarrow \uparrow SV \rightarrow \downarrow (ESV)$$

Figure 2.4 Changes in stroke volume depending on preload, afterload and inotropy.

The accurate measurement of LVSV is important for hemodynamic assessment, especially in critical care monitoring. In addition to the assessment of cardiac function, measurements of SV can also be valuable for evaluation of intracardiac shunts and valvular heart disease. 3D echocardiography can be used to evaluate chamber volumes to calculate SV by difference between EDV and ESV. Full volume measurements performed by 3D echocardiography are well validated for assessment of SV [65-68].

The most commonly used methods for SV assessment using 2D echocardiography is BPS and left ventricular outflow tract (LVOT)-velocity time integral (VTI) multiplied by the calculated 2D-area of LVOT. Occasional difficulties in defining LV endocardial borders as well as variations in LV geometry may jeopardize SV calculations with BPS method [69, 70]. SV measurements using the LVOT-diameter have a major limitation due to the LVOT-diameter being squared in order to determine SV and thus small errors in measuring LVOT area are amplified. Factors contributing to errors with these methods also include image quality, annular calcification, failure to measure true diameter and the presence of septal hypertrophy. Despite these difficulties both these methods are widely used for SV measurements.
The 3D modality enables simultaneous visualization of two views of the heart using split screen technology and seems to be useful for visualization of the LVOT in biplane (BP) mode, where a simultaneous visualization of the LVOT in long- and short-axis is allowed.

2.6 Variability of Measuring LV Volumes and Ejection Fraction in Atrial Fibrillation

Assessment of LV volumes and EF during AF has conventionally proved difficult because of beat-to-beat variation [71-74]. Due to the variability, the standard protocol for obtaining an accurate assessment of LV function during AF involves averaging an arbitrary number of consecutive cardiac cycles. The result is usually unreliable because the averaged value is dependent on a selected window of cardiac cycles and the mean number of cardiac cycles required in AF is approximately 3 times that required in sinus rhythm (SR), usually 3 to 5 beats [75]. It is time-consuming and not realistic in the clinical scenario to analyze more than 10 beats for the evaluation of LV performance. It is well known that LV systolic function during AF varies depending on the preceding cardiac cycle length [76, 77]. In clinical practice in AF patients, LVEF is commonly measured from a single beat either using a visual assessment for targeting a specific heart beat having a visually assessed representative EF, or looking for an average R-R interval for the representative heart beat to measure from. Thus in AF patients particularly, 3D echocardiography becomes impractical for these reasons. However, the new 3D technique, SB modality could have an advantage over the multi-beat technique since it is possible to choose a representitative heart beat similarly to 2D echocardiography, and furthermore due to the associated lack of stitching artifact.
The BP assessment of LV volume and EF during AF using traditional 2D echocardiography is difficult and inaccurate because cardiac cycles vary with the planes imaged. In AF, beat-to-beat variations in LV performance are caused by variability not only in ventricular loading but also in contractility [76-79]. The longer preceding cycle length allows more LV filling and evokes greater use of the Frank-Starling mechanism. As a result, there is a positive relation between the preceding cycle length and SV [80].

3 AIMS

The aims of the present thesis were as follows:

I. To study whether apical views are preferable to parasternal or subcostal views regarding the assessment of cardiac volumes using three-dimensional echocardiography.

II. To explore the feasibility of the non-invasive evaluation of left ventricular flow-volume dynamics using three-dimensional echocardiography, and to assess the diagnostic potential of such flow-volume loops in two different types of hemodynamic pathologies, the obstructive disorder due to aortic stenosis and the restrictive state resulting from mitral stenosis.

III. To investigate the correlation and variability of visually estimated ejection fraction by two-dimensional echocardiography and tri-plane echocardiography in comparison to quantitative three-dimensional echocardiographic ejection fraction measurements.

IV. To explore whether left ventricular stroke volume assessment using direct planimetric measurement of the left ventricular outflow tract cross-sectional area is superior to conventional methods for stroke volume calculation.

V. To study whether single-beat full volume three-dimensional echocardiography data reduces inter- and intraobserver variability in measurements of left ventricular volume and ejection fraction in comparison to four-beat ECG-gated full volume three-dimensional echocardiography acquisition in patients with atrial fibrillation.

4 METHOD AND MATERIALS

4.1 Study Population

All study populations in this thesis conform to standards laid out in the declaration of Helsinki, and all the studies were approved by the local ethics committee.

All patients in Study I and, Studies III-V were unselected patients. Two patients in Study IV were excluded due to significant valve insufficiency and eight patients in Study V were excluded due to a poor acoustic window or because endocardial border visualization was difficult. Thirty-one patients in Study II were patients referred to the Department of Cardiology, Malmö University Hospital for echocardiographic evaluation of MS and AS and ten subjects were healthy volunteers without any medical treatment for any cardiovascular disease. A simplified patient characteristic is presented in Table 4.1. A more detailed patient characteristic appears in each paper.

Table 4.1 Characteristics of patients in Studies I-V.

	Study I *(n=40)*	**Study II** *(n= 41)*	**Study III** *(n=30)*	**Study IV** *(n=28)*	**Study V** *(n=70)*
Age (years)	57±14	72±12	39±12	39±12	57±17
Female/male	10/30	20/21	7/23	6/22	20/50
Number of healthy subjects	0	10	0	0	0

4.2 Echocardiography Equipment

All subjects were examined in the left lateral position by the same experienced echocardiographer.

In **Studies I and II** the echocardiography equipment used was a Sonos 7500 (Philips, Andover, Mass., U.S.A) with an x4 transducer for the 3D recordings and an s3 transducer for the 2D acquisitions. In Study I the commercially available software Tometec 4D Echo-View 5.2© (Unterschlessheim, Germany) was used for off-line analysis of the 3D data and EnConcert Image Diagnosis Application version b.2.1 (Imaging Systems Division, Andover, MA, USA) for the analysis of the 2D recordings. In Study II Tomtec software 4D LV-Analysis CRT 1.0 (Unterschlessheim, Germany) was employed.

In **Studies III** and **IV** Vivid 7 Dimension ultrasound equipment, (GE Vingmed Ultrasound, Horten, Norway) was used with an standard 2D transducer (M4S) for the conventional 2D recordings and a 3D matrix-array transducer (3V) for the 3D acquisitions. The saved 2D and 3D images were transferred for off-line analysis using the commercially available software (EchoPAC, GE Vingmed Ultrasound, Version 108.1.4) and the available semi-automated tool, 4D auto LV volume quantification.

In **Study V** Vivid E9 (GE Healthcare, Horten, Norway) with a novel 3V matrix-array transducer was used and the images were analyzed using a commercially available semi-automated analysis tool, 4D auto LV volume quantification (4DLVQ, EchoPAC PC version 108.1.4, GE Healthcare).

4.3 Image Acquisition

In **Study I** 3D echocardiography recordings were made in apical, parasternal and subcostal views. Images were gathered over four cardiac cycles during breath-hold. Full volume and harmonic imaging was used, depth and focus position was adjusted to obtain best image quality. 2D images of four-, two- and three chamber, as well as parasternal long-axis and subcostal views, were acquired. All patients underwent more than one recording of the respective cardiac chambers to increase the chances of good quality.

In **Study II** 3D images of LV were acquired over four consecutive cardiac cycles during breath-hold from the apical window. The sample frequency of 3D data was 15-24 volumes/sec.

In **Study III** apical four- and two-chamber views were acquired with conventional 2D recordings. TP imaging was performed immediately following 2D echocardiography. Using this modality, once the primary image plane is optimized, secondary image planes can be automatically obtained and displayed in a quad-screen view. In this study, an apical four-chamber view was chosen as the primary image plane. The matrix transducer then allowed the visualization of 4ch, 2ch, and 3ch views simultaneously. The interplane sector angle was established by default at 60°, but it could be electronically steered to any desired angle in order to obtain adequate orientation of the three apical views. A full volume acquisition for EF evaluation was performed and served as reference method.

In **Study IV** a complete 2D echocardiography and Doppler study was performed. $LVOT_{VTI}$ from an apical five-chamber view was registered by placing the sample volume (3mm) of a pulsed wave-Doppler at the base of the aortic leaflets, and then moving slowly away towards the LVOT until a typical subvalvular flow profile was (approximately 1 cm below the aortic valve) obtained. A full volume recording of LV during four cardiac cycles was performed (used as reference method). The BP mode was used in this study, using the 3V transducer by manually placing the cursor in a parasternal long-axis view to display the LVOT both in long- and short-axis view simultaneously (Figure 4.1).

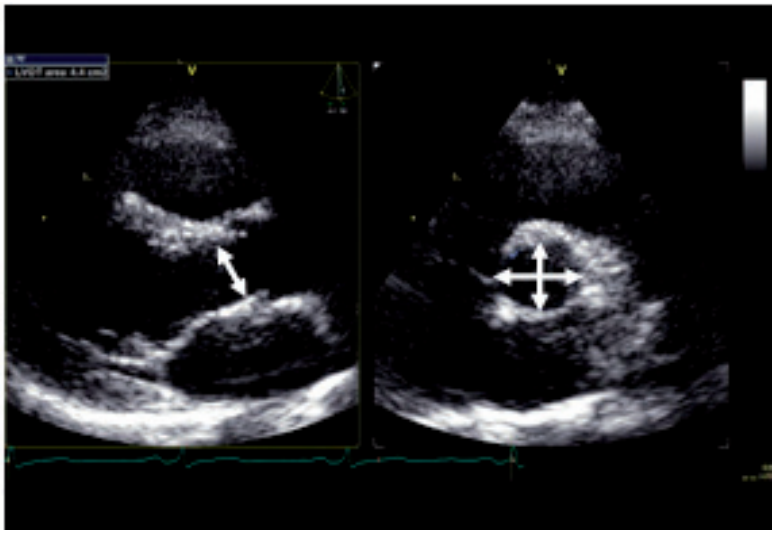

Figure 4.1 Simultaneous visualization of left ventricular outflow tract in parasternal long-axis (*left*) and in short-axis (*right*) using the biplane technique.

In **Study V** a full volume scan was acquired from four consecutive cycles and immediately after an SB three-dimensional echocardiography was performed. Recordings were carried out in patients with SR (Group A) as well as in patients with AF (Group B), Figure 4.2

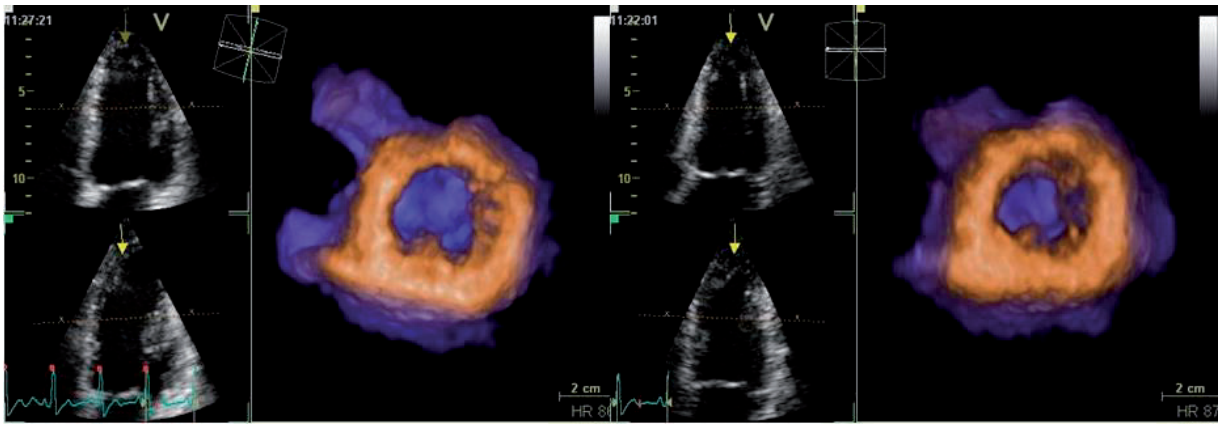

Figure 4.2 In the left panel a full volume scan using four-beat ECG-gated is illustrated whereas a SB acquisition is shown in the right panel.

4.4 Echocardiography Analysis

Study I. Single-plane Simpson´s rule was used for calculating LV volumes in end-diastole and end-systole, whereas ED was defined as the largest diameter and ES as the smallest. Atrial volumes were calculated using the single-plane Simpson´s rule in ES, immediately before the opening of the mitral valve. Atrial appendages, vena cava and pulmonary veins were excluded from the measurements. For 2D recordings RV dimensions were measured at ED in parasternal and apical 4ch view. 3D volumes were calculated using manual tracing of the endocardial border in 16 planes. End-diastole and end-systole were defined as with the 2D images. The volumes of all four chambers were calculated both in ED and ES. For a detailed methodological description, refer to Study II (Figure 4.3).

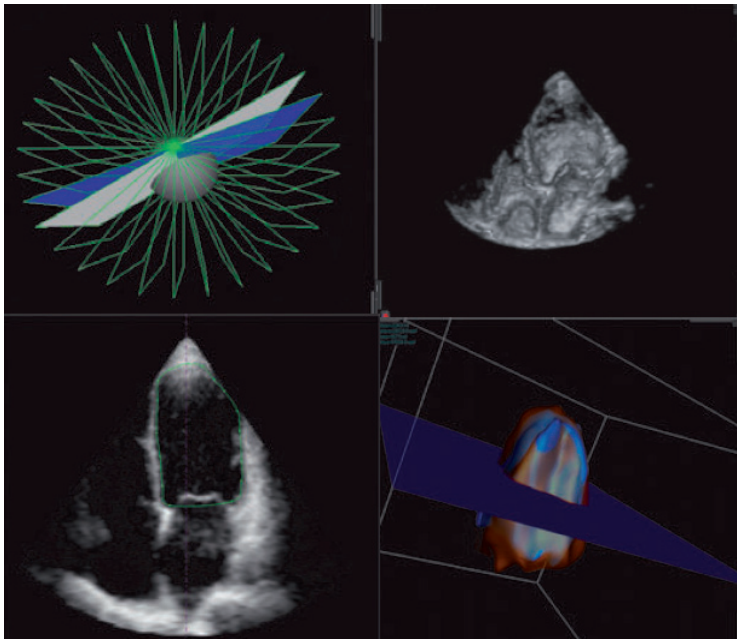

Figure 4.3 Left ventricular volume measurement in 16 planes (*top left*) using the Tomtec software 4D LV-Analysis CRT 1.0. A full volume image cropped in the middle is seen top right. Manual tracing of left ventricular is shown in the bottom left plane. The end-diastolic (brown) and end-systolic volume (blue) is demonstrated three-dimensionally (*bottom right*). Reprinted with permission [81]

Study II. The analysis of the 3D volumes started with the definition of long-axis plane in five-chamber view, whereupon 6 long axis image planes of LV were automatically generated. In each of the 6 image planes, the positions of mitral valve, aortic valve and apex were marked at ES and ED. The semi-automated border detection algorithm provided subsequently a delineation of LV endocardial border with a preconfigured ellipse that was manually adjusted so that the total endocardial border in all frames could be defined. The analysis program allowed a reconstruction of LV volumes in which LV wall motion was shown three-dimensionally. A graph showing LV volumes changes during each cardiac cycle was obtained. LVEDV and LVESV as well as LVEF were automatically provided by the software.

Construction of LV flow-volumes loops

Using the 3D data set, LV volumes were determined for each frame throughout the cardiac cycle and their respective first derivates were calculated using Matlab software (Version 6.5, TheMathWorks Inc. Natick, MA, USA). All volume variables were then adjusted for body surface area and plotted against its first derivate (describing LV flow), for each cardiac cycle, to create LV flow-volume loops. Subsequently, an average flow-volume loop for each examined patient group was constructed.

Study III. 2D-EF and TP-EF evaluations were performed using eyeballing by two experienced echocardiographers twice, with one week apart, and blinded to all clinical data and previous reading. The quantitative LVEF assessment of the 3D-EF was made by one reader twice, with one week apart, blinded to the first measurements. Analysis of the 3D-data started by placing a total of eighteen landmarks in ED and ES, two at basal marks of the mitral valve and one apical mark in four-, two- and three-chamber views respectively (Figure 4.4). The software automatically delineated the endocardial border in a 3D-model from ED and ES phases.

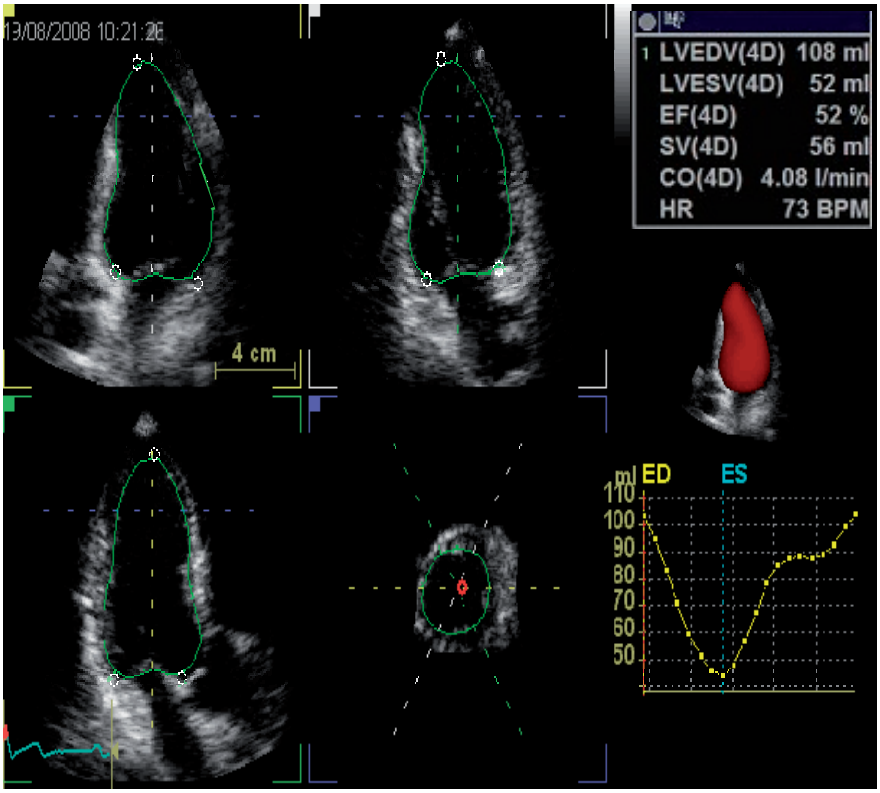

Figure 4.4 Three-dimensional echocardiography measurement of left ventricular volumes and EF using 4DLVQ, EchoPAC software. Manual input of apical and mitral annulus in all three long-axis views (*left panel*) is illustrated. Volume time plot and quantitative analysis panel is presented in the right panel.

Study IV. LVOT-diameter was measured in the parasternal long-axis at mid-systolic frame, according to trailing edge to leading edge below the aortic valve (1 cm). VTI of subvalvular flow was traced along the brightest part of the spectral display in three cardiac cycles and an average was made for SV calculation (SV_1). LVOT area was measured by manual contouring the area at mid-systole (Figure 4.5, *right image*) and the VTI of the subvalvular flow was traced as mentioned above (SV_2). LVOT-diameter was measured in BP-mode in the anterior-posterior and lateral directions. Four- and two-chamber images were analyzed using the BP Simpson rule for calculation of SV (SV_3). Analysis of the 3D-data was measured as in Study III and the calculated SV was served as a reference method (SV_{ref}).

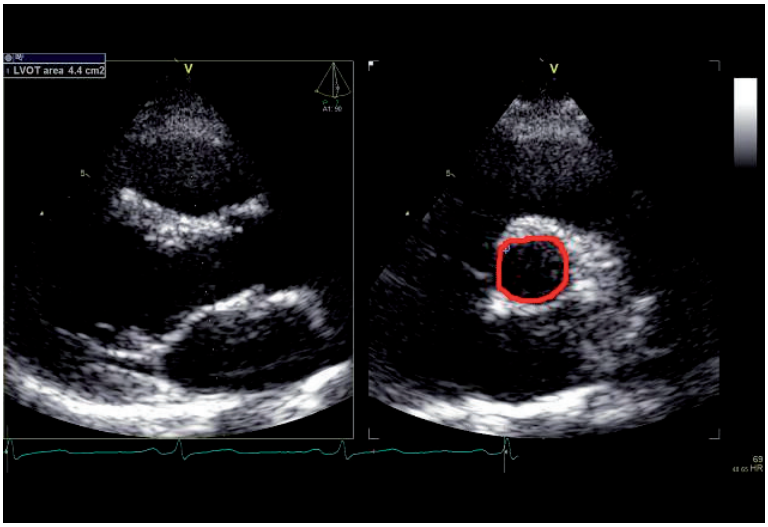

Figure 4.5 Manual tracing of the left ventricular outflow tract (*right*) in biplane mode.

Study V. The 3D-data from four-beat ECG-gated and SB 3D echocardiography were measured as described in Studies III and IV.

4.5 Statistical Analysis

Standard statistical software, (SPSS Version 16.0 and 12.0.1, Inc, Chicago, IL, USA) was used for the statistical analysis. A p-value < 0.05 was considered significant. All variables were tested for normality using the Kolmogorov-Smirnov test.

In **Study I**, descriptive analysis was used for visualization and time consumption. A student´s t-test was used for the degree of visualization. Measurements are expressed as mean ± SD and the student´s *t*-test was performed to detect significant differences between the mean values of two measurements. Linear regression analysis was used to compare 2D and 3D echocardiography

volumetric data and functional data of the LV and volumetric data of both atria. Pearson correlation and standard error of the estimate (SEE) were also calculated.

In **Study II**, a student´s *t*-test was used to compare if a mean value of two groups differed significantly.

In **Studies III** and **IV**, linear regression was performed for correlation analysis. Bland-Altman plots were used to illustrate agreement between different methods [82]. The difference between the methods was plotted against the mean of both methods for every set of measured values. The limits of agreement were marked as lines in the plot, specified as the average difference ± 1.96 SD of the difference. The observer variability was measured according to the following formula: (SD_{diff} x 100%)/total mean × √2 (Dahlberg´s formula), where SD_{diff} is the SD of the difference between measurements [83]. Group comparisons of continuous variables were made using analysis of variance (ANOVA). Student´s *t*-tests were used when suitable for comparisons of paired data.

In **Study V**, Bland-Altman analysis was performed to determine the systematic bias and limits of agreement of different variables between different methods. Different echocardiographic data were tested using paired t-tests. The observer variability was measured according to the following formula: (SD_{diff} x 100%)/total mean × √2, where SD_{diff} is the SD of difference between measurements.

5 RESULTS

Overviews of the results are presented in this chapter. All details are found in the papers attached.

5.1 Study I

In 85% of the population, the LV volumes were traceable in apical view by 3D echocardiography. Using the 4ch and 2ch view with 2D echocardiography, 100% and 92.5% was fully traceable, respectively. The LV volumes were only fully traceable in 7.5% of the population using parasternal view by 3D echocardiography. Using 2D echocardiography no patient could be traced in parasternal long-axis view regarding LV volumes. Neither could any patient be traced in the subcostal view by 3D echocardiography or by 2D echocardiography when measuring LV volumes.

One hundred percent (100%) of the patient population had traceable LA from the apical view with 3D echocardiography and 2D echocardiography in the 4ch view. In the 2ch view by 2D echocardiography, 92.5% had a traceable LA. In the parasternal view by 3D echocardiography, 55% of the LA was traceable in comparison to 30% by 2D echocardiography. In the subcostal view, only 5% of patients had a traceable LA with 3D echocardiography, compared to none with 2D echocardiography.

Seventy-eight percent (78%) of RA were traceable from the apical view with 3D echocardiography compared to 95% in 2D echocardiography 4ch view. In the parasternal and subcostal views one patient (2.5%) was traceable with 3D echocardiography in each projection. No patient could be fully traced in the parasternal and subcostal views with 2D echocardiography.

Thirty percent (30%) of RV was traceable in the 3D echocardiography apical view. No patient could be traced from the 3D echocardiography parasternal or subcostal view. High feasibility (97.5%) was detected with 2D echocardiography regarding the measurement of RV diameter in both parasternal and 4ch view. The measurement of the RV diameter was not managed in any patient from the subcostal view with 2D echocardiography. The possibility of tracing cardiac chambers in different views by 3D and 2D echocardiography is presented in Table 5.1.

Table 5.1 Feasibility of measuring heart chamber volumes with two- and three-dimensional echocardiography from different views.

	2DE			3DE		
Variable	**Parasternal**	**Apical**	**Subcostal**	**Parasternal**	**Apical**	**Subcostal**
LV volumes	-	100%	-	7.5%	85%	-
RV volumes	97.5%*	97.5%*	-	-	30%	-
LA volumes	30%	100%	-	55%	100%	5%
RA volumes	-	95%	-	2.5%	78%	2.5%

2DE, two-dimensional echocardiography; **3DE**, three-dimensional echocardiography; **LV**, left ventricular; **RV**, right ventricular: **LA**, left atrium; **RA**, right atrium. * Right ventricular diameter.

There was a significant difference in LVEDV by 2D echocardiography in 2ch view in comparison to apical 3D echocardiography (99 ± 52.8 ml vs. 117.8 ± 50.3 ml; $p<0.05$) and RA volume in 2D echocardiography in comparison to 3D echocardiography (41.5 ± 25 ml vs. 50.2 ± 23.5 ml; vs. $p<0.005$), Table 5.2. A good correlation was found between 2D echocardiography and apical 3D echocardiography regarding RA (r = 0.91, SEE 10 ml), LA (r = 0.91, SEE 12 ml), LVEDV (0.87, SEE 25 ml), LVESV (0.94, SEE 17 ml) and for LVEF (r = 0.94, SEE 5.4%) using 4ch view as the reference.

Table 5.2 Echocardiographic measurements using two- and three-dimensional echocardiography.

	LVEF (%)	**LVEDV (ml)**	**LVESV (ml)**	**LA (ml)**	**RA (ml)**
3DE	46.7±15.8	117.8±50.3	67.8±48.7	57.3±27.2	50.2±23.5
4ch	48.5±16.4	108.1±56.1	61.7±54.6	53.9±29.2	41.5±25**
2ch	47.9±14.9	99±52.8*	57±49.2	57±29.1	

3DE, apical three-dimensional echocardiography; **4ch**, four-chamber view; **2ch**, two-chamber view; **LVEF**, left ventricular ejection fraction; **LVEDV**, left ventricular end-diastolic volume **LVESV**, left ventricular end-systolic volume; **LA**, left atrium; **RA**, right atrium.*$p<0.05$ vs. 3D, **$p<0.005$ vs. 3D

5.2 Study II

Significant AS and MS were found in 74% of the patient population, whereas in the remaining 26% of the subjects no cardiac pathology was found. Patients with MS showed smaller LVEDV

than subjects without any valvular pathology ($p<0.05$), and also LVEF was smaller both in the patients with AS and MS, as compared to non-affected individuals ($p<0.05$). Patients with MS had higher heart rate than those with AS ($p<0.05$) and the normal subjects ($p<0.001$), Table 5.3.

Table 5.3 Distribution of the three-dimensional data and heart rate in the study population.

Valvular disease	LVEDV (ml)	LVESV (ml)	LVEF (%)	HR (beats/min)
AS	110±46	63±38	47±17*	74±14*
MS	83±26*	42±12	48±13*	88±13
None	110±20	46±10	59±4	66±5**

AS, Aortic stenosis; **MS**, mitral stenosis; **LVEDV**, left ventricular end-diastolic volume; **LVESV**, left ventricular end-systolic volume; **LVEF**, left ventricular ejection fraction. *p<0.05 vs. LVEDV/LVEF – no valvular disease, and heart rate – MS; ***P<0.001 vs. heart rate MS.

The average LV flow-volume loops in patients with severe valvular abnormalities and in individual without valvular pathology are presented in Figure 5.1. The flow-volume relationships were altered in both left-sided cardiac valvular abnormalities and differed from the typical loop in subjects with unaffected valves. In addition, flow-volume patterns differed between the two studied left-sided valvular pathologies as well. The patients with AS displayed readily apparent slower systolic volume decrease and lower ejection fraction despite maintained LVED volumes, thus reflecting hampered systolic function. On the other hand, in the patients with MS, the flow-volume loop indicated smaller LVED volumes and smaller EF implying reduced LV filling.

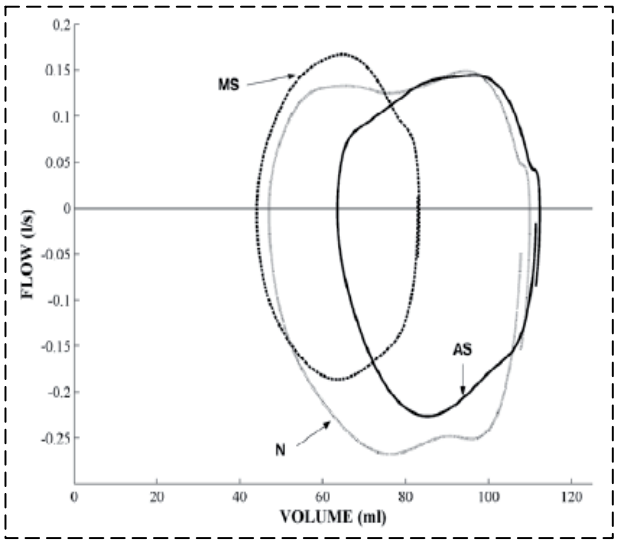

Figure 5.1 Flow-volume loops in normal subjects (**N**), and in patients with aortic- and mitral stenosis (**AS**, **MS**). Note the characteristic change of the loop form and position. Reprinted with permission [49].

5.3 Study III

EF measurements were feasible in all patients and there were no significant differences between the 2D echocardiography and 3D echocardiography methods. The mean value of EF by 3D echocardiography was 54.7 ± 8.9%, 55 ± 8% by eyeballing 2D and 55 ± 9% by eyeballing TP. Linear regression analysis (Table 5.4, Figure 5.2) showed excellent correlations between EF measured by 3D and eyeballing 2D echocardiography and TP (r = 0.91 and r = 0.95 respectively). Bland-Altman analyses (Table 5.4, Figure 5.2) showed mean differences of -0.5 ± 3.7% and -0.2 ± 2.9% for EF determined by 3D and eyeballing 2D and between 3D and eyeballing TP respectively. Inter- and intraobserver variability for eyeballing 2D was 7.5% and 3.8% respectively, 8.4% and 3.2% for eyeballing TP and 2.3% for intraobserver variability for quantitative 3D-EF.

Table 5.4 Comparison of ejection fraction between three-dimensional echocardiography and eyeballing biplane and tri-plane mode.

Variable	Mean difference	Limits of Agreement	R	SEE
3D-EF minus Eyeballing BP	-0.5	-7.9 to 6.9	0.91	3.71
3D-EF minus Eyeballing TP	-0.2	-6 to 5.6	0.95	2.9
Eyeballing BP minus Eyeballing TP	0.3	-6.7 to 7.3	0.92	3.31

3D-EF, three-dimensional ejection fraction; **BP**, biplane; **TP**, tri-plane; **R**, regression; **SEE**, standard error of estimate.

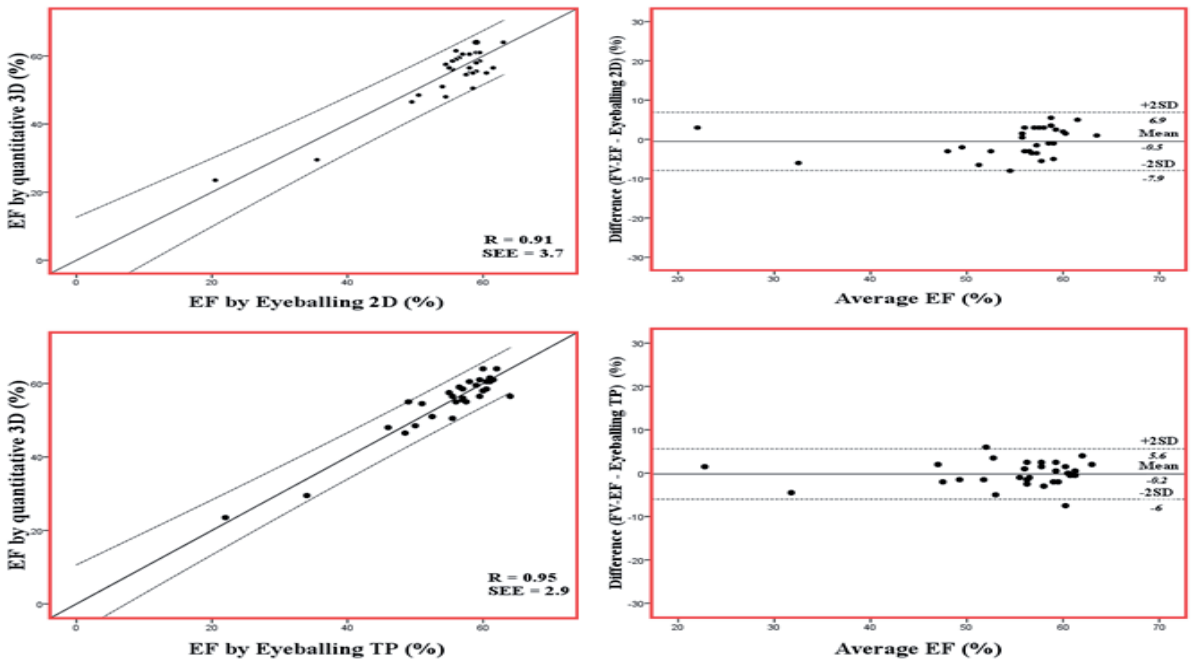

Figure 5.2 *Upper panel,* linear regression analysis (*left*) and Bland-Altman plots (*right*) of left ventricular ejection fraction (LVEF) between quantitative three-dimensional (3D) echocardiography and eyeballing two-dimensional. *Lower panel,* linear regression analysis (*left*) and Bland-Altman plots (*right*) of LVEF between quantitative 3D echocardiography and eyeballing tri-plane. The outer bounds represent 95% confidence interval.

5.4 Study IV

SV_3 significantly underestimated the mean SV in comparison to SV_2 and SV_{ref} ($p<0.0001$). The analysis time needed to evaluate SV was significantly longer with SV_2 (47.2 ± 8.4 sec), SV_3 (59 ± 8.3 sec) and SV_{ref} (47.4 ± 4.4 sec) in comparison to SV_1 (41 ± 5.5 sec). Linear regression analysis showed excellent correlations between SV_2 and SV_{ref}, r = 0.98. A weak correlation was found between SV_1 and SV_{ref}, r = 0.38. Bland-Altman showed a mean difference of -2 ± 17.6 ml and 0.5 ± 3.3 ml and 2SD being up to 70.4 ml and 13.2 ml between SV_1 and SV_{ref} and SV_2 and SV_{ref} respectively (Figure 5.3). A good correlation was found between SV_3 and SV_{ref}, r = 0.84 and a mean difference of -7.6 ± 8.7 ml. The limits of agreement analysis of SV measured by different methods are presented in Table 5.5.

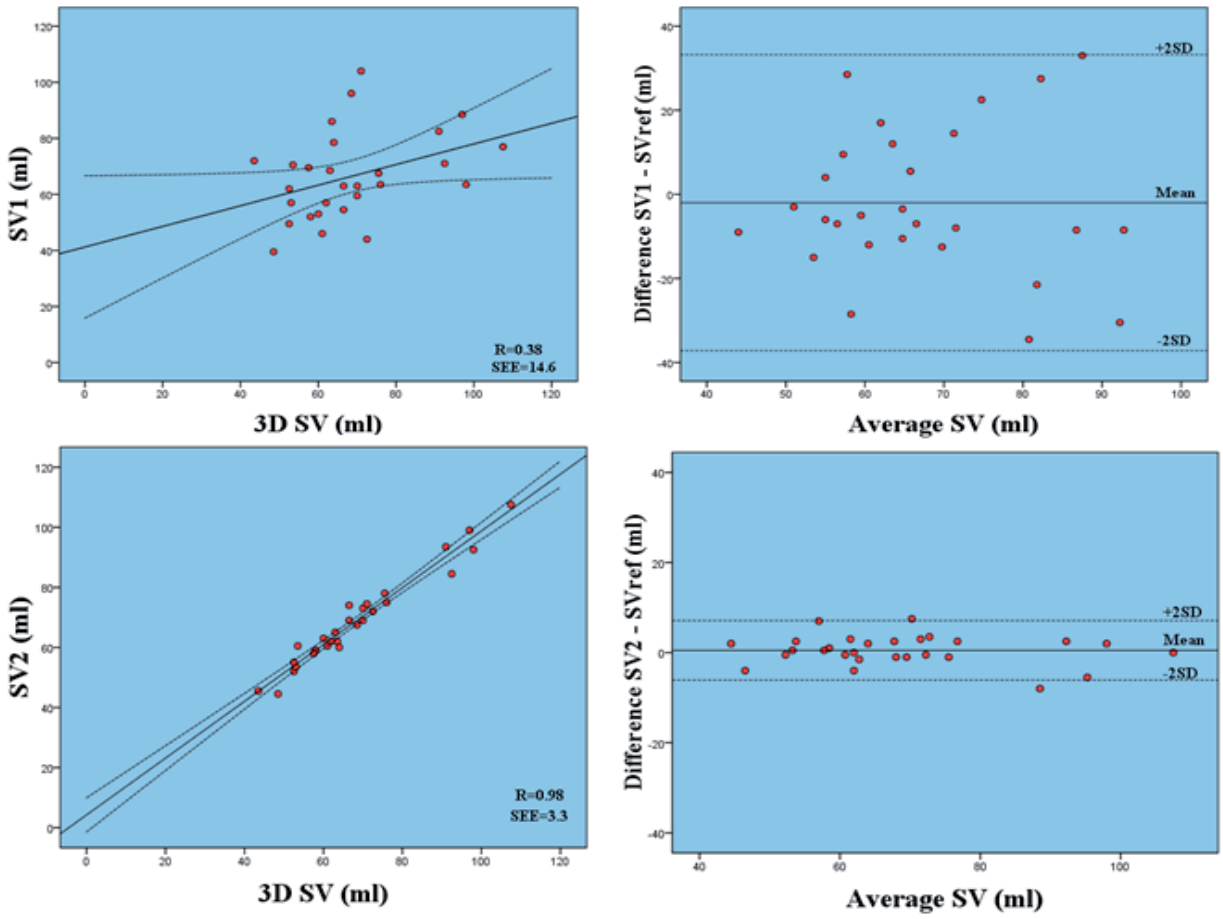

Figure 5.3 *Upper panel,* linear regression (*left*) and Bland-Altman plot (*right*) of stroke volume (SV) between three-dimensional (3D) echocardiography and SV assessed from left ventricular outflow tract (LVOT) diameter (SV_1). *Lower panel,* linear regression (*left*) and Bland-Altman plot (*right*) of SV between 3D echocardiography and SV assessed from the manual tracing of LVOT (SV_2). The outer bounds represent 95% confidence interval.

Table 5.5 Comparison of stroke volume by two- and three dimensional echocardiography using the Bland–Altman analysis

	SV_1 minus SV_2	SV_1 minus SV_3	SV_1 minus SV_{ref}	SV_2 minus SV_3	SV_2 minus SV_{ref}	SV_3 minus SV_{ref}
Mean difference ± SD	-2.5±16.8	5.5±16.1	-2±17.6	8.1±8.6	0.5±3.3	-7.6±8.7
Limits of agreement	-36.1 to 31.3	-26.7 to 37.7	-37.2 to 33.2	- 9.1 to 25.3	-6.1 to 7.1	-25 to 9.8
Correlation (r)	0.415	0.374	0.379	0.833	0.978	0.838

SV_1, stroke volume assessment using left ventricular outflow tract (LVOT) diameter
SV_2, stroke volume assessment by tracing LVOT in short-axis view
SV_3, using biplane Simpson to determine stroke volume
SV_{ref}, full volume three-dimensional quantification of stroke volume

Inter- and intraobserver variability of SV by different modalities is presented in Table 5.6. Inter- and intraobserver variability for the measurement of LVOT-diameter was 7.8% and 5.3% respectively and 4.5% and 3% for $LVOT_{VTI}$.

Table 5.6 Inter- and intraobserver variabilities for stroke volume measurements.

	LVSV	
	Intraobserver variability	**Interobserver variability**
SV_1	4.8%	6.3%
SV_2	5.7%	8.6%
SV_3	5.8%	8.9%
SV_{ref}	4.5%	6.2%

LVSV, left ventricular stroke volume; **SV_1**, SV assessment using left ventricular outflow tract (LVOT) diameter; **SV_2**, SV assessment by tracing LVOT in short-axis view; **SV_3**, using biplane Simpson to determine SV; **SV_{ref}**, full volume three-dimensional quantification of SV.

LVOT had a mean diameter of 20.2 ± 1.7 mm in the parasternal long-axis. The mean LVOT-diameter in anterior-posterior direction was significantly smaller in comparison to lateral direction (21.5 ± 1.8 mm and 24.6 ± 2.5 mm respectively; $p<0.001$) when measuring in BP modality. There was even a significant difference between LVOT-diameter in parasternal long-axis in comparison to anterior-posterior and lateral direction ($p<0.05$).

Assuming a heart rate of 60 beats/min for calculating CO from different SV modalities results in a mean difference of -0.12 ± 1.05 L/min (-2.21 to 1.98 L/min) between SV_1 and SV_{ref}, 0.03 ± 0.20 L/min (-0.37 to 0.43 L/min) between SV_2 and SV_{ref} and -0.45 ± 0.52 L/min (-1.49 to 0.59 L/min) between SV_3 and SV_{ref}.

5.5 Study V

In Group A the mean EDV using 4B was 102 ± 25 ml, the mean ESV was 47 ± 19 ml and mean the EF was 54 ± 10 %, and using SB modality the mean EDV was 99 ± 25 ml, the mean ESV was 47 ± 20 ml and the mean EF was 53 ± 10 %. Statistical analysis showed no significant difference between the variables using 4B in comparison to SB.

EDV, ESV and EF determined by 4B in Group B were 87 ± 27 ml, 52 ± 22 ml and 41 ± 11 % respectively. EDV, ESV and EF calculated by SB modality were 119 ± 34 ml, 64 ± 27 ml and 47 ± 12 % respectively. Statistical analysis showed significant differences between EDV, ESV ($p<0,001$) and EF ($p<0.05$) by 4B in comparison to SB.

Results of the intra- and interobserver variability in Groups A and B with both four-beat ECG-gated and SB modality are presented in Table 5.7. There were no significant differences between intra- and interobserver variability in Group A when comparing 4B vs. SB in measurements of LV volumes and EF.

Statistical analysis showed significant differences in inter- and intraobserver variability in Group B between the two modalities when calculating LV volumes and EF (Table 5.7).

Bland-Altman analysis in Group B showed mean differences of -32.5 ml, -12.2 ml, and -7% for EDV, ESV and EF. Confidence intervals (CI) for the respective measurements were 65 ml, 42 ml, and 40% using 4B and SB 3D echocardiography techniques (Figure 5.4).

Table 5.7 Intra- and interobserver reproducibility for left ventricular volumes and ejection fraction using four-beat ECG-gated and single-beat three dimensional echocardiography in patients with sinus rhythm and atrial fibrillation.

	SR-4B Intra/Inter observer variability	**SR-SB** Intra/Inter observer variability	**AF-4B** Intra/Inter observer variability	**AF-SB** Intra/Inter observer variability
LVEDV	4.4%/7.3%	3.9%/6.4%	9%*/10.4%*	4.5%/7.6%
LVESV	5.1%/8.5%	4.6%/6.5%	11.4%/15.2%*	2.9%/7.2%
LVEF	3.4%/3.9%	4.1%/4.5%	8.3%**/17.9%**	4.8%/5.6%

SR, sinus rhythm; **4B**, four-beat ECG-gated three-dimensional echocardiography; **SB**, single-beat three-dimensional echocardiography; **AF**, atrial fibrillation; **LVEDV**, left ventricular end-diastolic volume; **LVESV**, left ventricular end-systolic volume; **LVEF**, left ventricular ejection fraction, *p<0.05 and **p<0.001.

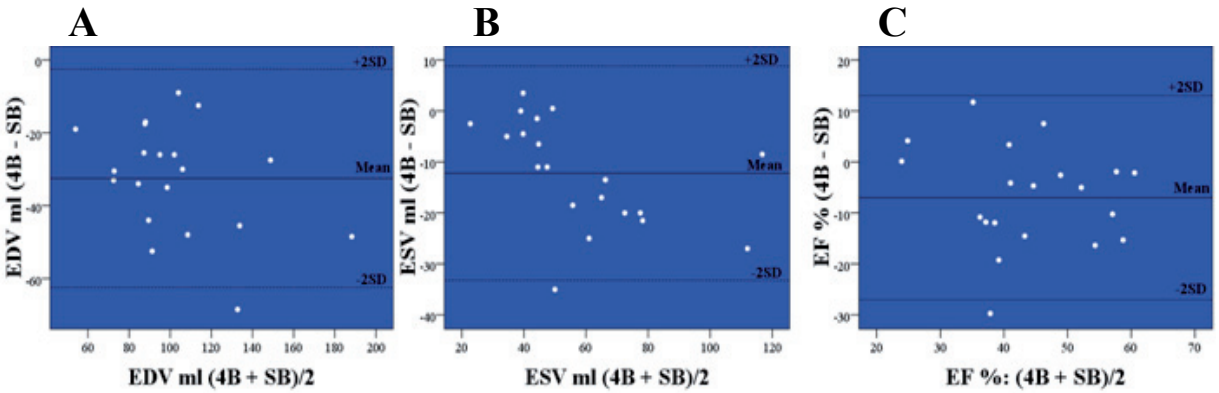

Figure 5.4 Bland-Altman plots of differences between end-diastolic volume, EDV (**A**), end-systolic volume, ESV (**B**) and ejection fraction, EF (**C**) determined by four-beat (4B) ECG-gated and single-beat (SB) three-dimensional echocardiography in atrial fibrillation patients.

6 DISCUSSION

Echocardiography has over the last decades become an indispensable diagnostic tool in any cardiovascular department. It has been proven to be safe and cost effective, and its clinical usefulness has gradually increased together with the continued integration of newer techniques, such as 3D echocardiography. 3D echocardiography, in various forms, has been used as a research tool for many years, but lately improvements in software and transducer technology have facilitated its integration into clinical practice.

LV function is one of the most common reasons for an echocardiography to be requested and there is a continual demand to improve accuracy and reproducibility. This is important when small differences in EF can mean the difference between offering and withholding proven therapies (e.i. Cardiac Resynchronization Therapy and Implantable Cardioverter Defibrillators). 2D echocardiography is less accurate and reproducible than 3D echocardiography. LV volumes and function can more accurately be assessed using 3D echocardiography [84-86], and serial calculations of LV volume and function by 2D echocardiography have been found to be inaccurate [20].

6.1 Feasibility of Measuring Heart Chambers from Different Views

Good visualization of LV and LA by apical 3D echocardiography was demonstrated in Study I in comparison to parasternal and subcostal views. Visualization of RA was reasonable using apical 3D echocardiography, whereas poor visualization of RV was discovered. There was a lack of incremental value on the feasibility of visualization by parasternal and subcostal views.

The value of 3D echocardiography imaging in the context of LV volumes and EF has been demonstrated by several studies [20, 87-91] that compared 3D echocardiography volume measurements with widely accepted reference techniques, including radionuclide ventriculography and MRI. These studies and others have demonstrated higher levels of agreement between the 3D echocardiography approach and the respective technique when compared with conventional 2D echocardiography. Additionally 3D echocardiographic measurements were found to be more reproducible than 2D echocardiography [20, 91].

LVEDV measured by 2D echocardiography in 2ch view was significantly smaller in comparison to 3D echocardiography in our study. We calculated 3D volumes from 16 interpolated cut planes, giving less space for geometrical assumptions. Additional verification and correction of the endocardial position is possible in the long- and short-axis views. These technical differences could explain why the volumes of 2D echocardiography and 3D echocardiography differ. In six

patients in our study, LV was not fully visualized with 3D echocardiography and one patient was not visualized with 2D echocardiography in 2ch view. Tighe et al. showed similar findings in patients with poor acoustic window not allowing all patients to be adequately visualized [90]. Furthermore, Tighe et al. demonstrated that 3D echocardiography volumes are reliable when more than 60% of the endocardium is visualized. In patients with dilated cardiomyopathy a more cranial intercostal space and/or more lateral approach was attempted to make sure that the entire LV was included.

Keller et al. showed that 3D echocardiography is superior to 2D echocardiography and M-mode regarding validity, accuracy and reproducibility of assessing LA and RA size and correlation to MRI [25]. The accurate measurement of LA size is of great importance for the management of arrhythmias as well as valvular and congenital diseases and the atrial function is changed with ischaemia [14, 15]. We found excellent feasibility of visualization of LA (100%) and good visualization of RA (78%). There was no incremental value in better visualization of LA and RA in parasternal and subcostal views. There were no correlations between ventricular or atrial size with the degree of visualization, even though one could have expected such a relationship in regard to depth and spatial resolution. To our knowledge no studies have investigated how many planes are needed for the accurate measurement of atria with 3D echocardiography. Unfortunately, only 12 patients had a good acoustic window from apical view of 3D echocardiography RV assessment. Kjaergaard et al. found good feasibility in assessing RV dimensions and they even used contrast echocardiography to enhance the border of endocardium [42]. Other investigators have investigated RV volumes using apical view by 3D- and 2D echocardiography [92, 45] and recently from both apical and subcostal views [93]. The RV was neither visualize-able in parasternal nor in subcostal view. We used a more off-axis approach to enhance the entire RV, which is in accordance with other investigators [92]**.** The irregular shape of the RV, the distance between the tricuspid and pulmonary valves, the difficulty to inline the RV out flow tract and to define the apex with the multiplanar method, all made it harder to measure RV volume. 2D echocardiography was superior in visualization of RV and RA. An explanation might be that 3D echocardiography measures the volume of the whole ventricle, while 2D echocardiography in our study measures diameter in a single plane. Caiani et al. used contrast echocardiography to enhance visualization of more patients [24].

Temporal and spatial resolution of the 2D echocardiography image is still superior to 3D echocardiography, especially when trying to image larger ventricles and/or higher heart rates.

6.2 Feasibility of Creating Flow-Volume Loops

Results from Study II revealed that measurement from 3D echocardiography creating flow-volume loops have a potential to separate groups of different hemodynamic states. The subject

having AS in our study showed a typical “obstructive” pattern with low values during early systole and larger ESV compared to the normal population. MS patients on the other hand demonstrated a “restrictive” pattern with reduced diastolic filling.

Flow-volume measurements are a conventional method as a clinical measure of lung function through its capacity to demonstrate the dynamic nature of an underlying obstructive or restrictive development [94]. LV pressure-volume loops are a reliable method for the monitoring of myocardial contractility [46], although the method is invasive. Ginzton et al. demonstrated a non-invasive approach to the evaluation of myocardial contractility by measurement of changes in end-systolic/volume ratio from rest to peak as a sensitive indicator of left ventricular function [95]. Several have followed this concept for the assessment of LV function by analysis of the dynamics of systolic pressure/end-systolic volume relationship during physical stress [96], pacing [97], or pharmacological stress with dobutamine [98]. The concept of LV flow-volume loop offered in the present study creates basis for yet another new, non-invasive approach to the assessment of LV function by focusing on a continuous quantitative evaluation of the flow-volume relationship throughout the entire cardiac cycle. In addition to quantifiable variables such as flow and volume, other characteristics of flow-volumes loops such as, for example, the course of ventricular filling and ejection, and the overall form of the flow-volume loop, may also be evaluated qualitatively. Söderqvist et al. originally proposed the concept of flow-volume loops based on the use of estimates of LV flow and volume derived from 2D echocardiography [48]. We used LV volumes measured from 3D data which are more accurate and reproducible than 2D echocardiography [21, 70, 99, 6]. The information retrieved from flow-volume loops will describe the hemodynamic characteristics of the flow-volume measures. Incorporation of the dynamics of LV flow and volume in the same loop provides an opportunity for a new and more detailed evaluation of cardiac hemodynamics from different points of view. The continuous information about LV flow and volume expressed by a flow-volume loop provides the fundamentals for hemodynamic pattern recognition in health and disease. The qualitative estimation of flow-volume loop form can be used as a tool for the quick evaluation of cardiac hemodynamics and differentiation between the normal condition and different cardiac pathologies, as for example, major valvular diseases that would change the normal pattern of LV filling and emptying.

6.3 Visually Estimated Ejection Fraction

Results from Study III showed that there is an excellent correlation between eyeballing EF using 2D and TP mode in comparison to quantitative measured EF using 3D echocardiography ($r = 0.91$ and $r = 0.95$ respectively) without significant bias. There was even a low interobserver variability for eyeballing EF using 2D and TP modality.

Since reliable assessment of LV systolic function expressed as EF is important for therapeutic decision-making in heart failure [53] an optimal method for evaluation of EF by echocardiography should be rapid and reliable. The major advantage of a visual estimation of LVEF is integrating all information regarding wall motion, atrioventricular plane displacement, etc. On the other hand the limitations are dependent on the skill of the reader.

Eyeballing EF has been validated against radioventriculography by Lavine et al. showing excellent correlation between these two methods for the determination of EF [100]. They compared eyeballing EF and wall motion scoring showing that wall motion scoring had better correlation ($r = 0.97$) in comparison to radioventriculography. Multi-plane imaging, TP allows the simultaneous presentation of a number of 2D slices (usually two or three) captured during a single cardiac cycle. Advantages with this technique are that TP overcomes problem with apical foreshortening and that the acquisition time is reduced. EF determination using eyeballing TP shows a trend towards a smaller variability in comparison to 2D. We think that there might be advantages in using TP over 2D for EF assessment in the clinical routine.

However, the value of eyeballing EF is still questioned by some and may differ between echocardiographic laboratories. Gudmundsson et al. showed similar results to ours when comparing eyeballing EF with quantitative 2D echocardiography measurements [57] indicating that eyeballing EF typically can be used with a high level of accuracy. One study demonstrated poor correlation ($r = 0.45$ - 0.51) between Simpson´s rule and EF evaluated by eyeballing, wall motion scoring and atrioventricular plane displacement in comparison to radionuclide imaging during myocardial infarction [58]. Akinboboye et al. showed in their study that eyeballing EF is an easy method to learn [101]. Sixty cases in joint reading are required to achieve the same accuracy as an experienced echocardiographer.

We recommend that the variability of visual estimation of LVEF should be regularly tested in any echocardiography laboratory and that EF determination using eyeballing EF is an accepted method.

6.4 Improvement of Accuracy in Stroke Volume Assessment

The accuracy of SV assessment using direct planimetry by LVOT area multiplied by $LVOT_{VTI}$ was tested in Study IV.

The conventional methods of measuring SV have major limitations. The most important source of error in measuring SV using the LVOT-diameter is based on the assumption of a cylindrical shaped LVOT, and that the LVOT-diameter is squared in order to determine SV. It seems more appropriate to directly planimeter the area, but this is limited by rotational errors in plane alignment and imprecision in plane positioning due to the movement of the heart during the cardiac cycle using 2D echocardiography.

Measurements of the aortic valve area using direct planimetry of LVOT instead of diameter correlates significantly better to invasive measurements and seem to improve agreement between continuity equations [102].

We found that the diameter in the parasternal long-axis is significantly smaller than the LVOT-diameter measured in BP mode in the anterior-posterior and lateral directions ($p<0.05$ and $p<0.001$ respectively) leading to a slightly larger LVOT area determined planimetrically (3.40 ± 0.81 cm^2 vs. 3.23 ± 0.59 cm^2).

We found poor correlation between SV_1 and SV_{ref} ($r = 0.38$) which is explained from the fact that LVOT is regularly not circular and that an assumption of a circularly shaped LVOT is magnifying the error from the quadration of the measured 2D radius. The variability of measuring LVOT-diameter in our study was 5% to 8%.

Additionally, the correlation between SV_2 and SV_{ref} was excellent ($r = 0.98$) with narrow limits of agreement (bias 0.5 ± 3.3 ml) and low inter- and intraobserver variability implying good reproducibility in the clinical circumstance; although, the analysis time was longer with this method in comparison to SV_1.

Despite a good correlation between SV_3 and SV_{ref} ($r = 0.84$) the limits of agreement were poor (bias -7.6 ± 8.7 ml), especially taking into account that this particular patient group had normal LV volumes. This method has a number of limitations, the most important perhaps being the geometric assumptions that are necessary for volume measurements and difficulties of defining the endocardial border in some patients [69, 70]. SV assessment using BPS were significantly underestimated in comparison to SV measurement by 3D echocardiography, and was also more time-consuming.

The accuracy in measuring LVOT is fundamentally important when calculating aortic valve area. SV measurement assessed by 3D echocardiography is more accurate in determination of the aortic valve area compared to continuity equation [103] using Gorlin´s equation as the reference method. Blot-Souletie et al. demonstrated the use of BP mode as a feasible and reproducible method for measuring aortic valve area in AS in comparison to continuity equation and transesophageal echocardiography ($r = 0.82$ and $r = 0.94$ respectively, $p<0.0001$) [104]. Khaw et al. demonstrated that manually tracing the LVOT in BP mode for the assessment of aortic valve area provides accurate assessment in comparison to invasive methods [105].

The agreement of CO measurements from SV_2 with SV_{ref} was up to 0.8 L/min (2SD) which was markedly better in comparison to the agreement between SV_1 and SV_3 with SV_{ref} (up to 4.19 L/min and 2.08 L/min respectively, 2SD). CO using this method could be clinically feasible.

6.5 Variability of Measuring LV Volumes and Function

The inter- and intraobserver variability of measuring LV volumes and EF in SR and AF was evaluated in Study V. 3D echocardiography is more accurate in comparison to 2D echocardiography regarding measurement of LV volumes and EF [106, 107]. EF measurement in AF is a difficult task for any echocardiographer because one has to make an average of several heart beats [75]. Experienced echocardiographers can overcome this difficulty by selecting visually estimated representative heart beats for EF measurement. Because of this, 4B modality seems to be impractical. However, the SB technique could have an advantage over 4B since it is possible to choose a representative heart beat similarly to 2D echocardiography, and furthermore due to the lack of stitching artifact.

LV volumes and EF were comparable in Group A measured by 4B and SB without significant difference. SB technique showed a tendency for a low inter- and intraobserver variability in LV volumes in comparison to 4B modality in Group A, although, this was not significant. Our results are in accordance with others showing a low inter- and intraobserver variability in determination of LV volumes and EF [108, 109]. The inter- and intraobserver variability was significantly lower with SB in AF patients in comparison to 4B, except for ESV analysed by intraobserver variability.

We found significant differences in LV volumes and EF in Group B when comparing 4B and SB technique with poor limits of agreement, -32.5 ± 15 ml for EDV, -12.2 ± 10.5 ml for ESV and -7 ± 10% for EF, especially considering that this patient population had normal LV volumes. Additionally, CI for the respective measurements was rather wide, 65 ml, 42 ml and 40% respectively. The most striking result in this study is the lower variability of SB when compared to 4B in LV volumes and EF determination (e.g. 5.6% vs. 17.9% for EF determination, interobserver variability, $p<0.001$). We assume that the explanation might be that the software has difficulties in tracking the endocardial border in AF when gathering volume in 4B because of stitching artifacts due to the irregular heart rate (Figure 6.1). The geometrical model in 4D LVQ is flexible and allows a wide variety of shapes. Although, the software has difficulties in achieving an accurate balance between smooth surfaces and surfaces that are improbable [110]. Another explanation could be that prolonged acquisition time using 4B increases the chance of patient motion or artifatcs [6], resulting in unsuccesful 3D image reconstruction, which can be overcome using SB. Echocardiography is well known to be user dependent in image quality, e.g. small changes in manual optimization can have a large impact in image quality. The beat-to-beat variability might create a poorer image quality from cardiac movement throughout the 4B acquisition. Interestingly, LV volume and EF are significantly smaller with 4B in comparison to SB. This finding is difficult to explain from any other source than software algorithm, since the measured heart beat was not deliberately selected. In other words, there is no reason to believe that there would be any differences in LV volume between the methods. The only two possible

explanations are either random findings or, more probably, systematic software error. Providing that this is true, there should be an additional advantage in measuring more true volumes when using SB acquisition in patients with irregular heart rhythm.

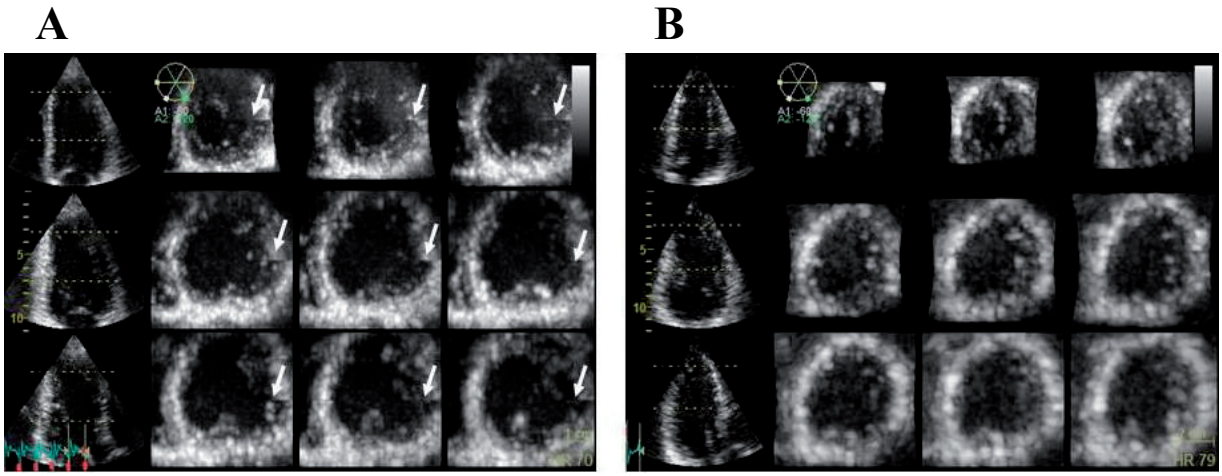

Figure 6.1 Four-beat ECG-gated full volume three-dimensional loop presented in a 9-slice image illustrating three apical segments of left ventricular in short-axis views (*upper top*), followed by three midventricular and three basal segments (A). Note the stitching artifacts due to an irregular heart rate in all 9-slices in an atrial fibrillation patient (*marked with arrows*). Single-beat three-dimensional echocardiography presented in a 9-slice image (B). No stitching artifacts can be detected in a patient having atrial fibrillation.

6.6 Limitations

The major limitation in Study II is the low temporal resolution of the 3D image. The other limitation is that the same data was used for calculation of volume and flow.

We demonstrated excellent correlation between eyeballing ejection fraction and quantitative assessment of EF by 3D in study III. The mean age of the study group was rather low with good image quality and having normal LVEF which could explain our findings.

The young study population and good image quality in Study IV could imply that the method we have used for assessment of stroke volume could be restricted to patients with good image quality. Another limitation in the assessment of stroke volume in our study was the absence of aortic calcification or septum hypertrophy which could lead to shadowing of the left ventricular outflow tract, making correct estimation of LVOT difficult. The measurements were not performed simultaneously and in the same cardiac cycle. Minor variations from beat-to-beat can therefore not be excluded.

The absence of a “gold standard” was the major limitation in Study V, since we can not prove the true superiority of single-beat three dimensional echocardiography over four-beat ECG-gated modality.

7 CONCLUSIONS

The conclusions of the each paper are listed below:

- Study I revealed that 3D echocardiography in the apical view provides superior visualization of all four chambers in comparison to parasternal and subcostal view. There were no additional improvements in feasibility regarding visualization using parasternal and subcostal views. The left ventricle and left atrium were well visualized with 3D echocardiography. Adequate assessment of right atrium volume with 3D echocardiography was shown, whereas assessment of the right ventricle was poor with 3D echocardiography.

- Study II demonstrated that 3D echocardiography offers the possibility of a non-invasive estimation of the dynamics of LV flow-volume relationship during the cardiac cycle. This approach provides new information about LV hemodynamics and function, and has a capacity to differentiate between normal LV hemodynamics and specific types of alterations of flow-volume relationships caused by valvular abnormalities, such as aortic and mitral stenosis. The method has the potential to provide additional hemodynamic information in the evaluation of cardiac and valvular function.

- Study III indicated that visual estimation of LVEF using both two-dimensional and tri-plane echocardiography by an experienced reader correlates well with quantitative EF determined by real-time 3D echocardiography. There is an apparently a smaller variability using tri-plane when compared to using two-dimensional imaging, this is however not statistically significant.

- The results from Study IV showed that direct measurement of the left ventricular outflow tract area is a feasible, accurate and reproducible method in measuring stroke volume and cardiac output, and correlates extremely well with 3D echocardiography volume measurements. Stroke volume and cardiac output calculation by left ventricular outflow tract area is therefore an appealing method for left ventricular stroke volume assessment in clinical routine.

- Study V demonstrated that single-beat assessment is a new tool offering the advantages of 3D echocardiography without stitching artifacts and leading to significantly lower inter-and intraobserver variability in LV volumes and EF measurements in patients having atrial fibrillation in comparison to four-beat ECG-gated acquisition. The methods are comparable in sinus rhythm patients regarding LV volumes and EF. More studies are needed to confirm this before implementing single-beat assessment into the clinical routine.

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