

**IMPROVED IMAGING IN CARDIAC PATIENTS:
ECHOCARDIOGRAPHY AND CT-CORONARY ANGIOGRAPHY**

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Colofon

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Verbeterde beeldvorming bij cardiale patiënten:
echocardiografie en CT-coronaire angiografie

Thesis

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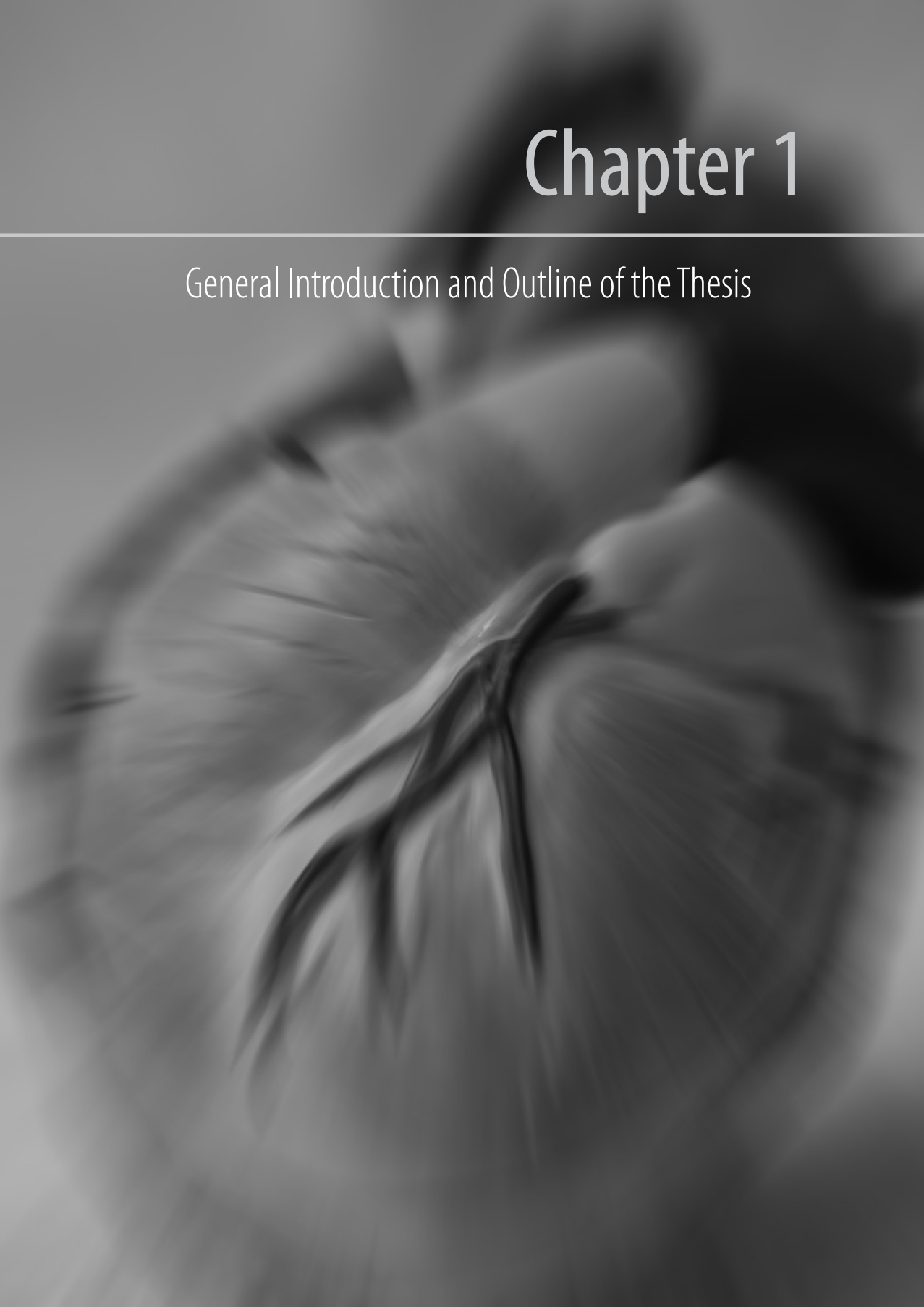
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Chapter 1

General Introduction and Outline of the Thesis



Different non-invasive imaging modalities are used for to assess cardiac anatomy and function. Echocardiography and MRI allow assessment of cardiac structures and function of the cardiac chambers and valves as well as perfusion of the left ventricular wall while CT-angiography in addition provides unique information on the structure of the coronary arteries¹. Nuclear cardiology offers measurement of global, and to some extent regional left ventricular function and perfusion of the left ventricular wall. While these different modalities continue to evolve, assessment of their accuracy, inter- and intraobserver reproducibility are crucial to assess their clinical value. In this thesis we present a series of studies of new applications of echocardiography.

Echocardiography is a very versatile tool for diagnosis of valvular disease, congenital heart disease and cardiomyopathy. Yet, assessment of left ventricular function is hampered by uncertainty to determine the precise endocardial borders. The latter may be improved by administration of echo contrast (**chapter 2**) or by harmonic imaging. In the studies presented in **chapter 3, 4 and 5** we assessed image quality and inter- and intraobserver variability of harmonic imaging and contrast enhanced echocardiography in comparison to standard echocardiography. The value of echo contrast is further illustrated in a case report of non-compaction cardiomyopathy (**chapter 6**).

Besides improved delineation of the endocardium of the cardiac chambers, contrast echocardiography provides information of perfusion² of the left ventricular wall. In **chapter 7** we analysed perfusion assessed by contrast echocardiography in comparison with single photon emission computed tomography (SPECT) as the golden standard. Furthermore we assessed the value of echo perfusion imaging and myocardial wall thickness to predict recovery of left ventricular function after primary PCI for acute myocardial infarction (**chapter 8**).

Doppler tissue imaging (DTI) provides additional information of regional and global left ventricular function which may be abnormal in patients with apparently global normal left ventricular function as measured by the ejection fraction³⁻⁵. We assessed the clinical value of such abnormal DTI in patients with severe aortic stenosis and a normal left ventricular ejection fraction. Measurements of DTI parameters were compared with an independent measure of cardiac function, NT-pro BNP (**chapter 9**). Furthermore we assessed whether abnormal DTI parameters improved after surgery for aortic stenosis (**chapter 10**).

Chest pain can be related to many cardiac and non-cardiac causes including coronary artery disease, pericarditis, cardiomyopathy, valvular heart disease but also pulmonary embolism, pleuritis and esophagitis^{6,7}. Echocardiography may be helpful in the diagnosis of several of these abnormalities. We assessed the clinical value of the systematic use of echocardiography in patients with chronic chest pain at the outpatient clinic (**chapter 11**).

In patients with chronic chest pain it is crucial to establish the presence of, or to rule out significant coronary artery disease. The presence and amount of calcium in the coronary arteries has been established as a powerful predictor of future coronary events⁸⁻¹¹. We assessed the diagnostic value of coronary calcium detected by computer tomography in patients with

chest pain in comparison with CT angiography and exercise testing (**chapter 12**). Finally the diagnostic value of the latter two methods was assessed in comparison with invasive angiography (**chapter 13**).

Although cardiologists are often impressed by new imaging modalities such as contrast echocardiography, Doppler tissue imaging, myocardial perfusion echocardiography and CT-angiography with or without PET, the clinical value needs to be carefully assessed. The results of different studies evaluating these imaging techniques are presented in this thesis.

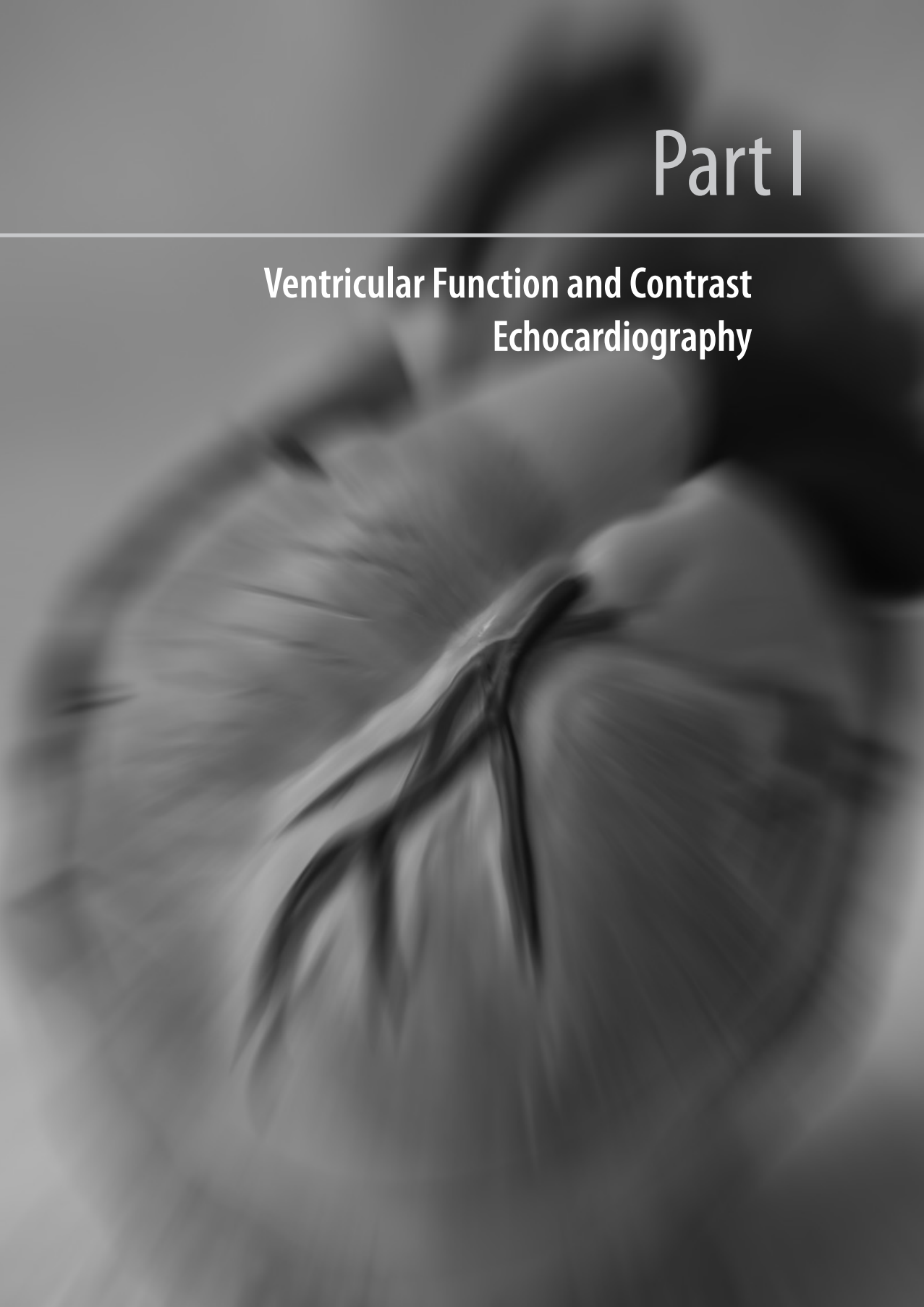
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Part I

Ventricular Function and Contrast Echocardiography



Chapter 2

Clinical Usefulness of SonoVue Contrast Echocardiography: the Thoraxcenter Experience

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Neth Heart J. 2007; 15(2): 55-60

ABSTRACT

Although other imaging techniques, such as magnetic resonance imaging and computer tomography, are becoming more and more important in cardiology, two-dimensional echocardiography is still the most used technique in clinical cardiology. Quantification of left ventricular function and dimensions is important because therapeutic strategies, for example implanting an ICD after myocardial infarction, are based on ejection fraction measurements. Because of the sometimes-low quality of echocardiographic images we started to use an ultrasound contrast agent and in this article we describe our experiences with SonoVue, a second-generation contrast agent, over a three-year period in the Thoraxcenter.

Keywords: *echocardiography, SonoVue, clinical practice.*

INTRODUCTION

Two-dimensional echocardiography is the main diagnostic technique for most cardiac diagnoses. Although considerable technical improvements have been achieved during the last decades, poor acoustic windows are still an important limiting factor of transthoracic echocardiography. Ultrasound contrast agents that traverse the pulmonary circulation and opacify the left cardiac chambers may overcome this limitation and have proven to be important for the assessment of left ventricular (LV) border detection and function.^{1,2} An overview of the use of ultrasound contrast agents was published in this journal in 1998.^{3,4} SonoVue, a commercially available contrast agent, has been used in the Netherlands since 2001. In this article we report our SonoVue experience during a three-year period from 2002 to 2004.

Contrast agent

SonoVue (Bracco, Milan, Italy) is based on stabilized sulphur hexafluoride microbubbles surrounded by a phospholipid shell with a mean size of 2.5 μm .⁵ After mixing with saline, a manual process that takes less than one minute (figure 1), a suspension is obtained with SonoVue microbubbles in a concentration of 1 to 5 x 10⁸ per ml. This suspension should be injected intravenously in a straight access through a three-way stopcock (to avoid destruction of the microbubbles) as a bolus (0.5 ml with additional 0.25 ml injections when necessary) followed by saline injection or as a continuous infusion by a dedicated pump delivered by the Bracco Company. In our institute we only use bolus injections. It should be emphasized that it is important to constantly shake the suspension to keep the microbubbles soluble. For virtually all indications 5 ml of SonoVue is sufficient; simple questions (LV ejection fraction) can often be answered with only half this volume in 15 minutes.

Figure 1: SonoVue file including syringe and needle

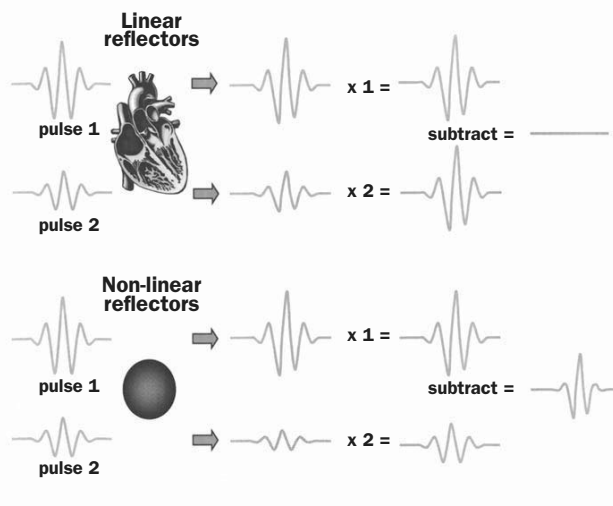


Echocardiography

Transthoracic echocardiography was performed with the Philips Sonos 5500 (Philips, Best, the Netherlands) system with a S3 transducer in the second harmonic contrast-imaging mode. Transmit/receive frequency was 1.6/3.2 MHz and the mechanical index was 0.4 for endocardial border detection and 0.1 for myocardial perfusion imaging. Mechanical index reflects the normalized energy to which a target (such as a microbubble) is exposed in an ultrasound field. Normally this index ranges from 0.1 to 2.0. For myocardial perfusion studies power modulation imaging was used. With this technique, differences in acoustic properties of microbubbles and tissue result in selective enhancement of microbubble-generated reflections but suppression of reflections from cardiac tissues. To visualize myocardial contrast bubble replenishment with real-time power modulation imaging, at peak contrast intensity the microbubbles in the myocardium were first destroyed with flash imaging with high a mechanical index (1.6).

The basic assumption underlying power modulation imaging is that the reflective properties of cardiac structures, unlike those of microbubbles, are mostly linear.⁶ Power modulation uses this assumption by transmitting repeated pulses of different intensities in the same direction (figure 2). Two consecutive pulses of identical shape but twofold difference in amplitude would result in identical reflections from the heart, other than the expected twofold difference in amplitude. The smaller pulse is then multiplied by 2 and subtracted from the larger one, resulting in a zero signal. When reflected by the nonlinear microbubbles, the same two

Figure 2: Upper panel shows myocardial reflection and lower panel microbubble reflection in power modulation mode (also see text for explanation).



Mor-Avi V, et al. *Circulation* 2001;104:352-357

pulses would differ from each other not only in amplitude but also in their shape. Amplifying the smaller pulse and subtracting it from the larger one would result in a nonzero signal. The amplitude of this signal is colour-coded and displayed in an overlay over the grey-scale image.

Real-time power modulation imaging was started after flash imaging with a high mechanical index (1.6) to destroy the microbubbles in the myocardium at peak contrast intensity in order to explore artifacts and to visualize myocardial contrast bubble replenishment.

Contrast applications

During the three-year period, 289 contrast studies were performed in 241 patients (48 patients underwent two studies because of a research protocol).⁷ As indicated in the next sections and in table 1, SonoVue was used for many different indications.

Table 1. Overview of SonoVue contrast echocardiography applications.

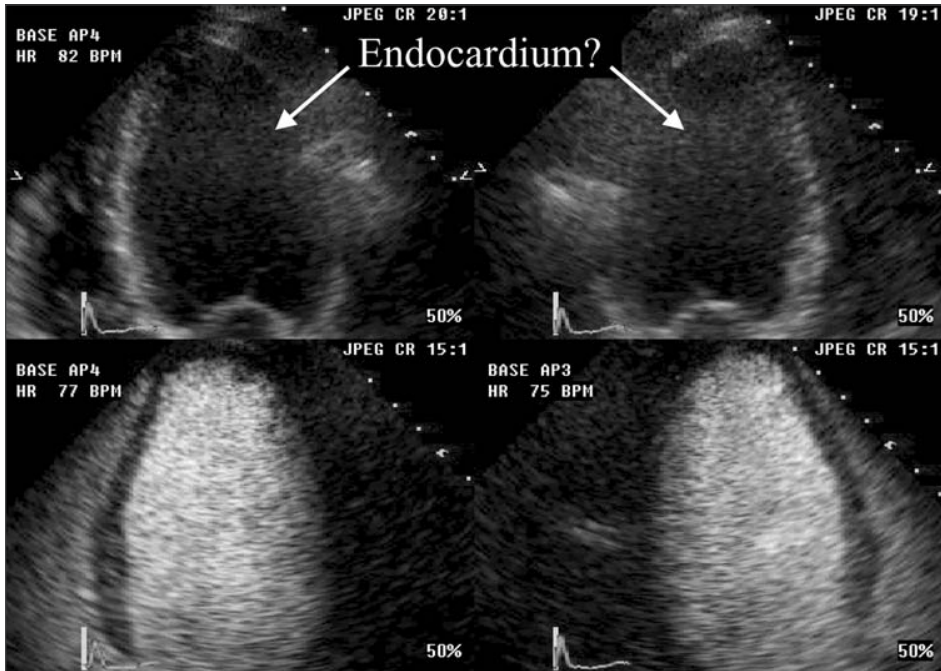
Application	Patients	Reference
Research – completed		
- Myocardial perfusion after acute myocardial infarction	96	5
- Right ventricular visualisation in congenital heart disease	20	16
Research – ongoing		
- LV ejection fraction interobserver variability*	96	
- LV ejection fraction versus nuclear imaging	29	
- 3D stress echocardiography	14	
- Noncompaction cardiomyopathy	34	
- Arrhythmogenic right ventricular cardiomyopathy	8	
- Percutaneous transluminal septal myocardial ablation	43	
Routine use		
- Left ventricular ejection fraction	50	
- Dobutamine stress echocardiography	25	
- Differentiation of extra- and intra-cardiac structures	12	

*The same patients as in reference 5.

LV ejection fraction

As seen in figure 3, echo contrast improves endocardial border detection and therefore makes LV wall motion analysis⁸ and LV ejection fraction assessment more reliable.^{9,10} This improvement is reflected by an increase in intra- and inter-observer agreement of LV ejection fraction and volumes.^{9,10} In a recently completed study in our centre, LV ejection fraction inter-observer variability decreased from 16.9% with second harmonic imaging to 7.0% with contrast imaging (unpublished data). Currently, we are using contrast for LV ejection fraction in several research protocols and in routine patients in whom accurate assessment of LV ejection fraction is necessary because of potential changes in clinical decision-making. Well known examples of this latter include initiation of chemotherapy and implantation of an internal cardiac defibrillator.¹¹

Figure 3: Visualisation of endocardial border in four- and three-chamber images without (upper images) and with (lower images) contrast.



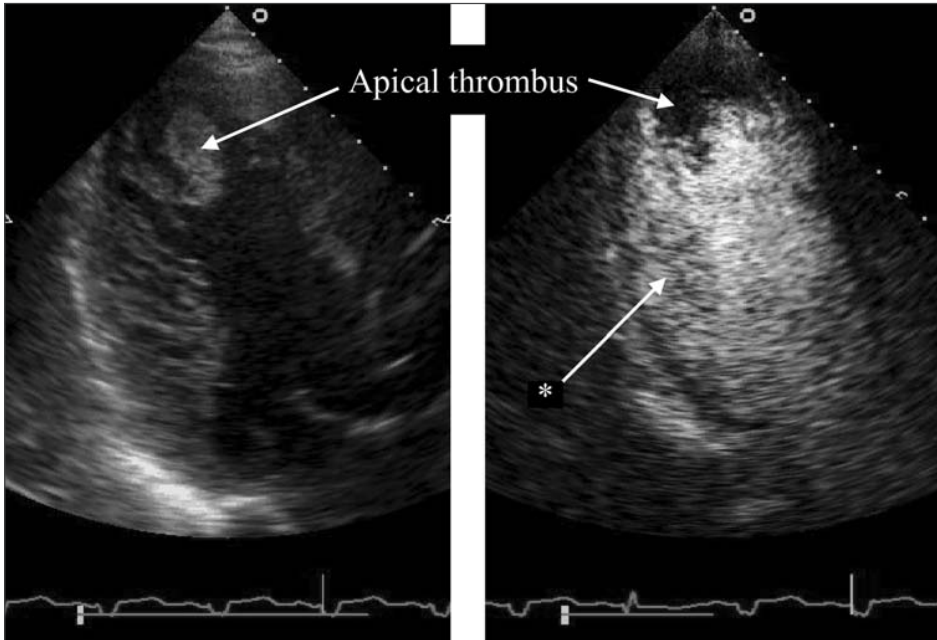
Myocardial perfusion

Contrast myocardial perfusion reflects total myocardial capillary blood volume. One of the most promising applications of this new modality is in patients with acute myocardial infarction. We and others have shown that intact myocardial perfusion of infarcted myocardium assessed by contrast echocardiography can predict functional recovery in time.^{12,13} In addition, contrast echocardiography contributes to a better measurement of interventricular septal thickness and the combination of wall thickness >11 mm in the infarct region and intact perfusion is an excellent predictor of functional improvement.⁷ Another application of myocardial perfusion is in patients with hypertrophic cardiomyopathy undergoing percutaneous transluminal septal myocardial ablation. During this procedure a localised chemical septal myocardial infarction is induced by injection of ethanol into one or more septal branches. By infusion of echo contrast the specific septal branch that supplies that part of the hypertrophied septum believed to produce LV outflow tract obstruction can be easily identified. In at least 10% of the procedures the echo contrast images change the selection of the septal branch.^{14,15}

Noncompaction cardiomyopathy

Noncompaction cardiomyopathy is a relatively rare congenital, unclassified cardiomyopathy that is characterised by excessively prominent trabecular meshwork and deep intertrabecular recesses, best evidenced by colour Doppler flow.¹⁶ Currently, we are studying the value of contrast echocardiography in these noncompaction patients. As seen in figure 4, we have described one patient in the literature in whom flow in the intertrabecular recesses could only be detected with the use of SonoVue contrast.¹⁷

Figure 4: Intertrabecular recesses filling with contrast (*) and apical mobile thrombus in a patient with noncompaction cardiomyopathy.



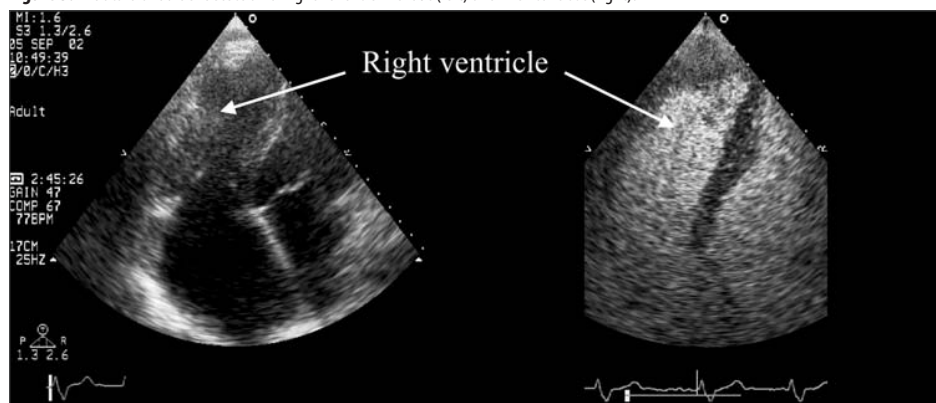
Right ventricular function and morphology

Echocardiographic visualization of the right ventricle remains a true challenge for the clinician. More reliable may be particularly useful in patients with congenital heart disease. In one study we demonstrated that in particular in the near-field images right ventricular contrast imaging gives a significantly better visibility of the endocardial border (figure 5).¹⁸ In addition, better identification of right ventricular trabeculation was possible, which may be important in the differentiation of right ventricular hypertrophy from marked trabeculation.

More recently, we started a research protocol in patients with a suspicion of arrhythmogenic right ventricular cardiomyopathy. According to existing guidelines echocardiography should be part of the diagnostic work-up. For the diagnosis of arrhythmogenic right ven-

tricular cardiomyopathy visualization of the right ventricle is important, but often difficult in routine echocardiography. We are currently examining whether contrast echocardiography can help in the visualization of right ventricular aneurysms, (segmental) right ventricular dilatation and (regional) right ventricular hypokinesia, all criteria for the diagnosis of this cardiac disease.¹⁹

Figure 5: Endocardial border detection of right ventricle without (left) and with contrast (right).

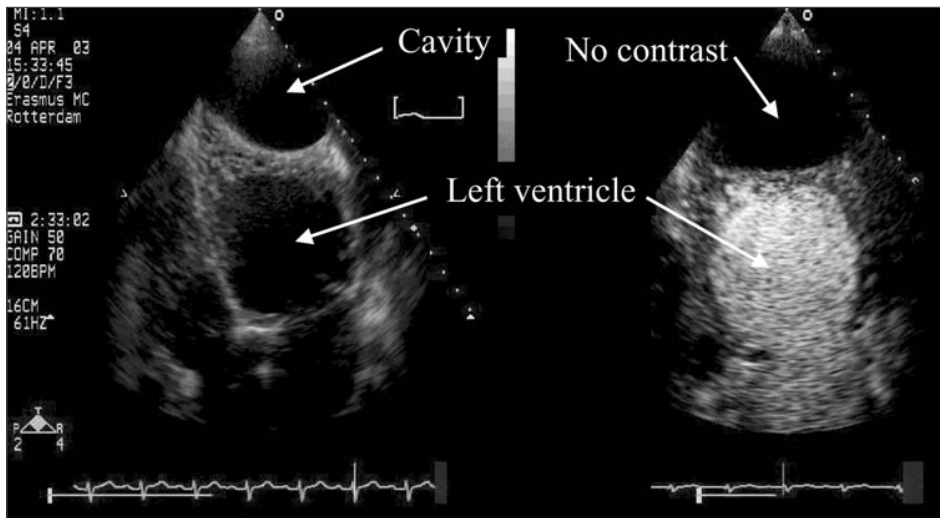


Stress echocardiography

The use of echo contrast improves interobserver agreement and diagnostic accuracy of dobutamine stress echocardiography, in particular in patients with suboptimal image quality.^{8,20,21} The limited use of contrast in stress echocardiography in our centre is mainly due to the confidence of the observer during the described time period in its interpretation quality and to a lesser extent SonoVue costs. Because 3D real-time stress echocardiography suffers from a significant decrease in image quality compared with conventional 2D imaging we are convinced that contrast may play an even more important role in this new stress modality. At the moment the role of contrast in 3D real-time stress echocardiography is one of our main research interests.

Differentiation of extra- and intracardiac structures

Contrast echocardiography may also be helpful in the identification of cavities of unknown origin. Since newer contrast agents such as SonoVue pass the pulmonary circulation, the microbubbles can reach all intracardiac cavities. If opacification with SonoVue is limited to the cardiac chambers, the cavity of interest has no luminal connection to a cardiac chamber and is thus diagnosed as located extracardially (figure 6).

Figure 6: Patient with echinococcus cyst; contrast image shows no connection with left ventricle.

Left ventricular thrombus detection

LV thrombus detection may have important implications with regard to the use of anticoagulant therapy. With conventional echocardiography it is sometimes difficult to image well-defined apical details. As seen in figure 4, besides the noncompaction cardiomyopathy, contrast echocardiography may also be of great help in the correct interpretation of the presence or absence of an apical LV thrombus.

Safety

During the described three-year study period, two of the 241 patients (1%) experienced mild hypotension, sinus tachycardia and skin flushing most likely caused by an allergic reaction to SonoVue. Both patients had received SonoVue for the second time and were successfully treated with intravenous clemastine and hydrocortisone. Before this study period we used SonoVue in a role-in phase in a patient to enhance endocardial border detection with dobutamine-stress echocardiography. He developed extensive skin erythema and anaphylactic shock with a decrease in blood pressure from 150/70 to 70/30 mmHg. After intravenously administered clemastine, hydrocortisone and volume, the patient rapidly recovered and was discharged the next day. This adverse event was reported to the EMEA. In 2004 several serious side effects with SonoVue were also reported by others²² and in a postmarketing analysis of 157,838 SonoVue studies 19 cases of severe (0.0012%) and three cases of fatal adverse events (0.002%) were described (<http://www.emea.eu.int/humandocs/Humans/EPAR/sonovue/sonovue.htm>). All three patients with a fatal outcome had severe coronary artery disease and

their clinical situation was far from stable. The allergic reactions may have been caused by the sulphur hexafluoride gas or the shell component polyethylene glycol (macrogel 4000).^{23,24} Subsequently, in May 2004 the European Medicines Agency (EMA) recommended not to use SonoVue as an ultrasound agent in cardiology. After a review of the cases by the Committee for Human Medicinal Products in November 2004 the recommendations changed and the use of SonoVue was again allowed in cardiac ultrasound. However, SonoVue is still contraindicated in patients with recent unstable cardiac symptoms, a recent (<7 days) coronary intervention, class III and IV heart failure or serious arrhythmias. An allergic reaction should always be anticipated and antiallergic drugs should be available in addition to standard resuscitation equipment. It is also recommended to keep the patient under medical supervision during and for at least 30 minutes following the infusion of SonoVue.

Limitations of SonoVue contrast

As described before, SonoVue may have important side effects, which makes the attendance of a physician mandatory. Contrast echocardiography needs a different pre-setting of the echo machine (mechanical index, second harmonic imaging). Another limitation for the widespread use of SonoVue is costs because there is only a small reimbursement for contrast echocardiography.

CONCLUSION

When detailed morphological and/or quantitative information of the heart is needed echo contrast agents such as SonoVue may provide better and more reliable results. Imaging of myocardial perfusion will be a main area for future applications, but in our opinion it is not applicable for routine practice at this moment. Costs and safety issues will most likely determine the clinical future of SonoVue.

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Chapter 3

Effect of Harmonic Imaging Without Contrast on Image Quality of Transesophageal Echocardiography

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Am J Cardiol 1999; 84: 1132-1134

ABSTRACT

Harmonic imaging (HI) has been developed to improve the potential of contrast echocardiography.^{1,2} It exploits the fact that microbubbles can resonate when hit by ultrasound producing harmonics as multiples of transmitted frequency.^{3, 4, 5} If the ultrasound machine is tuned to receive a second harmonic frequency selectively, it can differentiate contrast from tissue.⁶ However, baseline imaging is not deleted completely, because of nonlinear backscatter properties of tissue.^{7, 8} This allows one to use harmonic imaging without contrast agents; this modality has been called tissue HI or native HI. Recent transthoracic echo studies have shown the ability of tissue HI to improve endocardial border delineation.^{9, 10, 11} No previous study has been performed to assess the role of tissue HI during transesophageal echocardiography (TEE). Usually, TEE shows high-quality images, but at several occasions, as during cardiac surgery when the heart is dislocated from its normal position, image quality can be suboptimal. We developed a prototype transesophageal transducer that is able to obtain HI, and compared it with TEE image quality of harmonic and fundamental (conventional) imaging. The study was performed in the operating room during coronary artery bypass surgery (CABG).

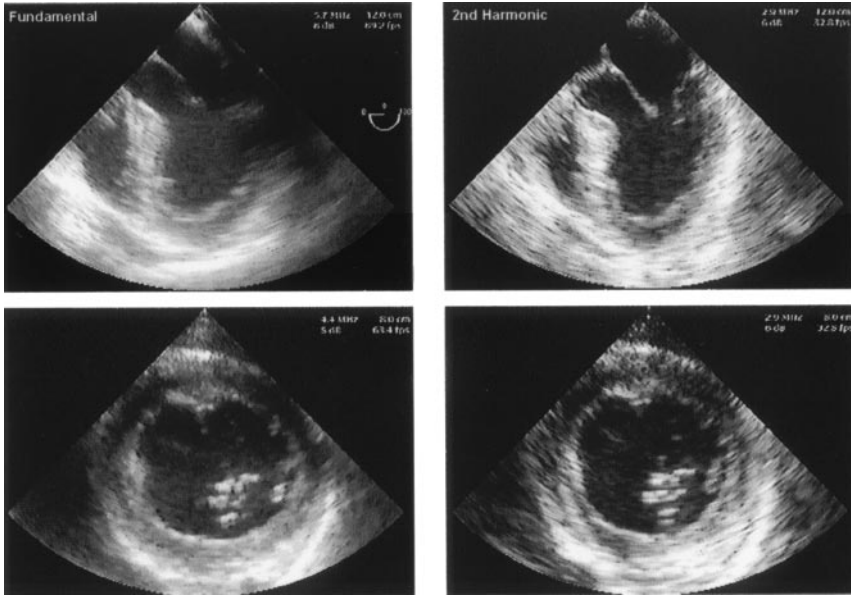
INTRODUCTION

Fourteen consecutive patients (mean age 60 ± 8 years) referred for CABG were enrolled in the study. Transesophageal echocardiograms in both harmonic and fundamental modes were performed before and immediately after CABG in the operating room. The second acquisition was performed just after termination of cardiopulmonary bypass pump to evaluate possible new wall motion abnormalities before its removal. A prototype transesophageal mono-plane transducer interfaced with a Vingmed System Five ultrasound machine (Vingmed, Oslo, Norway) was used for all studies. Transgastric short-axis and esophageal 4-chamber views were obtained in all patients. Fundamental images were obtained using a 4.4-MHz transmitted frequency, whereas for the harmonic mode the transducer transmitted at 2.9 MHz and received at 5.8 MHz. The 64-element broad-band transducer received wide band in fundamental and small band in the second harmonic mode. Mechanical index was set at 1.0. Imaging was optimized by increasing dynamic range or by adjusting overall gain. Dynamic range was set at >60 dB in all cases. In 5 patients an additional second transducer with a higher fundamental frequency (5.7 MHz) was tested after CABG to compare HI with fundamental imaging obtained by a commercial probe (Vingmed). Two experienced observers, blinded for the acquisition method used, scored each echocardiogram for visualization of endocardial borders. Visibility of endocardium was defined segment by segment using the following score: 0 = not visible; 1 = incomplete visualization during the all cardiac cycle; 2 = incomplete visualization during part of the cardiac cycle; and 3 = complete visualization. Wall motion was scored in a 4-grade model: 1 indicating normal wall motion, 2 hypokinesia, 3 akinesia and 4 dyskinesia.

Inter- and intraobserver variability for visibility of endocardial borders was scored by 2 independent observers and 30 days later by the first observer. Both observers were blinded for the acquisition method used. Kappa coefficients were calculated using a SAS system (SAS Institute, Cary, North Carolina). A κ coefficient of >0.4 , >0.6 , and >0.8 indicated fair, good, and excellent agreement, respectively. Data are presented as mean \pm 1 SD. Differences between fundamental and harmonic score were evaluated by analysis of variance for repeated measures or by paired Student's *t* test when appropriate. A *p* value <0.05 was considered significant. In all, 168 segments (12 segments \times 14 patients) were scored at both harmonic and fundamental imaging. Inter- and intraobserver variability for visibility of endocardium were both excellent (κ 0.81 and 0.88, respectively). Mean visibility score for endocardial border delineation was significantly higher for harmonic than for fundamental imaging (2.58 ± 0.72 vs 2.24 ± 0.98 ; $p < 0.001$). Endocardial border delineation improved with HI in 26% of segments (44 of 168) compared with fundamental imaging, and worsened in only 2% (4 of 168) ($p < 0.001$) Figures 1 and 2.

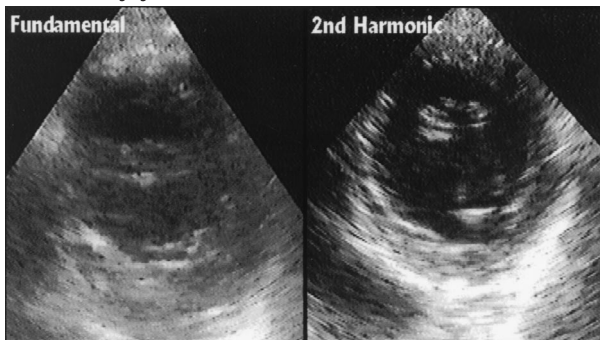
Visualization of 37% of segments (31 of 84) improved in the transgastric short-axis view with HI; no decrease in endocardial visibility was seen using HI. Visualization of 18% of seg-

Figure 1: Transesophageal echocardiography. Fundamental imaging (5.7 MHz) compared with harmonic imaging (2.9 to 5.8 MHz) in the same patient.



ments (15 of 84) improved in the 4-chamber view with HI and 5% (4 of 84) worsened. The number of segments improving endocardial visualization with HI was significantly higher in the transgastric view than in the transesophageal view (37% [31 of 168] vs 18% [15 of 84]; $p = 0.01$). Scoring of wall motion was altered in 7% of segments (12 of 168) when viewed with HI compared with fundamental imaging. In the 5 patients in whom we also used a commercial fundamental TEE transducer at 5.7 MHz, a total number of 60 segments (12 segments \times 5 patients) were compared. HI (2.9 to 5.8 MHz) improved endocardial border delineation in 23% of segments (14 of 60) and worsened in 3% (2 of 60); ($p = 0.003$).

Figure 2: Transgastric short-axis view in a patient with a suboptimal acoustic window. Harmonic imaging (2.9 to 5.8 MHz) compared with fundamental imaging (4.4 MHz).



Tissue HI has been shown to improve image quality when compared with fundamental imaging during transthoracic echocardiography. A recent transthoracic study showed that HI improved endocardial border delineation in 64% of analyzed segments and worsened in only 3%.⁹ The results of this study showed that also during TEE, HI improves endocardial border visualization compared with fundamental imaging. The improvement was seen in 26% of analyzed segments. Worsening of endocardial visibility was seen in 2% of segments. However, with use of HI, a change in wall motion score was determined in only 7% of segments. Transesophageal image quality is much better than transthoracic image quality, and this can explain the lower degree of improvement shown with HI. During this study TEE image quality improvement was higher in the transgastric view than in the transesophageal view (37% vs 18%; $p = 0.01$), probably because of lower quality of transgastric fundamental images. However, overall TEE quality improvement with HI was highly significant ($p < 0.001$). To be sure that the improvement was due to the harmonics and not to the tuning of the transducer, we used both the prototype transducer in fundamental (4.4 MHz) and harmonic mode (2.9 to 5.8 MHz), and a commercially available transducer with a higher fundamental frequency (5.7 MHz) in 5 patients. The results confirmed the previous findings, with a significant improvement in endocardial visualization with HI ($p = 0.003$). Physical properties of the harmonic mode are described in the following formula that relates the power of the second harmonic backscatter to several variables⁸: $P_2 = (B/A + 2) \times (\pi f / 2 \rho c^3) \times l \times p_{ac}^2$, where P = power (decibel); P_2 = power with second harmonic mode; B/A = nonlinear parameter of the medium; f = frequency; ρ = density of the medium; c = acoustic velocity; p_{ac} = applied acoustic pressure; and l = distance travelled from the source.

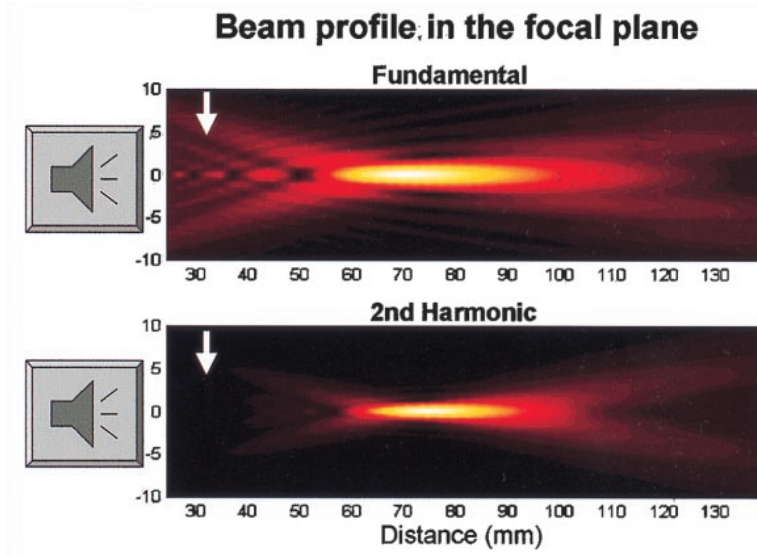
Harmonic signal intensity is related to the distance between the acoustic transducer and the tissue. The farther the tissue is from the transducer, the higher the reflected harmonic signal will be.¹² This produces 2 results: (1) It reduces the near-field clutter that is the acoustic noise near the transducer usually present with a phased-array system. (2) It increases the image quality in the far field, because the signal reflected from the far field, which usually is weak, with the harmonic mode is higher.

B/A is the acoustic parameter of nonlinear properties of biological media. Experimental studies showed that the myocardium has a higher B/A (between 6.8 and 7.4) than the blood (≈ 5.7).^{8,13} This means that the myocardium has a higher tendency to reflect ultrasound with different frequencies from the transmitted one. For this reason the myocardium produces a higher signal in the second harmonic mode than does the blood, and this can improve the endocardial border delineation, increasing the contrast between myocardium and blood.

The reflected beam generated by normal diagnostic equipment is narrower using the harmonic versus the fundamental mode. According to Ward et al, the reflected beam width decrease is: $W_n/W_1 = l/n^{0.78}$, where n is the harmonic number.¹⁴ It means that with the second harmonic mode ($n = 2$) the reflected beam is 42% narrower. A narrow reflected beam increases the lateral resolution of the image (Figure 3).

Side lobes are extraneous beams of ultrasound not in the direction of the main ultrasonic beam, and they can produce artifactual information. The harmonic beam has a lower level of side lobes than the fundamental beam (Figure 3). This is mainly due to the lower transmitting frequency. If the side lobes are reduced, it increases the signal-to-noise ratio, improving the image quality.¹⁵

Figure 3: Comparison of beams generated by normal diagnostic equipment in harmonic and fundamental modes. The reflected beam generated in the second harmonic mode is narrower. This increases the lateral resolution of the image. White arrows indicate the side lobes level in the near field. A diminished side lobe level increases the signal-to-noise ratio in the harmonic imaging.



CONCLUSION

In conclusion, although conventional TEE shows good quality images, tissue HI further improves delineation of endocardial borders. This allows a better assessment of left ventricular function during cardiac surgery. Feasibility and the high-image quality of TEE HI suggest a future role of this modality for contrast echo studies of myocardial perfusion.

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Chapter 4

Assessment of Left Ventricular Ejection Fraction after Myocardial Infarction using Contrast Echocardiography

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ABSTRACT

Aims: Despite its relatively high intra- and inter-observer variability for left ventricular ejection fraction (LV-EF) echocardiography is clinically still the most used modality to assess LV-EF. We studied whether adding a second-generation microbubble contrast agent could decrease this variability.

Methods and results: Forty-eight patients underwent transthoracic echocardiography in second-harmonic mode (SHI) with and without contrast within 5 days after an acute myocardial infarction. LV-EF was determined using the Simpson's biplane method. With contrast intra-observer variability decreased from $12.5 \pm 11.5\%$ to $7.0 \pm 7.0\%$ ($p < 0.001$) and inter-observer variability decreased from $16.9 \pm 9.9\%$ to $7.0 \pm 6.2\%$ ($p < 0.001$). Bland-Altman analysis confirmed these findings by demonstrating smaller 95% limits of agreement for both the intra- and inter-observer variability when contrast was used. This improvement in intra- and inter-observer variability was seen to a comparable extent in patients with moderate-to-poor and good quality SHI echocardiograms.

Conclusion: Echo contrast significantly improves intra- and inter-observer variability for LV-EF, both in patients with moderate-to-poor and good quality SHI echocardiograms.

Keywords: *Echocardiography, contrast, ejection fraction, myocardial infarction*

INTRODUCTION

Left ventricular ejection fraction (LV-EF) after acute myocardial infarction (AMI) is an important marker for mortality.^{1,2} LV-EF may be assessed by nuclear imaging, magnetic resonance imaging, and echocardiography.^{3,4,5} Nuclear imaging and magnetic resonance imaging provide relatively reliable information and with acceptable intra- and inter-observer variability.^{6,7} However, the use of these imaging modalities is limited by radiation exposure during nuclear imaging, high costs and non-availability in the coronary care unit and catheterization laboratory. Echocardiography is currently the most frequently used imaging modality for the assessment of LV-EF. However, echocardiographic images are sometimes of poor quality and in a recent review article high intra- and inter-observer variabilities were reported for echocardiographic LV-EF assessment.⁵

Left ventricular opacification (LVO) with echo contrast has been shown to improve image quality and in particular endocardial border delineation and this may improve intra- and inter-observer variability.^{8,9} Therefore, we conducted a post-AMI trial in which LV-EF was assessed with second harmonic imaging (SHI) and LVO.

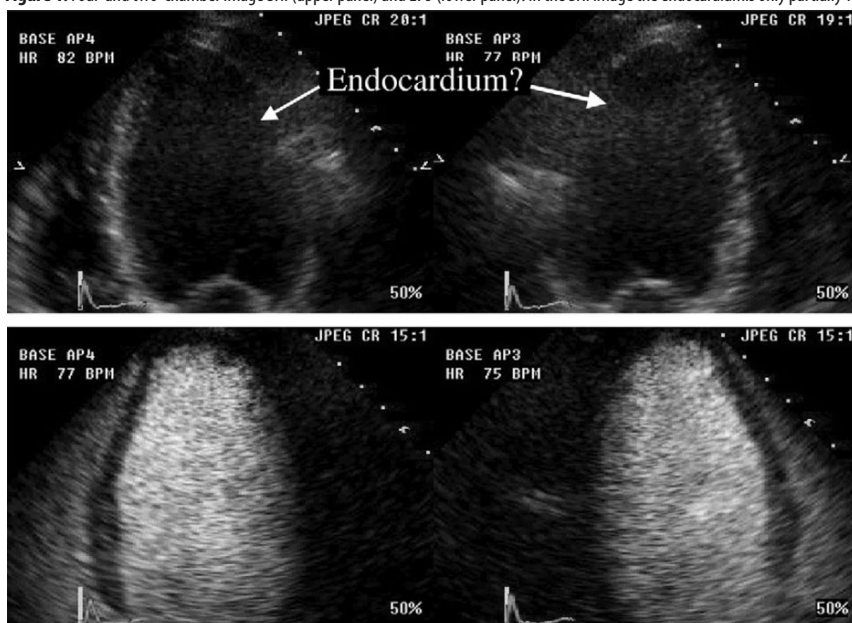
METHODS

Both SHI and LVO echocardiography were performed in 48 consecutive (regardless of image quality) patients within 5 days after primary angioplasty for AMI by one single experienced sonographer (WBV). Imaging was performed using the Sonos 5500 system (Philips, Best, The Netherlands). SHI images were acquired with a transmitted frequency of 1.6 MHz and a received frequency of 3.2 MHz, mechanical index was 1.6 and frame rate 50 Hz. For LVO imaging mechanical index was 0.3 and frame rate 25 Hz. Contrast agent SonoVue (Bracco, Milan, Italy) was used. This contrast agent consists of stabilized sulfur hexafluoride micro bubbles surrounded by a phospholipid shell with a mean size of 2.5 μ m.¹⁰ The contrast agent was given as a bolus of 0.5 ml with additional boluses of 0.25 ml when needed. Care was taken to record the images at a phase when contrast flow was relatively stable with absent or minimal swirling of contrast in the apex.

Non-foreshortened apical 2 and 4 chamber views were used for assessment of LV-EF (Figure 1). Manual tracing of LV end-systolic and end-diastolic frames was performed off-line according to Simpson's method, recommended by the American Society of Echocardiography,¹¹ using commercially available Enconcert software (Philips, Best, The Netherlands) by two experienced cardiologists (TWG, EB). Papillary muscles were considered as part of the LV cavity, and thus included in LV volume. To determine the inter-observer variability for both SHI and LVO images, all measurements were repeated by a second observer (EB) blinded to the values obtained by the first observer (TWG). To assess intra-observer variability, all

measurements were repeated one month later by an observer (TWG) blinded to the results of the previous measurements. Endocardial border visualization was scored for 12 segments derived from the 2- and 4 chamber apical views in SHI mode to investigate if intra- and inter-observer variability was influenced by quality of SHI. Endocardial border visualization was scored according to a 3-level scoring system where 0 = border invisible, 1 = border visualized only partially throughout the cardiac cycle and/or incomplete segment length, and 2 = complete visualization of the border.⁹ An endocardial visualization score was calculated by adding the score of all 12 segments in every patient. On basis of the quality score two image quality groups were defined: good (score 19-24), and moderate-to-poor (score <19) quality echo. The local ethics committee approved the study protocol and all patients gave written informed consent.

Figure 1: Four-and two-chamber image SHI (upper panel) and LVO (lower panel). In the SHI image the endocardium is only partially visible (arrow).



Statistical analysis

Continuous variables are expressed as mean \pm standard deviation (SD). Intra- and inter-observer variabilities were calculated as the absolute difference between two measurements in percent of their mean. To test differences in intra- and interobserver variability between techniques a paired *t* test was used. A two-tailed *p*-value < 0.05 was considered statistically significant. In addition, Bland-Altman analysis was used to determine the 95% limits of agreement (1.96SD) between measurements.¹²

RESULTS

Patients: Baseline characteristics of all patients are summarized in Table 1. Mean age of the patients was 52 ± 13 years. The AMI-related coronary artery was the LAD in 54%, the RCA in 31%, and the LCX in 15%. Multivessel disease was present in 48% of patients. Two of the 48 patients (4%) experienced mild hypotension, sinus tachycardia and skin flushing most likely caused by an allergic reaction of SonoVue. Both patients were successfully treated with intravenous clemastine and hydrocortisone.

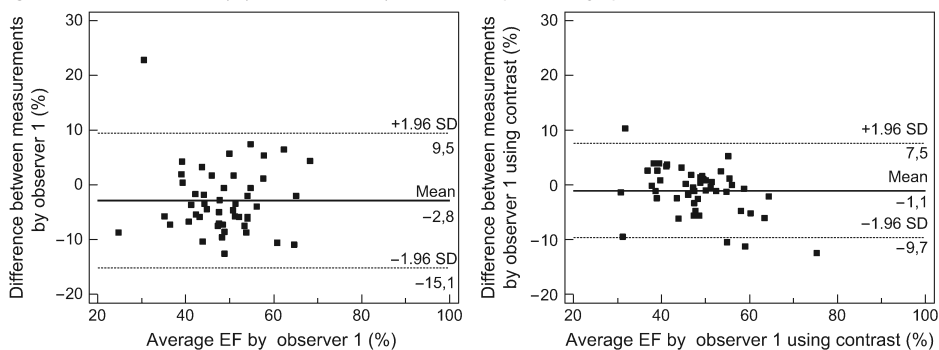
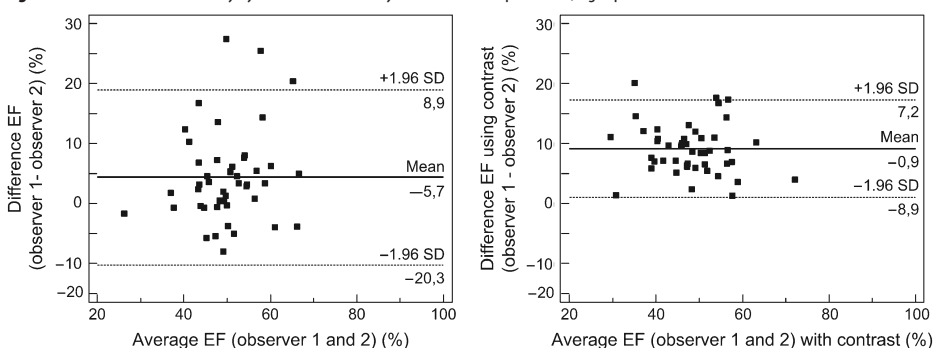
Clinical feature	
Age (years)	53 ± 13
Male	41 (85%)
Current smoker	29 (60%)
Diabetes	4 (8%)
Hypertension	14 (29%)
Hypercholesterolemia	30 (63%)
Prior myocardial infarction	6 (13%)
Prior PCI/CABG	1 (2%)
Infarct related vessel	
LAD	26 (54%)
LCX	7 (15%)
RCA	15 (31%)
Multivessel disease	23 (48%)

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LAD, left anterior descending; LCX, left circumflex artery; RCA, right coronary artery.

Ejection fraction: Mean LV-EF for observer 1 was $47.1\% \pm 9.1\%$ with SHI and $47.5\% \pm 8.3\%$ with LVO. Intra-observer variability (expressed as absolute difference in percent of their mean) decreased from $12.5 \pm 11.5\%$ to $7.0 \pm 7.0\%$ ($P < 0.001$) with LVO. Inter-observer variability decreased from $16.9 \pm 9.9\%$ to $7.0 \pm 6.2\%$ ($P < 0.001$) with LVO (Table 2).

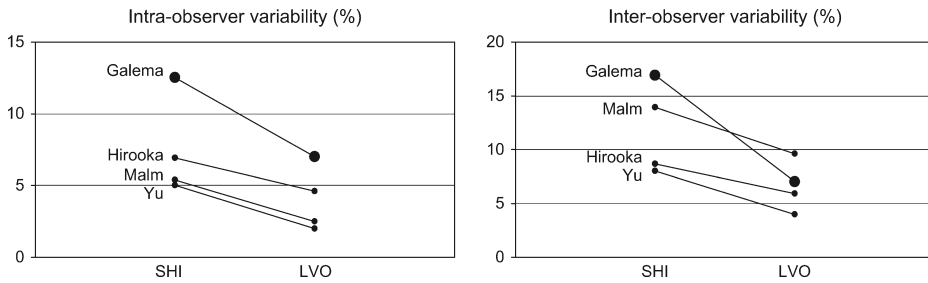
In addition, Bland-Altman analysis confirmed these results by demonstrating smaller limits of agreement for LV-EF when contrast was used for both intra- and inter-observer variability (Figures 2,3). Good and moderate-to-poor image qualities were present in 15 (31%) and 33 (69%) patients, respectively. As seen in Table 2 significant improvements in intra- and inter-observer variability were found for both image quality groups. Again this was confirmed by Bland-Altman analysis showing smaller limits of agreements when contrast was used regardless of image quality (Figures not shown).

	Intra-observer variability (%)			Inter-observer variability (%)		
	SHI	LVO	<i>P</i> -value	SHI	LVO	<i>P</i> -value
Total (<i>n</i> = 48)	12.5 ± 11.5	7.0 ± 7.0	< 0.001	16.9 ± 9.9	7.0 ± 6.2	< 0.001
Good (<i>n</i> = 15)	10.4 ± 7.1	5.8 ± 5.2	0.06	16.0 ± 6.7	7.5 ± 7.3	0.001
Moderate/poor (<i>n</i> = 33)	13.4 ± 13.0	7.5 ± 7.7	0.002	17.3 ± 11.1	6.8 ± 5.7	< 0.001

Figure 2: Intra-observer variability by Bland–Altman analysis for LV-EF. Left panel: SHI, right panel: LVO.**Figure 3:** Inter-observer variability by Bland–Altman analysis for LV-EF. Left panel: SHI, right panel: LVO.

DISCUSSION

LV-EF after AMI is an important marker for mortality and is becoming increasingly important because the selection of patients who benefit from an internal cardiac defibrillator is based on LV-EF.^{1,2,13} Currently, echocardiography is the imaging modality most often used to assess LV-EF. However, echocardiography is limited by high intra- and inter-observer variability.⁵ Reliable contour detection of the LV is only possible if the endocardial border is visible during end-systole and end-diastole. Although SHI improves endocardial border detection compared to fundamental imaging, even in good quality echocardiograms it is sometimes difficult to delineate the endocardium in the still frames whereas with LVO this may be more reliable.⁹ So, in our study, SonoVue echo contrast further improved endocardial border detection in post-AMI patients resulting in a significant decrease in intra- and inter-observer variability for LV-EF. Our findings confirm the results published recently by others.^{14,15} In Figure 4, the intra- and inter-observer variabilities for LV-EF reported in studies using SHI and LVO imaging are summarized.^{14,16,17} Due to the consecutive character of patient inclusion in our study (no patient was excluded because of image quality) our SHI result seem worse than those reported by others. Although some authors showed an improvement in LV endocardial

Figure 4: Intra- and inter-observer variabilities for LV-EF reported in studies using SHI and LVO imaging.

border detection with SHI compared to FI⁹, optimal intra- and inter-observer variability in LV-EF can only be achieved when echo contrast agent is added to SHI imaging. In a study by Hoffmann et al. inter-observer variability between three readers from different institutions was best (even compared to MRI images and cineventriculography) with contrast-enhanced echocardiography and worst with unenhanced echocardiography.¹⁸ In patients with moderate-to-poor image quality higher intra- and inter-observer variabilities were found for SHI imaging. However, the improvement with LVO imaging in intra- and inter-observer variabilities was almost similar in patients with moderate-to-poor and good image quality. These findings are in agreement with studies published by Malm et al., and Nayyar et al., although Hundley et al. noticed improvement in LV-EF variability particularly in subjects with two or more adjacent endocardial segments not seen at baseline.^{14,19,20} Unfortunately, we did not compare SHI and LVO LV-EF with a gold standard technique. However, several studies have shown an excellent correlation between LVO and magnetic resonance imaging.^{15,20,21} Furthermore, observers could not be blinded to the use of contrast or not.

CONCLUSION

Assessment of LV-EF is more reliable with LVO imaging, evidenced by better intra- and inter-observer variability. Our study supports the concept that when LV-EF may influence clinical decision-making, LVO imaging should not be limited to patients with moderate-to-poor echocardiographic windows. This is in disagreement with the ASE Task Force Guidelines which recommend to use LVO only when at least 2 of 6 contiguous segments in a standard apical view are not visualized.²²

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Chapter 5

Contrast Echocardiography improves Interobserver Agreement for Wall Motion Score Index and Correlation with Ejection Fraction

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ABSTRACT

Background: The wall motion score index (WMSI) is a surrogate marker for left ventricular ejection fraction (LV-EF). Unfortunately, there are only few data on the relation between these parameters and poor echo windows can make the WMSI unreliable. The value of contrast-enhanced imaging for WMSI assessment was not investigated before.

Aim of the study: To compare interobserver agreement for segmental wall motion and WMSI in patients who underwent both two-dimensional second harmonic (SH) and contrast LVO echocardiography and to study the correlation between the LVO-imaged WMSI and LV-EF.

Methods: The study comprised 100 consecutive patients (mean age 57 ± 13 years, 85% males). Two independent physicians assessed LV segmental quality and wall motion for both the SH and LVO studies according to a 17-segment model. Systolic wall motion was defined as (1) normokinesia, (2) hypokinesia (systolic inward endocardial motion $<7\text{mm}$), (3) akinesia, and (4) dyskinesia. LV-EF was assessed from the LVO images according to the biplane modified Simpson's method.

Results: Of the 1,700 analyzed segments, 453 (26.6%) were poorly visualized with SH imaging, and 173 (10.2%) with LVO imaging ($P < 0.0001$). The two observers agreed on segmental wall motion score in 1,299 segments (agreement 76%, Kappa 0.60) with SH imaging and in 1,491 segments (agreement 88%, Kappa 0.78) with LVO imaging. Interobserver correlation (r^2) was 0.86 for the SH-imaged WMSI and 0.93 for the LVO-imaged WMSI. The limit of agreement for interobserver LVO-imaged WMSI (mean relative difference $-1.0\% \pm 6.8\%$, agreement -14.6% , 12.6%) was lower than that for SH-imaged WMSI (mean relative difference $-2.3\% \pm 10.1\%$, agreement -22.5 , 17.9). The LVO-imaged WMSI correlated well with LV-EF ($r^2 = 0.71$). LV-EF could be estimated according to the formula $1.01 - 0.32 \times \text{WMSI}$.

Conclusion: Echo contrast improves interobserver agreement for wall motion scoring and the WMSI. The LVO-imaged WMSI correlates well with LV-EF.

INTRODUCTION

Left ventricular ejection fraction (LV-EF) is a strong predictor of mortality in cardiac patients¹ and is a crucial variable in clinical decision-making for valvular surgical interventions,² implantation of an internal cardiac defibrillator,³ and the initiation of chemotherapy.⁴ However, for routine applications LV-EF measurements are time-consuming and often a wall motion score index (WMSI) is provided as a surrogate marker for LV-EF. Despite its common clinical use, there are only few studies in which the relation between the WMSI and LV-EF was investigated.^{5,6} Surprisingly, in none of these studies definitions for hypokinesia were provided. In addition, poor echo windows make the WMSI (and LV-EF) unreliable in an important number of patients.⁷ In several studies it has been shown that LV opacifying (LVO) contrast improves endocardial border detection⁷⁻¹⁰ and interobserver agreement for classifying segmental wall motion.^{11,12} The purpose of the present study was to compare interobserver agreement for segmental wall motion and the WMSI for two-dimensional second harmonic (SH) and contrast LVO echocardiography and to study the correlation between the LVO-imaged WMSI and LV-EF.

METHODS

Patient population: The study comprised 100 consecutive patients who underwent both SH and LVO echocardiography for clinical evaluation of LV function. Mean age of the patients was 57 ± 13 years and 85 were males (85%). Ten patients (10%) were not known with cardiovascular disease, 84 patients (84%) had a history of first acute myocardial infarction treated with coronary angioplasty and 6 patients (6%) were referred for LV-EF assessment for internal cardiac defibrillator screening. None of the patients had a dilated cardiomyopathy, defined as a LV end-diastolic diameter >60 mm.

Echocardiographic imaging: Echocardiography was performed with a Sonos 5500 or 7500 system (Philips, Best, The Netherlands). SH images were acquired with a transmitted frequency of 1.6 MHz and a received frequency of 3.2 MHz, mechanical index was 1.6, for LVO imaging mechanical index was 0.3. LVO imaging was done with SonoVue (Bracco, Milan, Italy),¹³ administered as a bolus of 0.5 ml intravenously with repeated boluses of 0.25 ml when necessary. Care was taken to record the images at a phase when contrast flow was relatively stable. All acquired SH and LVO images were digitally stored.

Echocardiographic analysis: The LV was analyzed according to the recommended 17-segment model.¹⁴ Two independent physicians (MLG, AvdV) assessed segmental quality and wall motion for both the SH and LVO studies. Quality was scored on a binary scale as poorly visualized (absent or no clear endocardial delineation) or adequately visualized. Segments

were considered poorly visualized when at least one physician noticed this score. Systolic wall motion was defined as (1) normokinesia (systolic inward endocardial motion ≥ 7 mm), (2) hypokinesia (systolic inward endocardial motion < 7 mm), (3) akinesia (absence of systolic endocardial motion), and (4) dyskinesia (systolic outward endocardial motion). After the initial independent segmental wall motion scoring by the two observers, a segmental consensus score was reached between the two observers. To resolve consensus issues, electronic calipers were used when necessary. The WMSI was defined as the summed segmental wall motion scores divided by the number of analyzed segments. LV-EF was assessed from the LVO images according to the biplane (apical 2- and 4-chamber views) modified Simpson's method by two other blinded physicians (TWG, OHS) using EnConcert software.¹⁵

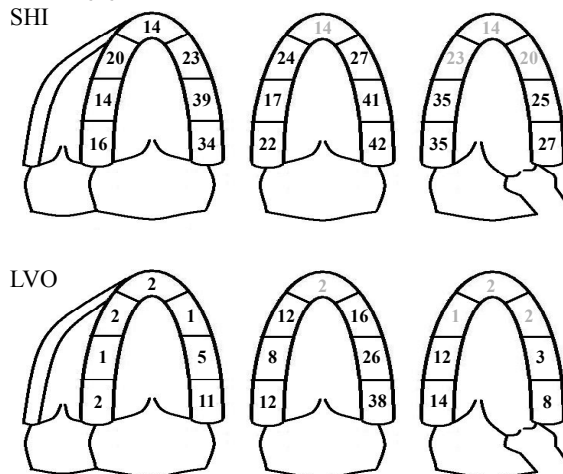
Statistical analysis

The limits of agreement between readings of the two independent observers were estimated as the relative mean difference ± 2 SD of this difference, as described by Bland and Altman.¹⁶ The kappa (κ) coefficient was calculated to determine interobserver agreement. A kappa value < 0.4 was considered poor, 0.4 to 0.7 moderate, and > 0.7 good.

RESULTS

Segment visualization: Of the 1,700 analyzed segments, 455 (26.7%) were poorly visualized with SH imaging, and 173 (10.2%) with LVO imaging ($P < 0.0001$). The distribution of poorly

Figure 1: Diagram showing the distribution of poorly visualized segments with second harmonic (SHI, top) and left ventricular opacifying (LVO, bottom) imaging.



visualized segments with SH and LVO imaging is depicted in Figure 1. For both SH and LVO imaging anterior segments were most problematic (110 and 80 anterior segments were poorly visualized, respectively). With LVO imaging segment visibility increased towards the apex (poor visualization was present in 14.2% of basal segments, 9.2% of mid segments, and 6.6% of apical segments, respectively).

Segmental interobserver agreement: As seen in Figure 2, the two observers agreed on segmental wall motion score in 1,299 of the 1,700 segments (agreement 76%, Kappa 0.59) with SH imaging and in 1,491 of the 1,700 segments (agreement 88%, Kappa 0.78) with LVO imaging. The segmental distribution of agreement with SH and LVO imaging is depicted in Figure 3a and 3b.

Figure 2: Segmental wall motion score by the two observers with second harmonic (left) and left ventricular opacifying (right) imaging.

		Observer 1						Observer 1			
		normal	hypokinesia	akinesia	dyskinesia			normal	hypokinesia	akinesia	dyskinesia
Observer 2	normal	644	143	0	0	Observer 2	normal	831	66	0	0
	hypokinesia	176	549	23	0		hypokinesia	82	557	21	0
	akinesia	1	57	99	1		akinesia	2	34	98	3
	dyskinesia	0	0	0	7		dyskinesia	0	1	0	5

Segmental Agreement = 0.76 Kappa value = 0.59

Segmental Agreement = 0.88 Kappa value = 0.78

Figure 3a: Segmental distribution of agreement with second harmonic imaging.

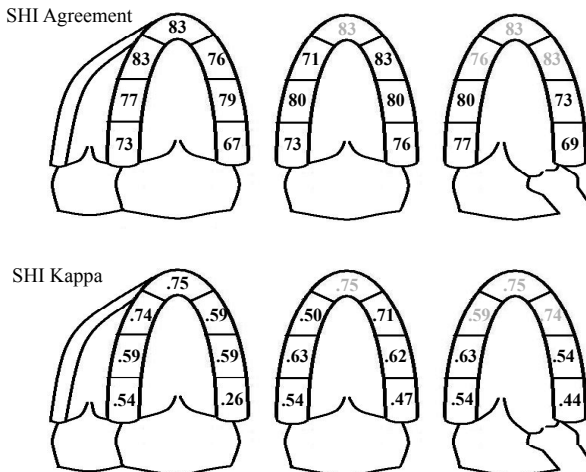
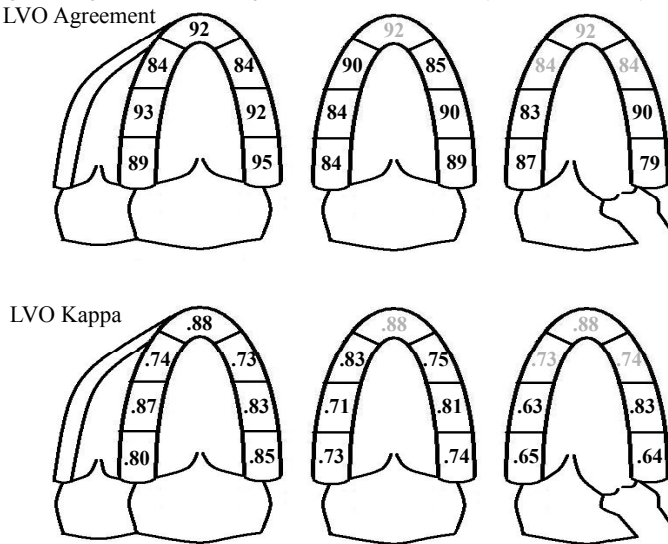


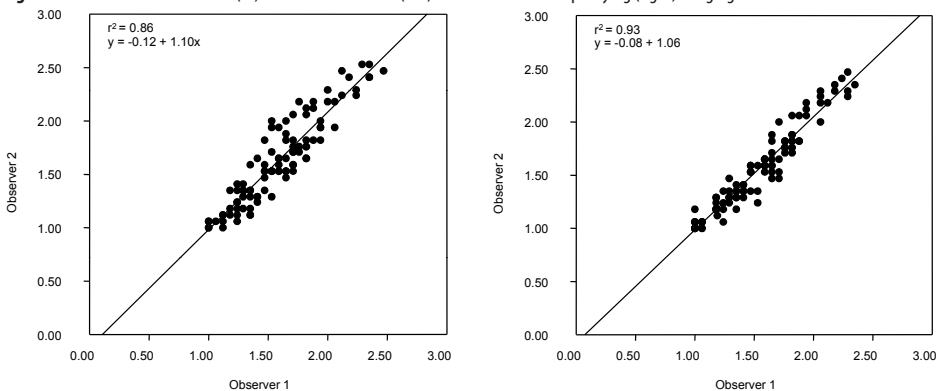
Figure 3b: Segmental distribution of agreement with second harmonic (top) and left ventricular opacifying (bottom) imaging.



Interobserver agreement according to segment visualization: Interobserver agreement and the Kappa value for SH imaging in the 455 poorly visualized segments vs. the 1,245 adequately visualized segments was 72% and 0.52 vs. 78% and 0.62. Interobserver agreement and the Kappa value for LVO imaging in the 173 poorly visualized segments vs. the 1,527 adequately visualized segments was 78% and 0.62 vs. 89% and 0.80.

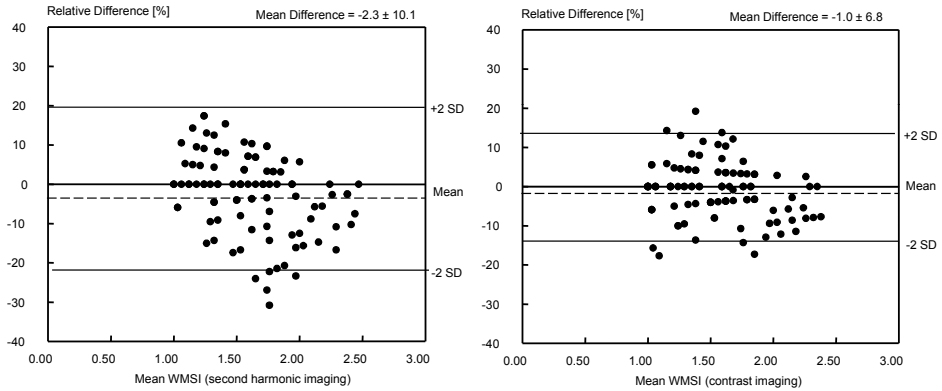
Improvement with LVO according to segment visualization: In the 455 poorly visualized SHI-segments, LVO imaging improved interobserver agreement from 72% to 84% and the Kappa value from 0.52 to 0.72. In the 1,245 adequately visualized SHI-segments, LVO imaging improved interobserver agreement from 78% to 89% and the Kappa value from 0.62 to 0.80.

Figure 4: Interobserver correlation (r^2) for second harmonic (left) and left ventricular opacifying (right) imaging.



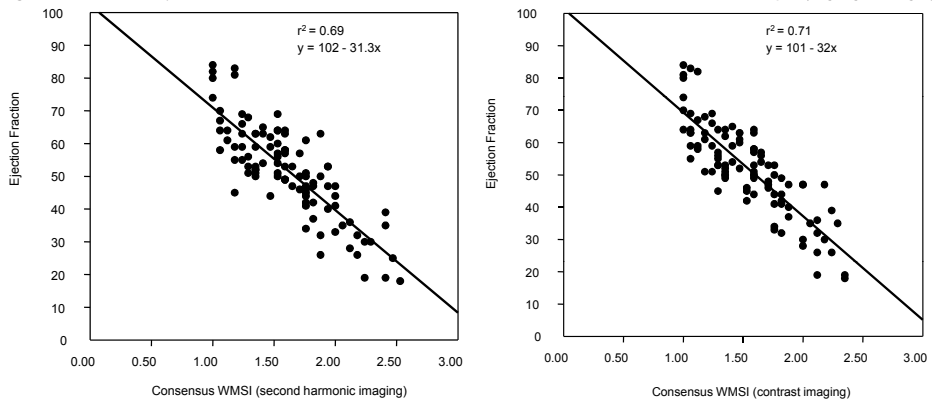
WMSI interobserver agreement: As seen in Figure 4, interobserver correlation (r^2) was 0.86 for the SH-imaged WMSI and 0.93 for the LVO-imaged WMSI. As seen in Figure 5, interobserver limits of agreement for LVO-imaged WMSI (mean relative difference $-1.0\% \pm 6.8\%$, agreement -14.6% , 12.6%) was better than that for SH-imaged WMSI (mean relative difference $-2.3\% \pm 10.1\%$, agreement -22.5 , 17.9).

Figure 5: Interobserver limits of agreement for second harmonic (left) and left ventricular opacifying (right) imaging.



Correlation of WMSI with LV-EF: Mean consensus WMSI was 1.62 ± 0.37 for SH and 1.55 ± 0.37 for LVO imaging and mean LV-EF was $52 \pm 14\%$ (range 18 to 84%). As seen in Figure 6, the 17 segments based on SH and LVO imaging WMSI correlated well with LV-EF ($r^2 = 0.69$ and 0.71 , respectively).

Figure 6: Correlation of ejection fraction with the wall motion score index based on harmonic (left) and left ventricular opacifying (right) imaging.



DISCUSSION

Calculation of LV-EF by manual tracing of endocardial borders at end-diastole and end-systole in at least two views remains a tedious and time-consuming task. In many cases, identification of the endocardial border requires analysis of the moving and still standing images using both the cine-loop and frame-by-frame features of the system. The semi-quantitative WMSI forms an alternative global estimate of systolic LV function. In this index, endocardial motion for each defined myocardial segment is described as normal, hypokinetic, akinetic, or dyskinesic, with a score ranging from 1 to 4 corresponding to these descriptive terms.¹⁵ An overall WMSI can be derived by dividing the sum of scores for each myocardial segment by the number of segments evaluated. In our study 17 LV segments were evaluated, in accordance to the latest recommendations.¹⁴ It is surprising that in only a few studies the WMSI was validated and that in these studies the extent of endocardial excursion that defined hypokinesia was not mentioned at all.^{5,6,17} In our study we defined hypokinesia as segmental motion <7mm, a value derived from normal values for end-diastolic and end-systolic LV dimensions described in standard references.¹⁸

Accurate identification of the LV endocardial border is crucial in the echocardiographic evaluation of LV systolic function. Unfortunately, endocardial border definition is sometimes negatively influenced by anatomic and technical (poor lateral resolution, skill of the sonographer) factors.⁷ Therefore, we used LVO contrast to optimize LV endocardial border definition and for the first time determined the value of the contrast-enhanced WMSI. Compared to SH imaging, LVO-imaged myocardial segments were visualised better and interobserver agreement for segmental wall motion and the WMSI improved. Surprisingly, this was not only true for poor visualized segments with SH imaging but also for moderate-to-good visualized segments.

The clinical importance of the WMSI was recently confirmed in a study from the Mayo clinic.⁵ The WMSI is not only a more readily available estimate of systolic LV function but had also greater predictive power than LV-EF in patients after acute myocardial infarction.⁵ As seen in the Table, the results of all published^{5,6} and our formulas to estimate LV-EF from the WMSI are quite similar, regardless of the golden standard for LV-EF (standard or contrast echocardiography, or nuclear). In most patients the following rule of thumb can be applied for 16 or 17-segment LV models: $LV-EF = 70\% - 2\%$ for each wall motion abnormality (akinesis equals $2 \times 2\%$ penalty points) or $LV-EF = 1 - (0.3 \times WMSI)$. In patients with mild to moderate impaired LV function ($WMSI < 2.50$) this rule of thumb has an error margin less than 5% when compared to all the formulas shown in the Table. In patients with severely impaired LV function ($WMSI \geq 2.50$), LV-EF is somewhat underestimated by this rule of thumb, as it is with eyeballing. In these patients the following common sense rules can be used in addition: a LV-EF below 10% is very rare and when some LV motion is seen the LV-EF is usually in the range of 15 to 20%.

CONCLUSION

Echo contrast improves interobserver agreement for wall motion scoring and the WMSI. The LVO-imaged WMSI correlates well with LV-EF and may serve as an accurate surrogate marker for LV-EF.

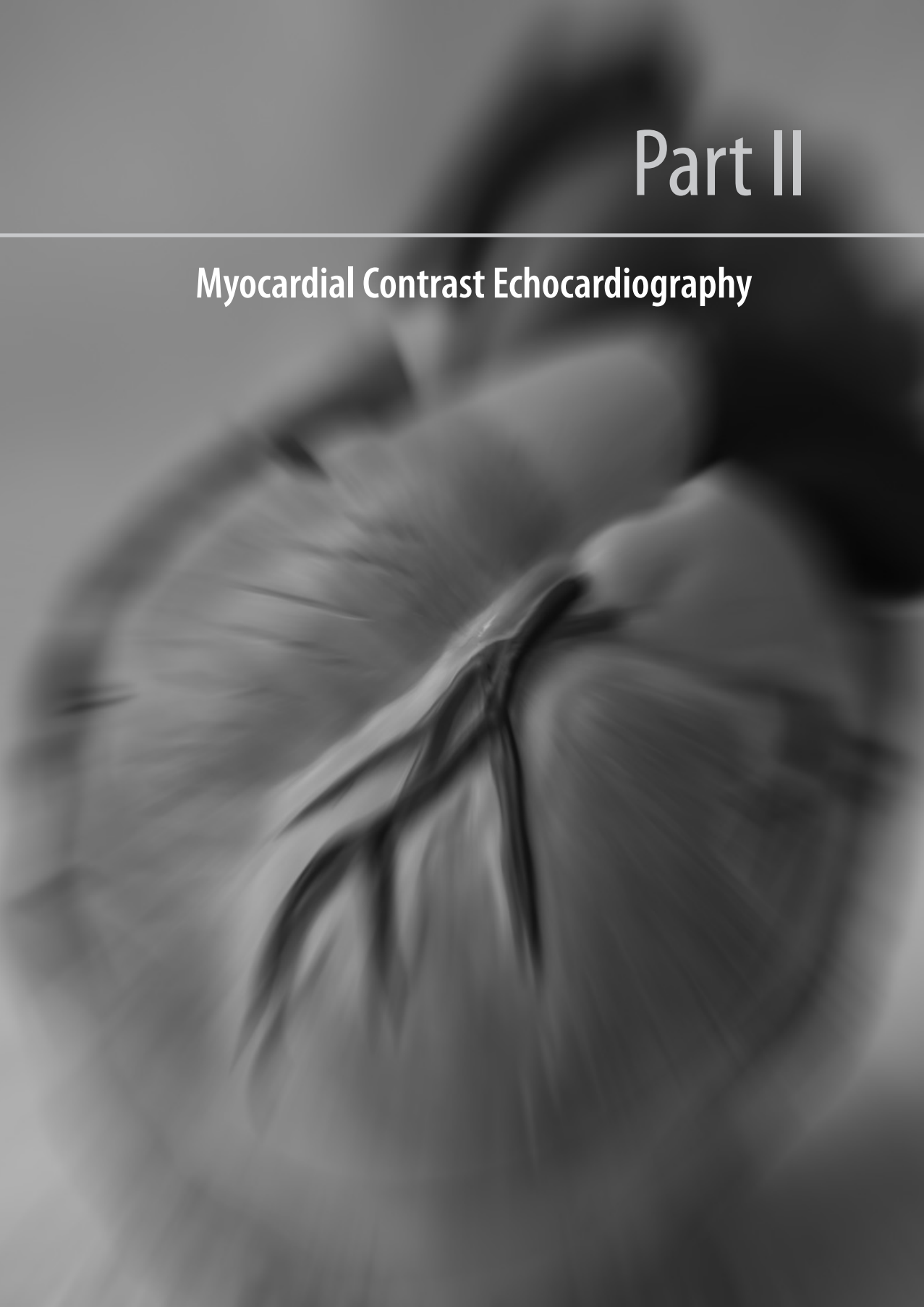
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Part II

Myocardial Contrast Echocardiography



Chapter 6

Diagnosis of Non-Compaction Cardiomyopathy with Contrast Echocardiography

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Roelandt JR

Int J Cardiol. 2004; 94(1): 127-8.

INTRODUCTION

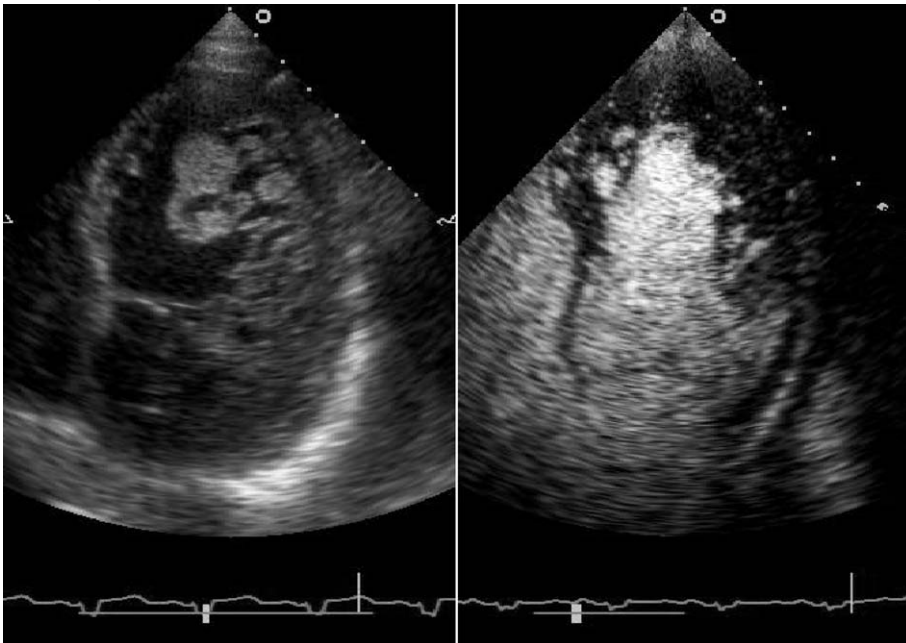
Non-compaction cardiomyopathy (NCC) is a rare disorder characterized by excessive and prominent trabeculation of the left ventricle (LV). Prominent trabeculae are seen in the right ventricle (RV) but this is very unusual after birth in the left ventricle. We describe a patient with obvious non-compaction cardiomyopathy diagnosed with contrast echocardiography.

CASE REPORT

A 35-year-old man consulted our hospital for gradual onset of dyspnea, orthopnea, palpitations and nausea since 2 months. Physical examination showed signs of heart failure: elevated jugular venous pressure, enlargement of the liver and edema of both lower legs. His pulse rate was 120 bpm and blood pressure 110/85 mm Hg. Electrocardiography demonstrated sinus rhythm, right axis deviation and left bundle branch block. Chest X-ray showed bilateral stasis.

Admission transthoracic echocardiography revealed a dilated left atrium and LV with severely impaired systolic function (Figure 1). An echo-dense mobile mass was visible at the apex. Multiple prominent muscular trabeculations were present in the LV most evident

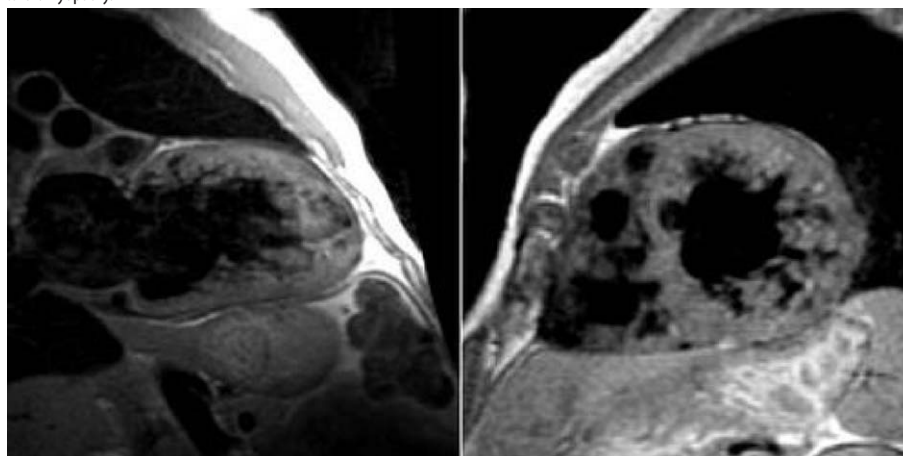
Figure 1: Two-dimensional echocardiography apical four-chamber view with (right) and without (left) contrast. Excessive and prominent trabeculation of the left ventricle is visible. The contrast shows the communication between the recesses and ventricular cavity. A thrombus is visible at the apex.



at the apical and the infero-lateral wall. Deep intertrabecular spaces were evident on the two-dimensional echo with contrast. These findings are pathognomonic for ventricular non-compaction. Both the RV and right atrium (RA) were enlarged with decreased RV function.

Treatment with enoximon, dopamin, nitroglycerin and heparin was started. After 5 days had the patient a clinical recovery and he is now treated with an ACE-inhibitor, anticoagulants and diuretics. Three days after admission, magnetic resonance imaging (MRI) confirmed trabeculations of both the LV and RV and the mass in the apex seen a few days earlier was disappeared (Figure 2). This was confirmed by repeated echocardiography with and without contrast.

Figure 2: MRI two-chamber (left) and short-axis view (right). Multiple prominent trabeculations are present in the LV at the apical and the infero-lateral wall with an end-systolic ratio of non-compacted to compacted layer of 3. More than 2 is diagnostic for non-compaction cardiomyopathy.



DISCUSSION

During normal embryogenesis, the loosely interwoven meshwork of myocardial fibers becomes more compact towards the epicardial surface and condenses to a compact wall. NCC is thought to be related to an arrest in this process resulting in a thickened left ventricular wall with deep intertrabecular recesses.¹

Many diagnostic modalities have been evaluated for diagnosis of NCC. CT and MRI can provide high-resolution imaging of non-compacted myocardium and may indicate a disturbed microcirculation due to fibrosis and thrombus formation.²

Characteristics on echocardiography have been defined as absent coexisting cardiac abnormalities, non-compacted trabecular endocardium with deep endomyocardial spaces, predominant localisation of the trabeculation to mid-lateral, apical and mid-inferior segments, and a colour Doppler evidence of deep perfused intertrabecular recesses.³

As bloodflow is low in the spaces between the trabeculations, the communication between the recesses and the ventricular cavity can be missed using conventional colour Doppler. For

that reason, we used intravenous contrast (Sonovue®, Bracco, Italy). Only one previous case report described the use of contrast to diagnose NCC.⁴The echo-dense mass was assumed to be a ventricular thrombus and was treated with heparin.

CONCLUSION

In echocardiography, the use of echo contrast can be very helpful to confirm the connection of the intertrabecular spaces and the LV cavity. It can also be helpful to improve visualisation of trabeculations in patients with poor baseline echo images. Together with greater understanding and awareness, it is likely that an increased number of patients will be diagnosed with NCC in an earlier disease stage.

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Chapter 7

Usefulness of Power Doppler Contrast Echocardiography to identify Reperfusion after Acute Myocardial Infarction

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Am J Cardiol. 2001; 87(3): 278-82.

ABSTRACT

Microvascular integrity, as seen by myocardial contrast echocardiography (MCE), assesses whether myocardium has been successfully reperfused after an acute myocardial infarction. Until now this has been demonstrated only with intracoronary injection of an ultrasound contrast agent. Power Doppler imaging is a recently developed myocardial contrast echocardiographic method that counts the contrast microbubbles destroyed by ultrasounds and displays this number in colour. This study sought to evaluate whether power Doppler MCE is able to visualize myocardial reperfusion during intravenous contrast injection. Thirty patients were evaluated 2 days after their first myocardial infarction during intravenous infusion of perfluorocarbon-exposed sonicated dextrose albumin (PESDA). Coronary artery angiography and single-photon emission computed tomography (SPECT) were used as reference techniques. A 16-segment left ventricular model was used to relate perfusion to coronary artery territories. Sensitivity and specificity of power Doppler MCE for segments supplied by infarct related arteries were 82% and 95%, respectively. Accuracy of power Doppler MCE and SPECT were similar (90% vs. 92% on segmental basis and 98% vs. 98% on coronary artery territory basis). Two-dimensional echocardiography was repeated after 6 weeks. Segments recovering wall motion after 6 weeks were defined as stunning myocardium. Dysfunctional but perfused myocardium at day 2 after the infarction showed a better late recovery of wall motion compared with dysfunctional but nonperfused myocardium ($p < 0.001$). In conclusion, harmonic power Doppler imaging is a sensitive and specific method for the identification of myocardial reperfusion early after myocardial infarction. It yields prognostic information for late recovery of ventricular function differentiating stunning (dysfunctional but perfused) from necrotic myocardium (dysfunctional and nonperfused).

INTRODUCTION

The best approach to determine whether myocardium has been successfully reperfused after an acute myocardial infarction is to assess microvascular integrity.^{1,2} Despite the presence of an open artery, myocardial perfusion may not be achieved because of microvascular disruption (“no reflow phenomenon”).^{3,4} Moreover, it has been shown that microvascular integrity predicts the outcome in patients with a first acute myocardial infarction.⁵⁻¹⁰ Of currently available techniques, intracoronary myocardial contrast echocardiography (MCE) is a recognized method to assess microvascular integrity.³⁻¹⁰ It uses microbubbles that are pure intravascular tracers that allow unique information about capillary flow to be obtained. Recently, it has been shown that myocardial perfusion could be studied using a peripheral intravenous injection of echocontrast agents.¹¹⁻¹³ Particularly, the newer ultrasound contrast agents that contain a high molecular weight gas show great promise for the detection of myocardial ischemia.¹⁴⁻¹⁷ Current studies have either used gray-scale harmonic imaging or colour-coded imaging obtained from subtracted gray-scale images.^{11,12} Power Doppler imaging is a recently developed myocardial contrast echocardiographic method that counts the contrast microbubbles destroyed by ultrasounds and displays this number in colour. Therefore, it can selectively evaluate the signal coming from an ultrasound contrast agent. We hypothesized that this new imaging modality could provide an assessment of myocardial reperfusion after a recent myocardial infarction.

METHODS

Patients: Thirty consecutive patients with a first acute myocardial infarction were enrolled in the study. The diagnosis of acute myocardial infarction was made on the basis of chest pain lasting >30 minutes, ST elevation of ≥ 2 mm in 2 contiguous electrocardiographic leads, and an increase in serum creatine kinase to more than twice the upper limit of normal. All patients were in stable clinical condition at day 2 after the infarction. No patient underwent coronary artery angioplasty (primary or rescue). Ten patients (33%) did not receive thrombolytic therapy because of delayed arrival to the hospital. Patient characteristics are described in Table 1. The institutional review board of the hospital approved the study protocol, and the patients gave oral informed consent for participation in the study.

Control group: Fifteen healthy volunteers with normal wall motion were enrolled in the study to check for accuracy of power Doppler MCE imaging in normal patients. Images were analyzed by technicians who were blinded to wall motion score, in a random order with the MCE images of the 30 patients with acute myocardial infarction.

Study protocol: Each patient underwent intravenous MCE on the second day after admission. Coronary angiography was performed as close as possible to MCE and was considered the primary gold standard technique. Technetium-99m-sestamibi single-photon emission computed tomography (SPECT) at rest was performed in 18 patients, also before hospital discharge. Follow-up 2-dimensional echocardiography was performed after 6 weeks to evaluate possible wall motion recovery.

Myocardial contrast echocardiography: MCE was performed with a Hewlett-Packard Sonos 5500 (Andover, Massachusetts) during continuous intravenous infusion of perfluorocarbon-exposed sonicated dextrose albumin (PESDA) using second harmonic mode (1.8 to 3.6 MHz) and power Doppler imaging. Images were acquired at end-systolic triggering every fifth cardiac cycle. Standard apical 4-, 2-, and 3-chamber views were acquired.

Contrast medium: PESDA was prepared as previously described.¹⁵ Briefly, 8 ml of perfluorobutane was hand agitated with a 3:1 mixture of 5% dextrose and 5% human albumin. This mixture then underwent electromechanical sonication for 80 seconds. The mean microbubble size of PESDA is $4.7 \pm 0.2 \mu\text{m}$ with a mean concentration of 1.3×10^9 microbubbles per milliliter.¹⁵ The total amount of infused PESDA was 0.04 ml/kg. This dose was diluted in 40 ml of saline 0.9% and was administered intravenously using an infusion pump. The rate of infusion was adjusted accordingly to the operator's opinion of image quality. Mean rate of infusion was $1.8 \pm 0.4 \text{ ml/min}$.

Power Doppler setting: Before starting the contrast injection, the pulse repetition frequency was set to 2.5 kHz and power Doppler gain was adjusted from its maximal setting downward until colour (wall motion artifact) disappeared and the myocardium was gray. In case of colour persistence at low gain (<50%), the power Doppler pulse repetition frequency was increased until the myocardium was gray (maximum pulse repetition frequency 3.0 kHz). This setting was fixed before contrast injection and held constant throughout all of the acquisition. When premature ventricular contraction or deep breath occurred, the relative frames were ignored because of possible wall motion artifact. The mechanical index was set at 1.5 MPa. Because the displayed mechanical index reflects only the value around the focal point, the focus was moved at the level of potential perfusion defects to eliminate false-positive perfusion defects.

Analysis of myocardial contrast echocardiographic perfusion: A 16-segment left ventricular model was used for myocardial perfusion analysis. Myocardial perfusion was scored as 0 = contrast deficit, 0.5 = partial perfusion, and 1 = complete perfusion. Perfusion pattern was scored separately by 2 observers who were blinded to wall motion data. Analysis was performed on 5 consecutive single stop-frames acquired during end-systolic triggering. Ob-

servers were unaware of clinical, angiographic, and wall motion data. Grade 1 was considered normal and grades 0 and 0.5 abnormal. Each of the 16 segments was assigned a priori to 1 of the 3 coronary arteries (left anterior descending, left circumflex, or right coronary artery). Both apical segments of the lateral wall and inferior wall were assigned to the left anterior descending artery. At the end of the analysis the observers had to relate the myocardial perfusion defect to the coronary artery territory.

Wall motion assessment: Wall motion was scored by a third experienced observer using the same 16-segment left ventricular model. The observer was unaware of clinical data and MCE perfusion data. Each segment was examined for systolic thickening and wall motion was scored using a 4-point scale: normal = 1, hypokinetic = 2, akinetic = 3, and dyskinetic = 4. Baseline and follow-up (after 6 weeks) data were compared to evaluate late wall motion recovery of dysfunctional segments.

Single-photon emission computed tomography: SPECT was performed at rest for assessment of myocardial perfusion by intravenous administration of 600 MBq of technetium-99m-sestamibi. Images were acquired by a large field-of-view gamma camera (Siemens Corp., Erlangen, Germany). Tomographic images were created. The horizontal and vertical longaxis images closest to the echocardiographic apical 4- and 2-chamber views were chosen for the analysis (12-segment model). Two observers, blinded to the MCE and coronary angiography data, scored the myocardial perfusion as normal or abnormal in each available segment that was assigned a priori to 1 of the 3 coronary arteries, which is consistent with the model used for MCE analysis.

Coronary angiography: Angiography was performed before hospital discharge for identification of the infarct-related coronary artery as the end point test.

Variability analysis: Inter- and intraobserver variability for MCE perfusion were determined by 2 independent observers and by 1 observer at 2 different readings 30 days apart. Kappa coefficients were calculated by test of symmetry.

Statistical analysis: Differences were evaluated by analysis of variance for repeated measures or by paired Student's *t* test when appropriate. A *p* value <0.05 was considered statistically significant.

RESULTS

Control group: Myocardial perfusion was detectable in all 15 healthy volunteers (mean age 51 ± 11 years, 10 men). Using power Doppler imaging, normal perfusion was seen in 93% of healthy volunteers (14 of 15). One false-positive defect was detected in the lateral wall.

Patients characteristics: The clinical and angiographic characteristics of patients are described in Table 1. No patients were excluded from the study for nonadequate acoustical window. All the 30 patients had had their first acute myocardial infarction and were clinically stable at day 2. At coronary angiography, 5 patients had >1 coronary lesion. In these patients, the infarct-related artery was determined according to the electrocardiographic data.

Age (yrs)	56 ± 11
Men	22 (73%)
Anterior MI on ECG	11 (37%)
Inferior and/or posterolateral MI on ECG	19 (63%)
Thrombolytic therapy	20 (67%)
No thrombolysis	10 (33%)
Peak creatine kinase	$1,545 \pm 1,031$
Q-wave infarction	28 (93%)
Non-Q-wave infarction	2 (7%)
Infarct artery	
Left anterior descending	11 (37%)
Left circumflex	13 (43%)
Right	6 (20%)
Occluded vessel	3 (10%)
Occluded vessel with collateral flow	3 (10%)
Stenotic vessel ($>70\%$) \leq TIMI 2 flow	11 (37%)
Stenotic vessel ($>70\%$) TIMI 3 flow	11 (37%)
Mild stenotic vessel ($<70\%$) TIMI 3 flow	2 (6%)

ECG = electrocardiogram; MI = myocardial infarction.

Variability of power Doppler myocardial contrast echocardiography: Table 2 shows the inter- and intraobserver concordance and agreement for power Doppler MCE images. Concordance was calculated for segmental score and for normal versus abnormal perfusion (score 1 vs 0, 0.5). Inter- and intraobserver concordance and agreement were excellent.

	Intraobserver	Interobserver
For actual segmental scores	95% (k=0.90)	92% (k=0.84)
For abnormal vs normal segments	97% (k=0.94)	95% (k=0.89)

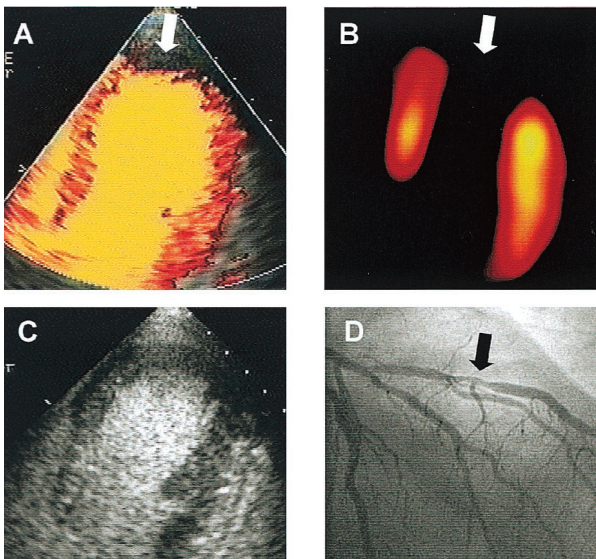
Myocardial contrast echocardiography: As was mentioned previously, no adverse events occurred during the PESDA infusion. Myocardial perfusion was detectable in all the patients. Of the 480 potentially available segments, 429 were analyzable. Thirty-seven percent of segments (158 of 429) were supplied by an infarct-related coronary artery as shown by coronary

angiography, which was the end point of the study. Mean perfusion score in normal segments was higher than in segments supplied by infarct-related coronary artery (0.97 ± 0.12 vs 0.50 ± 0.32 ; $p < 0.001$). Sensitivity and specificity for detection of segments supplied by the infarct-related coronary artery were 82% (129 of 158) and 95% (407 of 429), respectively.

Table 3 compares sensitivity and specificity of power Doppler MCE and SPECT for the detection of the infarct-related vessel as assessed by coronary angiography. The results of power-Doppler MCE and SPECT were comparable (Figure 1). Concordance between power Doppler MCE and SPECT for detection of abnormal versus normal myocardial perfusion in a segment-by-segment analysis was high (93% [181 of 195], kappa = 0.82). The angiographic

TABLE 3 Accuracy for Infarct-Related Coronary Artery (left anterior descending, circumflex, and right coronary)		
	SPECT	Power Doppler MCE
Segment by segment analysis		
Sensitivity	84% (48/57)	82% (130/158)
Specificity	94% (151/159)	95% (257/271)
Accuracy	92% (199/216)	90% (387/429)
Territory by territory analysis		
Sensitivity	94% (17/18)	93% (28/30)
Specificity	100% (36/36)	100% (60/60)
Accuracy	98% (53/54)	98% (88/90)
No significant difference was found between SPECT and power Doppler MCE.		

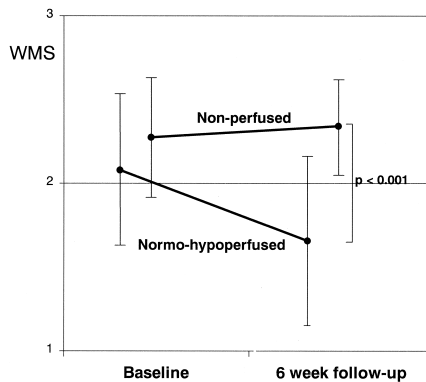
Figure 1: An apical defect of myocardial perfusion is visible both in the power Doppler myocardial contrast echocardiography 4-chamber view (A) and in SPECT (B). Gray-scale contrast echocardiography is shown for comparison (C). Angiography shows the lesion of the left anterior descending coronary artery related to the infarction (D).



Thrombolysis In Myocardial Infarction (TIMI) flow had a strong correlation with MCE perfusion: excluding the 3 patients with occluded vessels but collateral flow, 10 of the 13 patients (69%) with TIMI 3 flow had MCE perfusion in the infarct-related area, whereas only 1 of the 14 patients (7%) with TIMI flow ≤ 2 had MCE perfusion in the infarct-related area (10 of 13 vs 1 of 14; $p = 0.003$). Creatine kinase peak was also strongly related to MCE perfusion (inverse correlation): excluding the 2 patients with prolonged resuscitation, the 13 patients with MCE perfusion (score 1, 0.5) had significantly lower creatine kinase peaks compared with the 15 patients with no perfusion in the infarct-related area (948 ± 866 vs $2,019 \pm 935$; $p = 0.004$).

Follow-up: Figure 2 shows wall motion changes of dysfunctional segments from baseline to 6-week follow-up, comparing hypo- or normoperfused segments with nonperfused segments as assessed by power Doppler. Late wall motion recovery was higher in dysfunctional segments that were perfused at day 2 after infarction (-0.41 ± 0.38 vs. $+0.06 \pm 0.24$; $p < 0.001$).

Figure 2: Wall motion score (WMS) changes of dysfunctional myocardium from baseline (day 2 after the infarction) to 6-week follow-up. Dysfunctional but perfused myocardium (stunning myocardium) recovered wall motion at follow-up, whereas dysfunctional but nonperfused myocardium (necrotic myocardium) worsened. The difference was statistically myocardium significant.



DISCUSSION

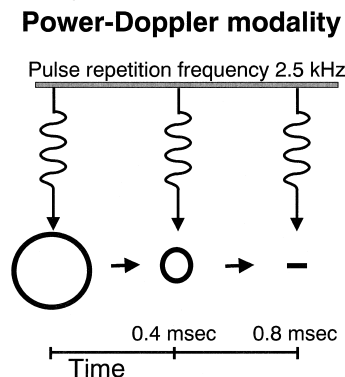
This study demonstrates that harmonic power Doppler imaging, using intravenous infusion of ultrasound contrast agent, detects myocardial perfusion defects in patients with a recent Q-wave myocardial infarction. Power Doppler MCE imaging and SPECT imaging showed excellent concordance for myocardial perfusion in a segment-by-segment analysis (93% [$\kappa = 0.82$]). In the group of healthy volunteers, power Doppler imaging assessed normal perfusion in 93% of patients.

Assessment of reperfusion: Follow-up echocardiographic results showed that dysfunctional but perfused myocardium recovered wall motion, whereas dysfunctional but nonperfused myocardium worsened. The difference was statistically significant ($p < 0.001$) (Figure 2). We

considered reperfused both normoperfused and hypoperfused segments (partial or patchy perfusion), because both perfusion patterns indicate microvasculature integrity. Therefore, power Doppler MCE on day 2 after myocardial infarction was able to predict functional recovery of myocardium, differentiating stunning myocardium (dysfunctional but perfused or hypoperfused) from necrotic myocardium (dysfunctional and nonperfused).¹⁸ In this respect, these results confirm earlier studies performed using intracoronary injection of ultrasound contrast agents.^{5,8} Moreover, there were strong correlations with angiographic TIMI flow and creatine kinase peak.

Rationale for power Doppler myocardial contrast echocardiography: Power Doppler modality is completely different from the gray-scale modality. In gray-scale, the medium is interrogated only once with a short pulse. The scatter magnitude is displayed as a gray value. In power Doppler imaging, the medium is interrogated several times and the subsequent scatter responses are compared with each other. Usually, 3 to 8 pulse trains are sent in series with a short interval between them. The first pulse train hits the microbubbles of the contrast agent. The microbubbles start to resonate, producing harmonics at the end break. The following pulse train finds the microbubbles in a different state or does not find the microbubbles at all (Figure 3). Therefore, the backscatter will be different and the system will display this difference in colour. If the myocardium is not perfused, it does not receive any microbubbles and there will be no difference between the signal generated from the first pulse and the following pulse. In this case, power Doppler imaging will not show any colour. If microbubbles are present in the myocardium (microvascular integrity), it will show the predefined colour that represents the number of microbubbles that change state and are destroyed in that region. By using power Doppler imaging, the presence of microbubbles (perfusion or no perfusion) is easy to assess. Therefore, in this study, intra- and interobserver variability for myocardial perfusion were excellent (Table 2).

Figure 3: Power Doppler mode sends several pulse trains in series with a short interval after each one (pulse repetition frequency). The first pulse train hits the microbubble, which starts to resonate and at the end breaks. The second pulse train finds the microbubble in a different state. The third pulse train does not find the microbubble. The 3 reflected scatter signals are different. The power Doppler mode analyzes these differences of backscatter and displays the grade of comparison in color.



Study limitations: The main clinical limitation of this study is that MCE was performed on day 2 after infarction. The higher usefulness of myocardial perfusion identification should be in the acute phase of myocardial infarction for the assessment of reflow immediately after thrombolysis. However, the infarct size may be underestimated by MCE immediately after reflow because of the possibility of reactive hyperemia. Previous reports have suggested that the best time to assess microvascular perfusion may be 12 to 24 hours after myocardial infarction, when hyperemia is not present anymore.^{1,19} The main limitation of power Doppler mode is the presence of wall motion artifacts. Power Doppler mode analyzes differences between the backscatter of the first pulse train and the following pulse train. This difference is generated by microbubbles that change state and at the end break when hit by ultrasound. Unfortunately, tissue movement also generates differences of backscatter. However, when baseline setting of power Doppler is well done before contrast injection, no signal comes from the contracting myocardium that is completely gray (without any colour). This setting is held constant throughout acquisition. Therefore, power Doppler imaging is not due to wall motion because colours appear only after contrast injection. Wall motion artifacts can appear only because of premature ventricular beats or deep breath, but the operator can easily recognize the problem and ignored the relative frame.

CONCLUSIONS

Power Doppler imaging during intravenous infusion of perfluorocarbon microbubbles is accurate in detecting reperfusion early after an acute myocardial infarction. By assessing microvascular integrity and consequent myocardial viability, power Doppler contrast echocardiography is a non-invasive technique able to predict late ventricular function recovery differentiating stunning (dysfunctional but perfused) from necrotic myocardium (dysfunctional and nonperfused).

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Chapter 8



Myocardial Wall Thickness predicts Recovery
of Contractile Function after Primary Coronary
Intervention for Acute Myocardial Infarction

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ABSTRACT

Objectives: We sought to determine whether end-diastolic wall thickness (EDWT) can predict recovery of regional left ventricular contractile function after percutaneous coronary intervention (PCI).

Background: Regional contractile function does not recover in all patients after PCI for acute myocardial infarction (AMI). Prediction of functional recovery after AMI may help in clinical decision making.

Methods: Forty consecutive patients with AMI were studied with left ventricular contrast echocardiography for accurate wall thickness and function measurement and myocardial perfusion immediately after and two months following PCI.

Results: Out of 640 segments, 175 (27%) dysfunctional segments in the infarct territory were analyzed for EDWT, wall function, and perfusion. One hundred and three (59%) dysfunctional segments presented with an EDWT <11 mm and 72 (41%) presented with an EDWT \geq 11 mm. Perfusion (partial or complete) was present in 63 segments with an EDWT <11 mm (61%) and 71 segments with an EDWT \geq 11 mm (99%) ($p < 0.001$). At two months' follow-up, 66 of 72 segments with an EDWT \geq 11 mm (92%) improved, whereas only 35 of 103 of the dysfunctional segments with an EDWT <11 mm (34%) improved ($p < 0.0001$).

Conclusions: Wall thickness is an easy parameter to predict recovery of function after revascularization. Moreover, combining EDWT and perfusion, segments with an EDWT \geq 11 mm, and presence of perfusion have the highest chance of recovery; segments with an EDWT <11 mm and perfusion have an intermediate chance of recovery. In segments with an EDWT <11 mm and no perfusion, chances of recovery are very low.

INTRODUCTION

Early revascularization by percutaneous coronary intervention (PCI) is associated with a good clinical outcome in patients with acute myocardial infarction (AMI).¹ However, in some patients successful PCI does not result in recovery of contractile function in the infarct territory.² Two-dimensional contrast echocardiography allows assessment of wall function and myocardial perfusion simultaneously. It has been shown in several studies that myocardial contrast echocardiography (MCE) allows researchers to predict recovery of regional contractile function after reperfusion in AMI.³⁻⁶ Until now, the end-diastolic wall thickness (EDWT) was not used as a simple parameter to predict functional recovery after PCI. Therefore, myocardial wall thickness was assessed to determine its value as a predictor of recovery of regional contractile function late after PCI. In this study, contrast echocardiography was used for optimal endocardial border delineation.⁷

METHODS

Study patients: This prospective study comprised 40 consecutive patients without history of hypertension, left ventricular hypertrophy, and primary cardiomyopathy, but with ST-segment elevation AMI and who underwent PCI within 6 h of onset of symptoms. Baseline characteristics of the 40 patients (34 male, mean age 53 ± 13 years) are summarized in Table 1. The diagnosis of AMI was made on the basis of symptoms of myocardial ischemia for ≥ 30 min and ≥ 2 mm ST-segment elevation in ≥ 2 contiguous electrocardiographic leads. The infarct-related artery was identified by the site of the coronary occlusion, and stent implantation was performed. Left ventricular hypertrophy was defined according to recommendations of the

Age (yrs, \pm SD)	53 \pm 13
Men	34 (85%)
Smoking	25 (62%)
Diabetes mellitus	4 (10%)
Hypertension	0
Hypercholesterolemia	6 (15%)
Family history of CAD	13 (32%)
Previous myocardial infarction	5 (12%)
EF (%)	45 \pm 6
CK peak (IU)	3,074 \pm 2,245 (n < 200 IU)
Site of infarction	
Anterior	22 (55%)
Lateral	16 (40%)
Septal	2 (5%)
Inferior/posterior	19 (47%)
TIMI flow grade 3 after PCI	33 (82%)

CAD = coronary artery disease; CK = creatine kinase; EF = ejection fraction; SD = standard deviation; TIMI = Thrombolysis In Myocardial Infarction.

American Society of Echocardiography and corrected following the suggestions of Devereux et al.⁸ The left ventricular mass index was derived with normal limits defined as ≤ 125 g/m² for men and ≤ 110 g/m² for women.⁹ The local hospital ethics committee approved the study protocol, and all patients gave informed consent.

Abbreviations and Acronyms

AMI	= acute myocardial infarction
EDWT	= end-diastolic wall thickness
LVEF	= left ventricular ejection fraction
MCE	= myocardial contrast echocardiography
PCI	= percutaneous coronary intervention

Echocardiography and contrast studies: Echocardiography was performed with a Sonos 5500 (Philips, Andover, Massachusetts) using second harmonic mode (1.8-MHz/3.6-MHz), within 24 h following revascularization. After recording baseline, myocardial perfusion images were obtained in real time (power modulation) using a low mechanical index (0.1). A slow bolus of 0.75 ml of Sonovue (Bracco, Milan, Italy) was intravenously injected followed by a slow saline flush (5 ml) over 5 s. Imaging was started before contrast injection and “flash” imaging with high mechanical index (1.6) was used at peak contrast intensity for four frames to destroy the microbubbles in the myocardium, to exclude artifacts, and to visualize myocardial contrast replenishment. To obtain maximal image information, the segments related to the infarct territory were placed in the center of the echo sector reducing the problem of artifacts. After the real-time perfusion study, left ventricular opacification images were recorded in all standard parasternal and apical views to improve quantitative assessment of myocardial function.⁷ Left ventricular ejection fraction (LVEF) was measured using the standard biplane Simpson method. Improvement of LVEF $\geq 5\%$ was considered significant.¹⁰ A follow-up study with MCE to reassess EDWT, function, and perfusion was performed at two months.

EDWT measurement: The EDWT was measured by two experienced observers unaware of the clinical data as previously described¹¹, using intravenous echo-contrast for better endocardial border detection.⁷ The EDWT was assessed at the center of each myocardial segment from the leading endocardial edge to the leading epicardial edge as the mean of three measurements. Dysfunctional segments were categorized as segments with an EDWT < 11 mm and an EDWT ≥ 11 mm.

Analysis of echocardiograms: Regional wall motion and myocardial perfusion were scored using standard parasternal long- and short-axis views and apical two-, three-, and four-chamber views, employing a 16-segment model.¹² Only segments related to acute infarct territory were considered for the analysis. Segments were graded as: 1 = normal, 2 = severe

hypokinetic, 3 = akinetic, and 4 = dyskinetic. Myocardial contrast perfusion was scored semi-quantitatively using a 3-point grading scale: 2 = normal/homogenous opacification, 1 = reduced/patchy opacification, and 0 = no opacification. Segments with a severely hypokinetic, akinetic, or dyskinetic wall motion pattern were considered dysfunctional. Recovery of contractile function was defined as an improvement of segmental wall motion score by ≥ 1 grade at the follow-up.

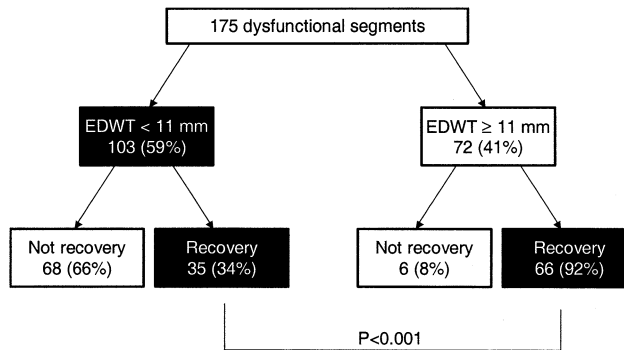
Statistical analysis: All continuous data are expressed as mean \pm SD; percentages are rounded. Differences between proportions were compared with the chi-square test. The agreement for the measurements of EDWT was assessed from 3 x 3 tables using weighted kappa statistics.¹³ A value of $p < 0.05$ was considered statistically significant. The EDWT that was related to a high likelihood of improvement of segmental contraction was determined by receiver operating characteristic curve analysis. The optimal cutoff value was the EDWT that yielded the highest sum of sensitivity and specificity.

RESULTS

Mean time from onset of chest pain to PCI was 3.8 ± 1.8 h. Of a total of 640 segments, 175 (27%) dysfunctional segments were located in the infarct-related territory, and EDWT, wall function, and myocardial perfusion were analyzed. A total of 103 (59%) segments had an EDWT < 11 mm, and 72 (41%) had an EDWT ≥ 11 mm. Both intra- and inter-observer agreements for the assessment of EDWT were 0.96 and 0.93, respectively (kappa value).

Mean EDWT was 9 ± 1 mm for the group with an EDWT < 11 mm, and 12 ± 1 mm for the group with an EDWT ≥ 11 mm. Real-time perfusion MCE imaging demonstrated that 11 (11%) of the 103 dysfunctional segments with an EDWT < 11 mm had normal perfusion, 52 (50%) had partial perfusion, and 40 (39%) had no perfusion. Of the 72 dysfunctional segments with an EDWT ≥ 11 mm, 33 (46%) had normal perfusion, 38 (53%) had partial perfusion, and 1 had absent perfusion.

Functional outcome: At two months' follow-up, 35 of the 103 (34%) segments with an EDWT < 11 mm improved, whereas 66 of the 72 (92%) segments with an EDWT ≥ 11 mm improved ($p < 0.0001$) (Figure 1). Sixty-nine of the 72 (96%) segments with an EDWT ≥ 11 mm became thinner at follow-up (12 ± 1 mm to 9 ± 1.5 mm; $p < 0.05$). Of these 69 segments, 64 (93%) had an EDWT < 11 mm at follow-up. Seventy-two of the 103 dysfunctional segments with an EDWT < 11 mm (70%) became thinner at follow-up (9 ± 1 mm to 7 ± 1.7 mm; $p < 0.05$). Of the 103 dysfunctional segments with an EDWT < 11 mm, 33 (32%) had normal perfusion, 39 (38%) had partial perfusion, and 31 (30%) showed no perfusion at follow-up. In the 72 dysfunctional segments with an EDWT ≥ 11 mm, myocardial perfusion at follow-up was normal in 49 (68%),

Figure 1: Relation between improvement of left ventricular contractile function and end-diastolic wall thickness (EDWT).

partial in 20 (28%), and absent in 3 (4%) segments. A subanalysis was performed considering only the akinetic segments. Of the 100 akinetic segments, 31 of 33 (94%) with an EDWT ≥ 11 mm improved at follow-up, whereas only 20 of 67 (30%) segments with an EDWT < 11 mm improved ($p < 0.001$).

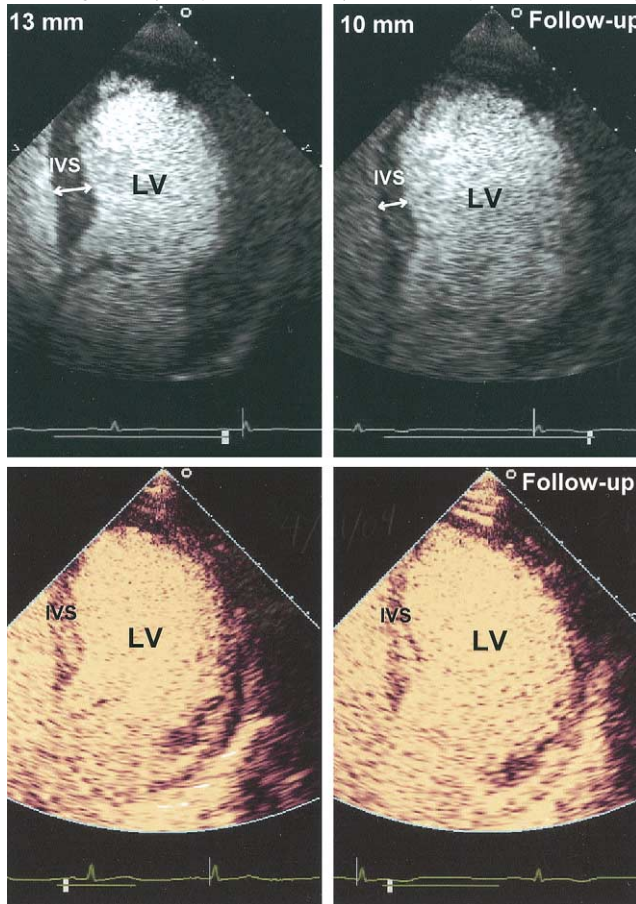
Nearly all patients (15 of 16 patients, 94%) in which ≥ 50% of the dysfunctional segments had an EDWT ≥ 11 mm showed an improved LVEF at follow-up. Conversely, none of the 24 patients in which < 50% of the dysfunctional segments had an EDWT ≥ 11 mm had an improved LVEF at follow-up.

Prediction of recovery by perfusion and wall thickness: To accurately predict functional recovery after revascularization in dysfunctional infarcted areas, information about perfusion and wall thickness should be combined (Table 2). Real-time perfusion MCE imaging demonstrated that perfusion was present in 134 of 175 (77%) dysfunctional segments. In particular, MCE showed that 44 (25%) of the 175 dysfunctional segments had normal perfusion, 90 (51%) had partial perfusion, and 41 (23%) showed no perfusion. However, only 98 (73%) of

Table 2. Comparison Between EDWT and Myocardial Perfusion as Prognostic Indexes of Recovery of Contractile Function at Two Months' Follow-Up	
Category	Number (%) of Segments With Functional Recovery
EDWT ≥ 11 mm	
P+	66/71 (93)
P-	0/1 (0)
EDWT < 11 mm	
P+	32/63 (51)
P-	3/40 (7)
EDWT = end-diastolic wall thickness; P = perfusion (normal or patchy); + = present; - = absent.	

the adequately reperfused segments recovered at follow-up. Adding EDWT measurements of the adequately reperfused segments, 71 (53%) had an EDWT ≥ 11 mm and 63 (47%) had an EDWT < 11 mm. At two months' follow-up, recovery of contractility was present in 66 (93%) of the adequately perfused segments with an EDWT ≥ 11 mm, whereas only 32 (51%) of the adequately perfused segments with an EDWT < 11 mm recovered ($p < 0.001$) (Table 2, Figure 2,3).

Figure 2: Two-dimensional echocardiograms showing end-diastolic wall thickness (upper panels) and perfusion (lower panels) in an infarcted region directly after percutaneous coronary intervention (left panels), and after recovery at two months' follow-up (right panels).

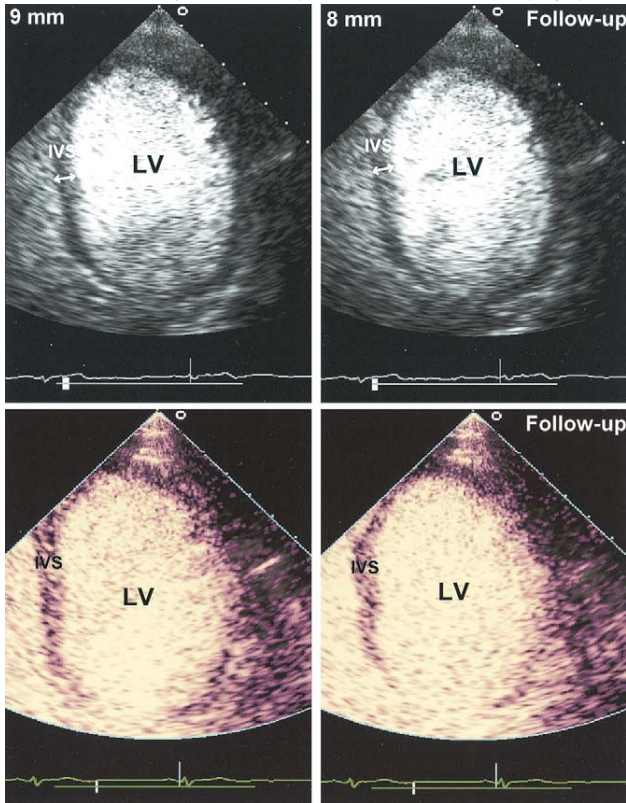


IVS = interventricular septum; LV = left ventricle.

DISCUSSION

Restoration of coronary vessel patency does not automatically result in recovery of contractile function in patients undergoing PCI in the setting of AMI. The main finding of the present study is that a relatively simple measurement of EDWT, obtained with two-dimensional

Figure 3: Two-dimensional echocardiograms showing end-diastolic wall thickness (upper panels) and perfusion (lower panels) in a patient directly after percutaneous coronary intervention (left panels) and at two months' follow-up (right panels), in a case where regional function did not recover.



IVS = interventricular septum; LV = left ventricle.

echocardiography combined with contrast agent, predicts recovery of regional contractile function after PCI for AMI. Using EDWT alone, dysfunctional segments with an EDWT ≥ 11 mm showed a high likelihood of recovery of regional contractile function two months after PCI. Moreover, it appears that when at least 50% of the dysfunctional segments show an EDWT ≥ 11 mm, global recovery may be anticipated. In the present study only 98 (73%) of the adequately reperfused dysfunctional segments had recovery of function at follow-up.

Combining wall thickness and perfusion, segments with an EDWT ≥ 11 mm and presence of perfusion have the highest chance of recovery (93%). An intermediate likelihood of recovery was observed in segments with an EDWT < 11 mm and presence of perfusion (51%), whereas segments with an EDWT < 11 mm and no perfusion nearly never improved. The present results indicate that perfusion data do not provide much additional information for the prediction of recovery of contractile function in segments with an EDWT ≥ 11 mm, because most of them recover at follow-up. Perfusion data are more relevant for the prediction of functional outcome in segments with an EDWT < 11 mm.

Comparison to previous studies: In patients with AMI undergoing PCI, assessment of the amount of myocardial salvage is important for prediction of functional recovery and long-term prognosis. Main et al.⁴ demonstrated that MCE compares favorably with low-dose dobutamine echocardiography for the assessment of myocardial viability after an acute anterior infarction. Balcells et al.⁵ demonstrated that the extent of microvascular integrity assessed by MCE after PCI correlates with recovery of resting left ventricular function and contractile reserve. Lepper et al.⁶ showed that assessment of restoration of myocardial perfusion by MCE after PCI corresponds closely to the evaluation of the microvascular integrity by coronary flow reserve. Moreover, an improvement of myocardial perfusion after revascularization was predictive for subsequent functional recovery. However, EDWT as a predictor of recovery of regional contractile function after PCI has not been specifically addressed.

Possible explanation for the findings: The pathophysiological mechanism underlying the relation between EDWT and long-term recovery of regional contractile function after PCI for AMI is currently not clear. It is conceivable (but speculative) that the high likelihood of recovery in segments with an EDWT ≥ 11 mm is related to hyperemia and tissue edema in adequately reperfused myocardium. During the early phase of reperfusion, reactive hyperemia may occur¹⁴ followed by myocardial tissue edema within the reperfused myocardium.¹⁵ Further studies are needed to elucidate this issue.

Study limitations: A potential limitation of echocardiography to determine myocardial wall thickness is image quality. The use of contrast echocardiography in the present study overcame this limitation because endocardial border detection and EDWT measurements were more accurately assessed, as was shown by Thomson et al.⁷ Another limitation is that wall thickness is heterogeneous throughout the left ventricle. The cut-off value of 11 mm, which was described previously¹⁶, is therefore to some extent arbitrary.

CLINICAL IMPLICATIONS AND CONCLUSIONS

The main finding of the present study is that a relatively simple measurement of EDWT, obtained with two-dimensional echocardiography combined with contrast agent, predicts recovery of regional contractile function after PCI for AMI. Dysfunctional segments with an EDWT ≥ 11 mm had a high likelihood of functional recovery two months after PCI. Moreover, combining wall thickness and perfusion, dysfunctional segments with an EDWT ≥ 11 mm and presence of perfusion have the highest chance of recovery, segments with an EDWT < 11 mm and perfusion have an intermediate chance, whereas segments with an EDWT < 11 mm and no perfusion have a very low likelihood of functional recovery at two months' follow-up. Prediction of recovery of contractile function early after AMI could be useful to identify patients

who have irreversible left ventricular dysfunction. In these patients, tailored therapy can be started, also considering the possibility of automatic defibrillator implantation.¹⁷ Moreover, identification of stunning as the cause of ventricular dysfunction may provide a rationale for the aggressive support of the patients with mechanical methods and perhaps caution against the use of inotropic agents, which may adversely influence the recovery of potentially ischemic segments.¹⁸

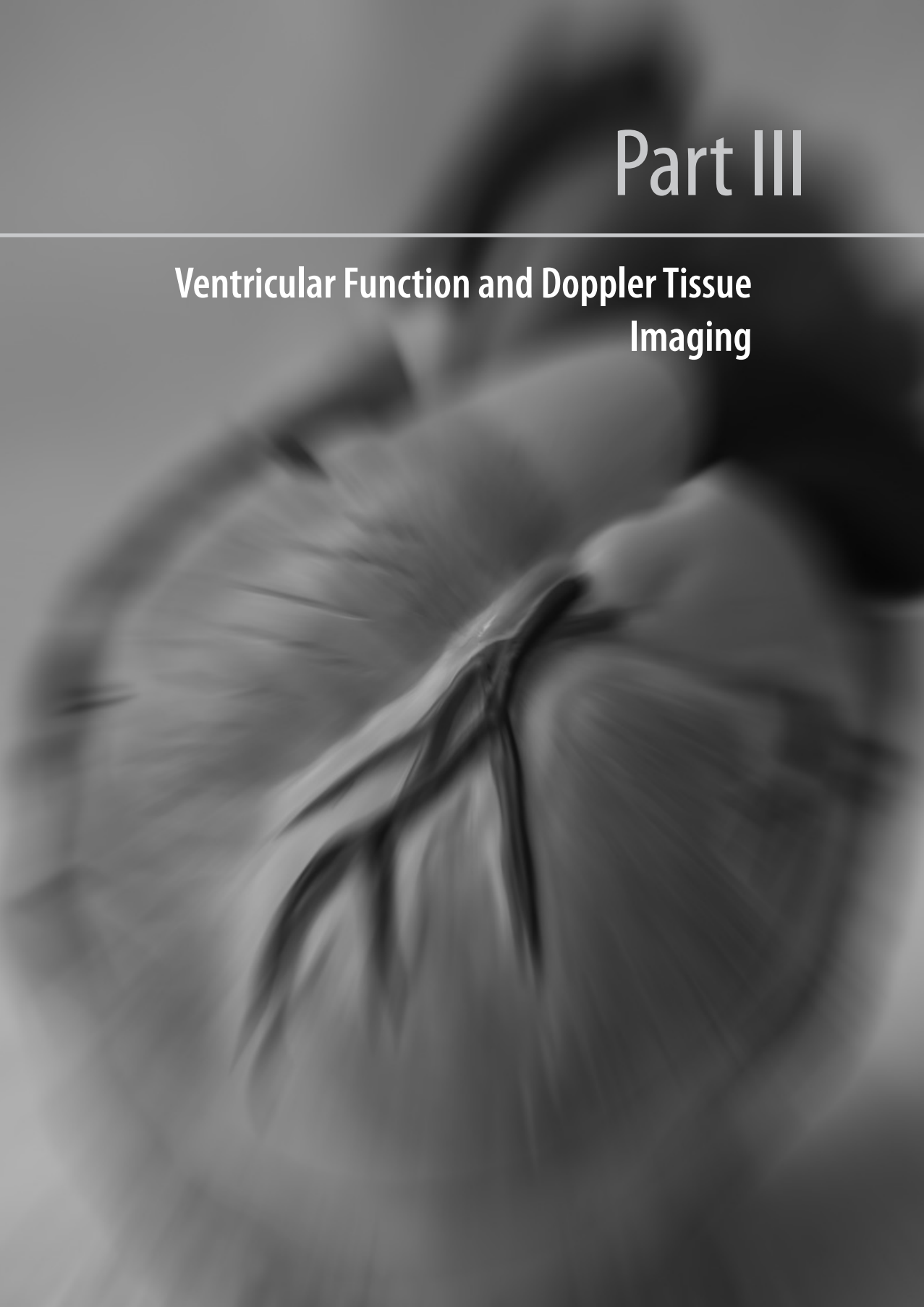
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Part III

Ventricular Function and Doppler Tissue Imaging



Chapter 9

Early Detection of Left Ventricular Dysfunction by Doppler Tissue Imaging and N-terminal-pro-BNP in Patients with Symptomatic Severe Aortic Stenosis

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ABSTRACT

Background: Patients with severe aortic stenosis (AS) require valve replacement before development of irreversible left ventricular (LV) dysfunction. It has been postulated that Doppler tissue imaging (DTI) parameters are more sensitive to detect subtle LV dysfunction compared to conventional echocardiographic parameters.

Objective: We sought to assess early LV dysfunction with DTI-derived echo parameters and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with severe AS and normal LV ejection fraction.

Methods: A total of 29 patients (mean age 65 ± 12 years, 15 male) with symptomatic severe AS and 17 control subjects were included in the study. DTI was performed at the level of the mitral lateral (m_{lat}) and septal (m_{sep}) annulus. Systolic (S_m), early (E_m) and late (A_m) diastolic velocities were measured, and E/E_m ratio was calculated. NT-proBNP was determined by an electrochemiluminescence immunoassay.

Results: Baseline characteristics between patients and controls were similar regarding LV ejection fraction and mitral inflow E/A ratio. However, AS patients had significantly lower DTI values (S_m , E_m , A_m) compared with control subjects. Moreover, LV filling pressures, expressed by the E/E_m ratio, were significantly higher in patients. Correlation analysis showed a relationship between the natural logarithm of NT-proBNP and aortic valve area, $S_{m_{lat}}$, and $E/E_{m_{sep}}$ ratio. Using stepwise multiple linear regression, $S_{m_{lat}}$ was found to be independently related to NT-proBNP.

Conclusions: In patients with severe AS and normal LV ejection fraction, DTI showed LV systolic and diastolic dysfunction compared to controls. DTI-derived variables, and especially $S_{m_{lat}}$, were correlated with NT-proBNP levels.

INTRODUCTION

Patients with symptomatic severe aortic stenosis (AS) are treated with aortic valve replacement for improvement of both symptoms and prognosis.¹ Valve replacement has to take place before irreversible left ventricular (LV) dysfunction develops as this adversely affects postoperative prognosis.² LV systolic dysfunction is most commonly defined as LV ejection fraction (LV-EF) less than 50%, assessed by the modified Simpson's biplane disc method.³ Unfortunately, LV-EF and other conventional echocardiographic parameters are relatively insensitive to detect early forms of LV dysfunction. It has been shown that Doppler tissue imaging (DTI) and N-terminal (NT) pro-B-type natriuretic peptide (BNP) levels can identify early LV dysfunction.^{4,5} In this study we assessed the presence of DTI parameters of early systolic and diastolic LV dysfunction in patients with symptomatic severe AS and normal LV-EF. Furthermore, we investigated the correlation between NT-proBNP, and conventional and DTI echocardiographic parameters.

METHODS

Study Population: The study comprised 29 consecutive patients (mean age 65 ± 12 years, 15 male) with symptomatic severe AS, defined as an aortic valve area (AVA) equal to or less than 1.0 cm^2 or a peak aortic jet velocity greater than or equal to 4.0 m/s and normal LV-EF ($\geq 50\%$). None of the patients had atrial fibrillation, a pacemaker device, significant mitral valve disease or significant aortic regurgitation. Fourteen patients had angiographic coronary artery disease. Seventeen subjects without known cardiac disease, matched for age, sex, LV EF and cardiovascular risk factors, served as control group. The local ethics committee approved the study protocol, and all patients gave written informed consent.

Conventional Transthoracic Echocardiography: Doppler echocardiography was performed with one system (Sonos 7500, Philips, Best, The Netherlands) by a single experienced sonographer. All images were acquired in the standard cardiac views according to the guidelines of the American Society of Echocardiography and digitally stored for offline analysis.⁶ The aortic jet velocity was obtained from multiple windows. Three measurements from the window with the highest velocity were averaged. AVA was calculated with the use of the continuity equation.⁷ LV-EF was assessed by the modified Simpson's biplane disc method.³ For assessment of diastolic function, peak velocities of early (E) and late (A) diastolic filling, E/A-ratio, deceleration time (DT), and isovolumic relaxation time were derived from Doppler recordings of the mitral inflow at the mitral leaflet tips and aortic outflow. LV mass was calculated using the modified Devereux formula.⁸

Tissue Doppler Measurements: Doppler tissue was applied in the pulsed wave Doppler mode at the level of the mitral annulus from the apical 4-chamber view. A 5-mm sample was placed sequentially on the mitral lateral (m_{lat}) and septal (m_{sep}) annulus. To acquire the highest wall tissue velocities, the angle between the Doppler beam and the longitudinal motion of the mitral annulus was adjusted to a minimal level. All recording were done end-expiratory. The average of 3 peak systolic (S_m), early (E_m) and late (A_m) diastolic velocities and E/E_m ratio were calculated, where E is the peak velocity of early diastolic mitral flow.⁹ DTI recordings were adequately obtained in all patients.

Measurements of Neurohormone Level: Venous blood samples were drawn from patients with AS after the Doppler echocardiography study from an antecubital vein into EDTA acid Vacutainer test tubes (Mediost BV, Doesburg, The Netherlands) after 30 minutes of supine rest. Samples were placed immediately on ice, and plasma separation was performed at 4°C. For NT-proBNP determination, an electrochemiluminescence immunoassay (ProBNP Elecsys, Roche Diagnostics GmbH, Mannheim, Germany) was used.

Statistical analysis: Continuous variables are expressed as mean \pm SD or median and ranges, where appropriate. Differences between groups were analyzed with the unpaired t test for continuous variables or χ^2 test for categorical variables. Correlations were sought with Pearson's correlation coefficient. Stepwise multiple linear regression analysis was performed for variables found to be significant in the univariate analysis. A value of P less than .05 was considered significant. For all analyses, commercially available statistical software package was used (SPSS, Version 12.0, SPSS Inc, Chicago, IL).

RESULTS

Clinical data: All patient characteristics are listed in Table 1. Patients with severe AS and the control group were similar with respect to body surface area and heart rate. Main symptoms in the patients with AS were angina in 18 patients (62%), exertional dyspnea in 10 patients (34%) and dizziness in one patient (4%).

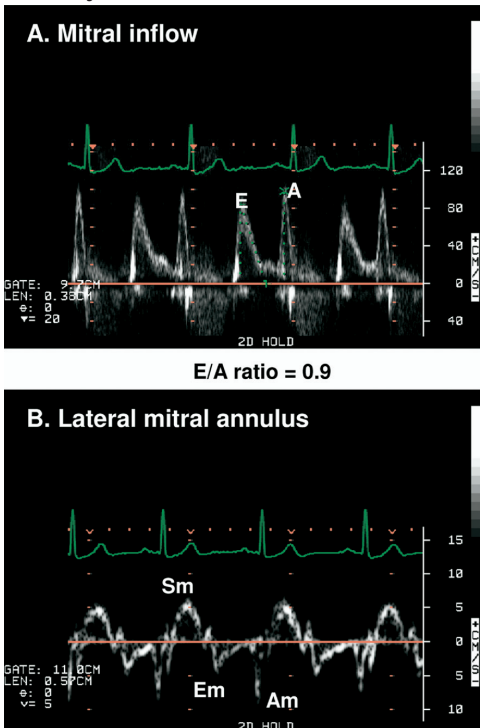
Conventional echocardiographic parameters: As shown in Table 1, mean AVA in the AS group was $0.7 \pm 0.3\text{cm}^2$. LV mass was higher in patients with AS as compared with control subjects. No significant differences were observed with respect to LV dimensions, volumes, or LV EF. In patients with AS, mitral E and A velocities were higher whereas deceleration time, E/A ratio, and isovolumic relaxation time were not different compared to control subjects (Figure 1, Table 2).

Table 1 Clinical and echocardiographic characteristics of patients and control subjects

Variable	Control subjects (n = 17)	Patients (n = 29)	P value
Age, y	61 ± 5	65 ± 12	NS
Male, n (%)	9 (53)	15 (52)	NS
BSA, m ²	1.9 ± 0.2	1.9 ± 0.2	NS
Heart rate, beats/min	76 ± 13	74 ± 10	NS
Aortic valve area, cm ²	—	0.7 ± 0.3	
Peak aortic gradient, mm Hg	—	85 ± 21	
Mean aortic gradient, mm Hg	—	51 ± 13	
LV mass index, g/m ²	86 ± 24	152 ± 53	<.001
LVEDD, mm	45 ± 5	47 ± 8	NS
LVESD, mm	30 ± 5	31 ± 7	NS
FS, %	33 ± 6	35 ± 9	NS
LVEDV, mL	90 ± 36	79 ± 26	NS
LVESV, mL	31 ± 12	30 ± 14	NS
LV EF, %	65 ± 8	62 ± 11	NS
NT-proBNP, pmol/L	—	82 (4-777)	
Ln NT-proBNP, pmol/L	—	4.3 ± 1.2	

BSA, Body surface area; *EF*, ejection fraction; *FS*, fractional shortening; *Ln*, natural logarithm; *LV*, left ventricular; *LVEDD*, LV end-diastolic diameter; *LVEDV*, LV end-diastolic volume; *LVESD*, LV end-systolic diameter; *LVESV*, LV end-systolic volume; *NS*, not significant; *NT-proBNP*, N-terminal pro-brain natriuretic peptide.

Figure 1 (A), Example of mitral inflow profile with measurement of peak early (E) and late (A) diastolic velocities in patient with aortic stenosis. E/A ratio of 0.9 is derived. **(B)**, Example of Doppler tissue imaging tracing of lateral mitral annulus with measurement of peak systolic (Sm), peak early diastolic (Em), and peak late diastolic (Am) annular velocities in same patient. Note low Sm velocity (5.8 cm/s) and high E/Em ratio of 17.4. Color figure online.



Echocardiographic DTI parameters: In patients with AS, DTI measurements of the mitral annulus were significantly lower with respect to peak systolic (Sm_{lat} and Sm_{sep}), early diastolic filling (Em_{lat} and Em_{sep}) and late diastolic filling (Am_{lat} and Am_{sep}) compared with control subjects (Table 2). Moreover, E/Em_{lat} and E/Em_{sep} ratios were significantly higher in patients with AS (Figure 1).

Variable	Control subjects (n = 17)	Patients (n = 29)	P value
E, cm/s	56 ± 13	80 ± 22	<.001
A, cm/s	70 ± 16	87 ± 27	<.05
E/A ratio	0.9 ± 0.3	1.0 ± 0.6	NS
Deceleration time, ms	207 ± 53	231 ± 57	NS
Isovolumic relaxation time, ms	99 ± 16	86 ± 29	NS
Sm_{sep} , cm/s	7.7 ± 1.8	5.8 ± 1.7	<.01
Em_{sep} , cm/s	7.4 ± 2.5	5.6 ± 1.8	<.01
Am_{sep} , cm/s	10.2 ± 2.6	7.8 ± 2.4	<.01
Em_{sep}/Am_{sep} ratio	0.8 ± 0.5	0.8 ± 0.5	NS
E/Em_{sep}	8.1 ± 2.8	15.5 ± 6.2	<.001
Sm_{lat} , cm/s	8.9 ± 2.0	6.4 ± 1.6	<.001
Em_{lat} , cm/s	9.0 ± 3.0	6.9 ± 2.7	<.05
Am_{lat} , cm/s	10.0 ± 4.2	7.8 ± 3.2	<.05
Em_{lat}/Am_{lat} ratio	1.2 ± 1.0	1.2 ± 0.9	NS
E/Em_{lat}	6.7 ± 2.3	12.5 ± 4.3	<.001

A, Late diastolic filling; *Am*, late diastolic myocardial velocity; *E*, early diastolic filling; *Em*, early diastolic myocardial velocity; *lat*, lateral mitral annulus; NS, not significant; *sep*, septal mitral annulus; *Sm*, systolic myocardial velocity.

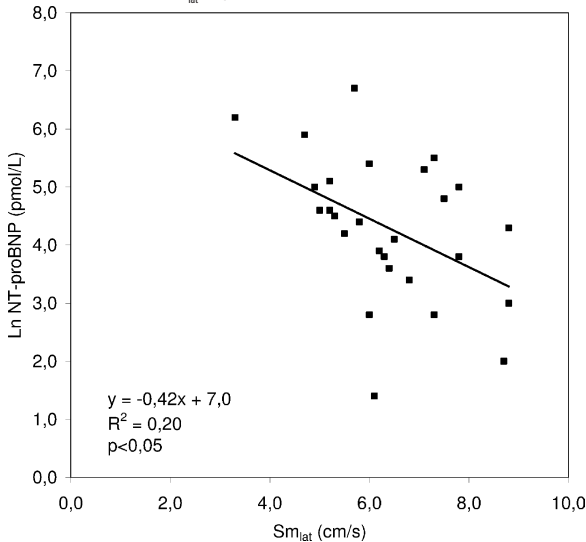
NT-proBNP and correlation with Echocardiographic Parameters: The median NT-proBNP value in patients with AS was 82 pmol/l (range: 4-777). The correlation between the natural logarithm (ln) of NT-proBNP and all echocardiographic parameters are depicted in Table 3. Univariate analysis revealed a significant negative relationship between ln NT-proBNP and AVA. Also, ln NT-proBNP was inversely correlated with Sm_{lat} and positively correlated with E/Em_{sep} ratio. Stepwise multiple linear regression showed that ln NT-proBNP was independently related to Sm_{lat} (Figure 2). When comparing ln NT-proBNP in patients with E/Em_{sep} ratio between 8 and 15 (n=13) versus those with a ratio greater than or equal to 15 (n=12), there was a trend towards a higher ln NT-proBNP in patients with an E/Em_{sep} ratio greater than or equal to 15 (4.60 ± 1.28 vs. 3.87 ± 1.00 , $P = .10$). Only two patients with AS had an E/Em_{sep} ratio of 8 or less. When restricting the univariate analysis to patients with an E/Em_{sep} ratio less than or equal to 15, there still was a significant negative relationship between ln NT-proBNP and Sm_{lat} ($R^2 = 0.28$, $P \leq .05$).

Table 3 Relation of natural logarithm of N-terminal pro-B-type natriuretic peptide levels to severity of aortic stenosis and conventional and tissue Doppler echocardiographic parameters of diastolic function

Variable	Univariate linear regression		Multivariate linear regression	
	r	P value	β	P value
Aortic valve area, cm ²	-0.40	<.05	—	NS
Peak aortic gradient, mm Hg	0.35	NS		
Mean aortic gradient, mm Hg	0.25	NS		
E, cm/s	0.32	NS		
A, cm/s	0.14	NS		
E/A ratio	0.16	NS		
Deceleration time, ms	-0.05	NS		
Isovolumic relaxation time, ms	0.10	NS		
A duration, ms	0.17	NS		
Sm _{sep} , cm/s	-0.12	NS		
Em _{sep} , cm/s	-0.11	NS		
Am _{sep} l, cm/s	-0.18	NS		
Em _{sep} /Am _{sep} ratio	0.23	NS		
E/Em _{sep}	0.39	<.05	—	NS
Sm _{lat} , cm/s	-0.45	<.05	-0.45	<.05
Em _{lat} , cm/s	0.10	NS		
Am _{lat} , cm/s	-0.31	NS		
Em _{lat} /Am _{lat} ratio	0.23	NS		
E/Em _{lat}	0.12	NS		

A, Late diastolic filling; Am, late diastolic myocardial velocity; E, early diastolic filling; Em, early diastolic myocardial velocity; lat, lateral mitral annulus; NS, not significant; sep, septal mitral annulus; Sm, systolic myocardial velocity.

Figure 2: Association between natural logarithm (ln) of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and peak systolic velocity of lateral mitral annulus (Sm_{lat}) in patients with severe aortic stenosis.



DISCUSSION

A stenotic aortic valve leads to LV pressure overload, hypertrophy and a decreased LV compliance. As expected, patients with AS had an increased LV mass compared with control subjects; however, LV-EF, mitral inflow E/A ratio, and deceleration time were comparable with control subjects. Whether this E/A ratio is normal or pseudonormal as a result of an increase in left atrial (LA) pressure can be assessed by combining mitral inflow and DTI-derived parameters. The E/Em ratio has been found to be a reliable estimate of mean LA pressure, and E/Em_{sep} greater than 15 indicates increased LA pressure, whereas E/Em_{sep} less than 8 indicates a normal pressure.⁹ In our patients with AS, the E/Em_{sep} ratio was significantly increased indicating elevated LA pressure and, thus, impaired LV diastolic function (pseudonormalization). Although the peak velocity and duration of pulmonary atrial reversal flow also provides important information about diastolic function, we did not include these parameters in our study because in the majority of patients it was not possible to reliably measure these parameters.^{10,11} In contrast, DTI measurements could be obtained in all our patients with AS and control subjects, confirming the high success rate reported by others.⁹

Concerning systolic LV function, our data raise the issue of whether patients with AS and normal LV-EF should be considered to have normal LV systolic function, as the systolic function measured by DTI was significantly lower compared with control subjects. It has been postulated that DTI is more sensitive to assess systolic LV dysfunction.¹⁵ In studies in Fabry's disease and patients with hypertensive it has been shown that DTI, but not conventional echocardiographic parameters, can detect subtle therapy-induced changes in LV function.^{12,13} Although measurements of LV-EF reflect the relative difference between end-diastolic and end-systolic volume (composite of longitudinal and radial LV function), DTI reflects long-axis LV function. Long-axis LV function is primarily determined by contraction of the longitudinally, mainly subendocardial-orientated muscle fibres. It is known that the subendocardium is affected earlier by ischemia, because of the pressure gradient across the myocardium, than the more epicardial-orientated circumferential fibres.¹⁴ This may explain the finding that DTI can detect LV systolic dysfunction earlier than LV EF.

Another marker of LV function is NT-proBNP, a neurohormone secreted by the ventricles in case of volume and pressure overload. This hormone is elevated in patients with hypertension¹⁵, congestive heart failure and LV hypertrophy.¹⁶ NT-proBNP is also elevated in some patients with severe AS, and may differentiate between symptomatic and asymptomatic patients.^{17,18} In our study, however, all patients were already symptomatic. As described by others, NT-proBNP levels were inversely related to AS severity.^{19,20} In the present study, NT-proBNP was not related to any of the conventional echocardiographic parameters of LV dysfunction, but significantly related to DTI parameters of both systolic (Sm_{lat}) and diastolic (E/Em_{sep}) dysfunction. Multivariate analysis showed only a correlation between NT-proBNP and systolic LV dysfunction assessed by DTI. No clear explanation exists as to why E/Em_{sep}

was not independently related to NT-proBNP. Perhaps the correlation between E/Em ratio and N-proBNP is curvilinear, ie, at higher Nt-proBNP levels the relationship with E/Em ratio flattens. Our patient population consisted of patients with symptomatic severe AS, forming one end of the spectrum of patients with AS with high Nt-proBNP levels.

Future studies should assess whether DTI markers for early LV dysfunction are reversible and in particular whether these markers predict LV dysfunction in terms of reduction in LV-EF after aortic valve replacement. If a certain level of DTI abnormality predicts postoperative impairment in LV-EF this may help identify patients with AS who should be operated on earlier, in an asymptomatic status. However, it is well known that even patients with severely impaired LV-EF may improve substantially in LV EF after aortic valve replacement.

Study limitations

Several potential limitations must be noted. First, 14 of 29 patients with AS (48%) had established coronary artery disease, which could influence the DTI measurements. However, no differences in DTI values were found between patients with AS with and without coronary artery disease.

Second, although both lateral and septal measured mitral annulus DTI values were significantly different in patients with AS and control subjects, the relationship with NT-proBNP was most significant with E/Em_{sep} and Sm_{lat} . However, all correlations between DTI-derived values and NT-proBNP were in the same direction, regardless of whether septal or lateral values were considered. Finally, because of the small sample size the conclusions of this study must be drawn with caution.

CONCLUSIONS

In patients with severe AS and normal LV-EF, DTI-derived parameters identified early systolic and diastolic LV dysfunction. Furthermore, DTI-derived parameters showed a significant correlation with NT-proBNP. Further studies are needed to examine the value of DTI and NT-proBNP in selecting patients with severe asymptomatic AS who will benefit from surgery.

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Chapter 10

Recovery of Long-Axis Left Ventricular Function after Aortic Valve Replacement in Patients with Severe Aortic Stenosis

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ABSTRACT

Background: Patients with aortic stenosis (AS) should undergo aortic valve replacement (AVR) before irreversible LV dysfunction has developed. Assessment of long-axis left ventricular (LV) function may assist in proper timing of AVR.

Objectives: To assess serial changes in long-axis LV function before and after AVR in patients with severe AS and preserved LV ejection fraction.

Methods: The study comprised 27 consecutive patients (mean age 64.9 ± 11.7 years, 15 males) with symptomatic severe AS, scheduled for AVR. Seventeen subjects without known cardiac disease, matched for age, gender, LV ejection fraction and cardiovascular risk factors, served as a control group. Long-axis LV function assessment was done with tissue Doppler imaging at 3 weeks, 6 months, and 12 months after AVR.

Results: Mean aortic valve area in the AS group was 0.70 ± 0.24 cm². Pre-AVR peak systolic mitral annular velocities were significantly lower compared to controls (6.7 ± 1.5 vs. 8.9 ± 2.0 cm/s, $P < 0.05$). Post-AVR peak systolic mitral annular velocities improved to 9.1 ± 2.9 at 3 weeks, 8.6 ± 2.7 at 6 months, and 8.1 ± 1.7 cm/s at 12 months ($P < 0.05$). Improvements were seen over the whole range of pre-AVR peak systolic mitral annular velocities. Patients with improved Sm after AVR (defined as $\geq 10\%$ compared to baseline values) did not differ in baseline characteristics as compared to those who did not improve.

Conclusions: In patients with severe AS and preserved LV ejection fraction, abnormal systolic mitral annular velocities improve after AVR, independent of the pre-AVR value.

Key words: *Aortic valve disease, aortic stenosis, aortic valve replacement, tissue Doppler*

INTRODUCTION

In patients with severe aortic stenosis (AS) long-standing left ventricular (LV) pressure overload results in LV hypertrophy, fibrosis, and ultimately LV dysfunction.¹ Aortic valve replacement (AVR) has to take place before irreversible LV dysfunction develops because this adversely affects post-operative prognosis.²⁻³ Long-axis LV function assessed with tissue Doppler imaging may identify early abnormalities in LV dysfunction, before LV ejection fraction (EF) is depressed.⁴ Others and us have shown that in patients with severe AS and normal LV-EF, systolic velocities of the mitral annulus may indeed be already abnormal.⁵⁻⁶ Occult LV dysfunction in AS may have important prognostic implications.^{1,3} Therefore, we investigated serial changes in long-axis LV function before and after AVR in patients with severe AS and preserved LV-EF.

METHODS

Study population

The study comprised 27 consecutive patients (mean age 64.9 ± 11.7 years, 15 males) with symptomatic severe AS, defined as an aortic valve area (AVA) ≤ 1.0 cm² or a peak aortic jet velocity ≥ 4.0 m/s and normal LV-EF ($\geq 50\%$), scheduled for AVR. None of the patients had atrial fibrillation, a pacemaker device, significant mitral valve disease or significant aortic regurgitation. Six patients with angiographically significant coronary artery disease underwent also concomitant bypass surgery. Echocardiographic and clinical follow-up was performed 3 weeks, 6 months, and 12 months after AVR. Seventeen subjects without known cardiac disease, matched for age, gender, LV-EF and cardiovascular risk factors, served as control group to compare the echocardiographic measurements. The local ethics committee approved the study protocol and all patients gave written informed consent.

Conventional echocardiography

Doppler echocardiography was performed with a Sonos 7500 system (Philips, Best, The Netherlands). All images were acquired from the standard cardiac views according to the guidelines of the American Society of Echocardiography and digitally stored for offline analysis.⁷ To obtain the highest aortic jet velocity multiple windows were used. Peak and mean aortic pressure gradient were calculated using the modified Bernoulli equation and tracing of the aortic velocity profile.⁸ Three measurements from the window with the highest velocity were averaged. AVA was calculated using the continuity equation. LV-EF was assessed by the modified Simpson's biplane disc method.⁹ For assessment of diastolic function, peak velocities of early (E) and late

(A), E/A-ratio and deceleration time were derived from Doppler recordings of the LV inflow at the mitral leaflet tips. LV mass was calculated using the modified Devereux formula.¹⁰

Tissue Doppler measurements

Tissue Doppler was applied in the pulsed wave Doppler mode at the level of the lateral mitral annulus from the apical 4-chamber view. This side was chosen because it is most easy to quantify¹¹ and is less influenced by cardiac surgery.¹² To acquire the highest wall tissue velocities, the angle between the Doppler beam and the longitudinal motion of the mitral annulus was adjusted to a minimal level. The average of three end-expiratory peak systolic (S_m), early (E_m) and late (A_m) diastolic velocities and E/ E_m ratio¹³ were calculated, where E is the peak velocity of early diastolic mitral flow.¹⁴

Statistical analysis

Continuous variables are expressed as mean \pm SD. Differences between groups were analyzed with the unpaired t test for continuous variables or χ^2 test for categorical variables. A value of $p < 0.05$ was considered significant. A commercially available statistical software package was used (SPSS version 12.0).

RESULTS

Clinical data

The baseline clinical characteristics of the control subjects and patients are listed in Table 1. Main cardiac symptoms were angina in 16 patients (59%), exertional dyspnoea in 10 patients

Variable	Control subjects n = 17	Patients n = 27
Age (years)	61.2 \pm 5.3	64.9 \pm 11.7
Male (%)	9 (53)	15 (55)
BMI (kg/m ²)	29.0 \pm 4.5	28.0 \pm 5.5
Heart rate (bpm)	76 \pm 13	74 \pm 10
AVA (cm ²)	-	0.70 \pm 0.24
AVA index (cm ² /m ²)	-	0.36 \pm 0.11
Aortic jet velocity (m/s)	-	4.63 \pm 0.65
Peak aortic valve gradient (mm Hg)	-	87.4 \pm 24.1
Mean aortic valve gradient (mm Hg)	-	51.2 \pm 14.2

BMI = body mass index, bpm = beats per minute, AVA = Aortic valve area.

(37%) and dizziness in one patient (4%). Implanted prostheses were: St Jude mechanical, sizes 17-27 mm (n = 11), Carpentier Edwards Perimount bio, sizes 21-29 mm (n = 15), and in one patient a homograft 23 mm was implanted.

Baseline echocardiographic data

As shown in Table 1, mean AVA in the AS group was $0.70 \pm 0.24 \text{ cm}^2$. No significant differences were observed between AS patients and control subjects with respect to LV-EF, whereas systolic mitral annular velocities were significantly lower (Table 2). Also, in patients with AS, the mitral E velocity and the E/Em ratio were significantly higher whereas the deceleration time and the E/A ratio were not different compared with control subjects.

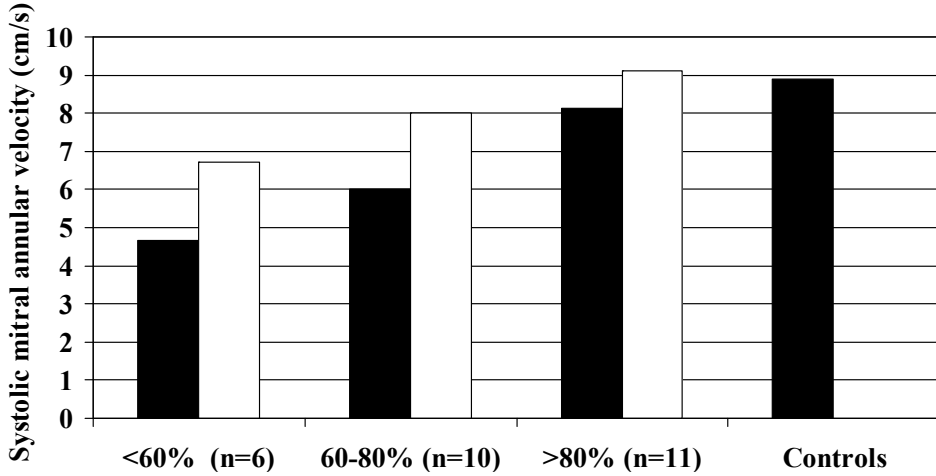
	Controls	Pre-operative	3 Weeks	6 Months	12 Months
Aortic valve area	--	0.7 ± 0.2	1.9 ± 0.6	1.9 ± 0.6	1.6 ± 0.5
Peak aortic valve gradient (mm Hg)	--	87.4 ± 24.1	19.2 ± 7.2	17.4 ± 7.1	18.6 ± 6.2
Mean aortic valve gradient (mm Hg)	--	51.2 ± 14.2	9.4 ± 3.9	8.9 ± 3.9	9.5 ± 3.7
LV-EDD (mm)	45.3 ± 5.1	46.8 ± 9.6	46.3 ± 8.6	46.8 ± 7.3	47.2 ± 5.1
LV-ESD (mm)	30.5 ± 5.1	31.2 ± 9.2	32.2 ± 8.9	30.9 ± 7.6	31.0 ± 6.5
LV-EF (%)	65.1 ± 7.7	63.2 ± 9.1	59.2 ± 12.9	59.8 ± 10.1	63.1 ± 10.7
LA diameter (mm)	32.8 ± 3.9	$43.2 \pm 7.6\#$	$43.4 \pm 7.9\#$	$45.6 \pm 8.0\#$	$43.9 \pm 8.2\#$
LV mass (g)	139 ± 43	$250 \pm 104\#$	$221 \pm 83\#$	$201 \pm 58\#$	$220 \pm 58\#$
LV mass index (g/m ²)	86 ± 24	$127 \pm 44\#$	$113 \pm 39\#$	$103 \pm 25\#$	$113 \pm 25\#$
E-wave (cm/s)	56 ± 13	$81 \pm 26\#$	$79 \pm 21\#$	$74 \pm 17\#$	$80 \pm 21\#$
A-wave (cm/s)	70 ± 16	80 ± 24	$84 \pm 25\#$	76 ± 18	$84 \pm 25\#$
E/A ratio	0.9 ± 0.3	1.1 ± 0.7	1.1 ± 0.8	1.0 ± 0.4	1.0 ± 0.2
Deceleration time (ms)	207 ± 53	211 ± 66	224 ± 60	228 ± 46	229 ± 52
Em lateral annulus (cm/s)	9.0 ± 3.0	7.3 ± 2.9	$10.2 \pm 2.8\&$	$9.5 \pm 2.5\&$	$9.2 \pm 2.2\&$
Am lateral annulus (cm/s)	10.0 ± 4.2	8.3 ± 2.9	9.4 ± 2.9	9.8 ± 3.2	9.8 ± 3.5
Sm lateral annulus (cm/s)	8.9 ± 2.0	$6.7 \pm 1.5\#$	$9.1 \pm 2.8\&$	$8.6 \pm 2.7\&$	$8.1 \pm 1.7\&$
E/Em lateral ratio	6.7 ± 2.3	$11.7 \pm 3.5\#$	$8.1 \pm 3.0\&$	$8.5 \pm 3.1\&$, #	$9.4 \pm 3.4\&$, #

& = p < 0.05 compared to pre-operative values
= p < 0.05 compared to control subjects
LV-EDD = Left ventricular end-diastolic diameter. LV-ESD = Left ventricular end-systolic diameter. LV-EF = Left ventricular ejection fraction, LA = Left atrial, E= peak early diastolic filling, A= peak late diastolic filling, Em = peak early diastolic myocardial velocity, Am= peak late diastolic myocardial velocity, Sm = peak systolic myocardial velocity.

Changes in echocardiographic data post aortic valve replacement

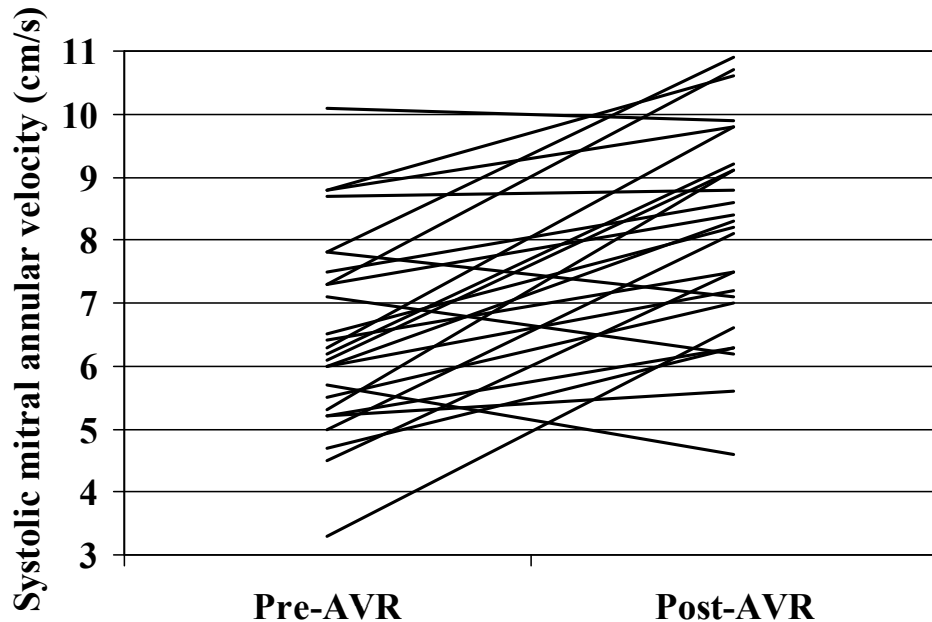
Three weeks after AVR, systolic and diastolic mitral annular velocities (including the E/Em ratio) improved, although the E/Em ratio remained higher compared to control subjects (Table 2). Individual changes in Sm values pre- and post AVR are displayed in Figure 1; in all but 4 patients Sm values improved. In the 6 patients with a Sm value <60% from normal a

Figure 1 Peak systolic mitral annular velocities pre (black bars) and post (white bars) aortic valve replacement according to the preoperative normalized values.



149% improvement was noted, in the 10 patients with a Sm value between 60 and 80% from normal a 133% improvement was noted, and in the 11 patients with a Sm value >80% from normal a 113% improvement was noted (Figure 2). As seen in Table 3, patients with improved Sm after AVR (defined as $\geq 10\%$ compared to baseline values) did not differ in baseline characteristics as compared to those who did not improve.

Figure 2 Individual peak systolic mitral annular velocity pre- and post aortic valve replacement.



Variable	Patients with improved Sm n = 20	Patients without improved Sm n = 7
Age (years)	66.6 ± 10.5	60.1 ± 14.5
Male (%)	9 (60)	6 (86)
Heart rate (bpm)	74 ± 11	73 ± 11
AVA (cm ²)	0.64 ± 0.19	0.80 ± 0.36
Peak aortic valve gradient (mm Hg)	87.6 ± 17.6	86.2 ± 36.8
Mean aortic valve gradient (mm Hg)	52.5 ± 11.2	48.4 ± 19.9
All P = non-significant		

DISCUSSION

The main findings of this study are 1) in patients with severe AS and preserved LV-EF systolic mitral annular velocities are abnormal and 2) these velocities improve after AVR, independent of the pre-AVR value.

In patients with AS, the increased pressure gradient across the aortic valve leads to sub-endocardial ischemia with contractile dysfunction of the longitudinal myocardial fibers, LV hypertrophy and reactive fibrosis.¹⁵ These alterations are major determinants of diastolic and systolic LV dysfunction in AS patients. Diastolic dysfunction or LV stiffness causes an increase in LV end-diastolic pressure, expressed in our study as high E/E' ratios in AS patients compared to controls. Systolic dysfunction may ultimately become visible by impairment in LV-EF, but as shown in this study mitral annular velocities are more sensitive to detect changes in long-axis LV systolic function.⁵⁻⁶

AVR reduces the pressure overload caused by AS. By this immediate decrease in afterload and a later correction in neurohormonal imbalance the LV may be reversely remodeled.¹⁶ We observed an improvement in mitral annular velocities both in diastole and systole as early as 3 weeks after AVR, although the E/Em ratio did not normalize. This improvement was most obvious after 3 weeks.

Timing of aortic valve surgery in patients with severe AS depends on symptoms and LV systolic function. According to current guidelines a LV-EF <50% is an indication for AVR because LV dysfunction adversely affects prognosis.^{2-3,17} Ideally, AVR should take place at an earlier moment when LV-EF is still preserved to definitely prevent irreversible LV dysfunction. Some have advocated systolic velocities of LV longitudinal contraction assessed with tissue Doppler imaging to time AVR, since these velocities are more sensitive to detect subtle changes in systolic LV function.¹⁸ Long-axis LV function is primarily determined by contraction of the longitudinally, mainly subendocardial-orientated muscle fibers. A critical lowering of systolic long-axis LV function in a patient with preserved LV-EF may predict post-AVR LV dysfunction. In our study the most severely depressed systolic LV long-axis velocities showed the best relative improvement after AVR, although they still did not normalize. In our opinion this makes it not very likely that this variable can be used to time AVR in routine clinical practice. One

problem of the use of LV longitudinal contraction is that it is not only affected by irreversible fibrosis but also by reversible subendocardial ischemia caused by the LV pressure overload.¹⁹

Comparison with other studies

Acute (24 hours after percutaneous AVR) improvements in long-axis LV function in patients with impaired LV function were reported by Bauer et al.²⁰ This acute improvement in long-axis LV function makes it most likely that afterload reduction is the main mechanism. Sub-acute (2 weeks after AVR) improvements in long-axis LV function in patients with preserved LV function were reported by Iwahashi et al.¹ More chronic (3 and 12 months after AVR) improvements in long-axis LV function in patients with preserved LV function were reported by Poulsen et al.¹⁸ Our study is the first to study both sub-acute (3 weeks after AVR) and chronic (6 and 12 months after AVR) changes in long-axis LV function in patients with preserved LV function. In the study by Poulsen et al. a progressive improvement in long-axis LV function was reported whereas in our study the best long-axis LV function was seen 3 weeks after AVR, thereafter a small, non-significant progressive deterioration was seen at 6 and 12 months post-AVR.¹⁸ The acute reduction in afterload after AVR may temporarily increase long-axis systolic function and returns to baseline values after adaptation to the new situation. Only one study showed a relation between outcome and TDI deformation imaging in 32 AS patients after AVR: a low radial deformation was a marker of persistent heart failure.²¹

CONCLUSIONS

In patients with severe AS and preserved LV-EF, abnormal systolic mitral annular velocities improve after AVR, independent of the pre-AVR value. This improvement is already present after 3 weeks, and sustained 12 months after valve replacement.

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Part IV

Echocardiography and CT-Angiography in Patients with chronic Cardiac Chest Pain



Chapter 11

Usefulness of Handheld Echocardiography in Patients referred for Evaluation of Chronic Chest Pain

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Geleijnse ML

Submitted

ABSTRACT

Aims: Cardiac investigations in patients with chronic chest pain (CCP) are focused on the detection of ischemia. In addition to stress tests, current guidelines recommend rest echocardiography in patients referred for the evaluation of CCP with an abnormal ECG, suspicion of heart failure and in the presence of murmurs. However, there are no prospective studies supporting this strategy.

Methods: In 500 consecutive patients without known coronary artery disease (CAD) and with intermediate and high risk for CAD we performed a diagnostic protocol that consists of physical examination, ECG, bicycle exercise test and CT angiography. Also we performed handheld echocardiography (HHE) in all patients and compared these results with the final diagnosis made by the other exams.

Results: Abnormal HHE results were found in 15,6% of all patients. In 346 patients with normal blood pressure, no murmurs or signs of heart failure and a normal ECC only 10,4% had abnormal HHE. The majority of the findings by HHE had no implications for patient management. In contrast, abnormal findings were detected in 49 out of 154 patients (32%) with a guideline indication for HHE.

Conclusions: Although systematic echocardiography in patients with chronic chest pain yields unexpected abnormalities in 10,4% of patients without abnormal findings by other investigations, the clinical relevance of these findings is limited. These results support the current guideline to perform echocardiography in selected cases only.

INTRODUCTION

In patients referred to a cardiologist for evaluation of chronic chest pain (CCP) the diagnostic process is focused primarily on detecting myocardial ischemia caused by significant coronary artery disease (CAD). Several non-invasive techniques can be used in the diagnostic assessment of CAD such as a resting ECG, ECG stress testing, and stress echocardiography or myocardial perfusion scintigraphy^{1 2}. In addition, echocardiography at rest may be used to detect other causes of CCP such as severe aortic stenosis³ and hypertrophic cardiomyopathy.⁴ According to current ESC guidelines, echocardiography is indicated in CCP patients with suspected valve disease, heart failure, prior myocardial infarction or ECG abnormalities such as left bundle branch block, Q-waves or other significant, abnormal findings.⁵ However, to our knowledge no studies are published in which echocardiography has been systematically performed in a series of consecutive patients with CCP.

Handheld echocardiography (HHE) has been evaluated as a useful tool for screening of patients for cardiac abnormalities such as hypertrophic cardiomyopathy, pericardial effusion, left ventricular dysfunction and valve disease.⁶ We prospectively performed HHE in a consecutive series of patients referred to the outpatient clinic for the evaluation of CCP and investigated whether systematic HHE adds important information in the diagnostic process in patients with CCP.

METHODS

Study population

Five hundred and twenty patients without a history of CAD were referred to the outpatient clinic of the Erasmus MC for the evaluation of CCP from September 2006 to February 2009. All patients underwent a standardized protocol including an ECG, blood examination, physical examination (focused on signs of heart failure and valve disease), computed tomography coronary angiography and HHE. Twenty patients (4%) with insufficient quality of HHE were excluded from the analysis. Invasive coronary angiography was performed when indicated. Significant CAD was defined as more than 50% narrowing of at least one epicardial coronary artery as detected by either CT-angiography or invasive coronary angiography.

Handheld echocardiography

HHE was performed with the OptiGo (Philips Medical Systems) device by one single experienced cardiologist (TWG). This system is equipped with a 2.5 MHz phased array broadband transducer and operates on a rechargeable lithium ion battery or alternating current. Two-

dimensional imaging, color flow Doppler imaging, and calipers for linear measurements are integrated in the system. The focus for the HHE was to detect cardiovascular abnormalities potentially causing CCP (Table 1). Also, findings that were not related to the symptoms but require echocardiographic follow-up or (more intensive) prescription of medication according to the current guidelines were reported.⁷⁻⁹

Table 1. Cardiac abnormalities associated with chest pain and the echocardiographic abnormality	
Cardiac abnormalities causing chest pain	Echocardiographic abnormality
Coronary artery disease (CAD)	Regional wall motion abnormality
Mitral valve prolaps	Bulging part of the mitral valve in left atrium
Pericarditis	Pericardial fluid, thickened pericardium
Hypertrophic cardiomyopathy	Severe left ventricular hypertrophy >16 mm
Severe aortic stenosis	Thickened aortic valve, CW Doppler >4 m/s
Pulmonary embolism	Dilated right ventricle and inferior vena cava
Aortic dissection	Dilated ascending aorta, intimal flap

RESULTS

Patients

Mean age of the patients was 55 ± 11 years (range 18 to 84) and 51% were male. Chest pain was characterized as typical angina in 154 (31%), atypical angina in 268 (54%) and non-anginal in 78 (14%).¹⁰ Diabetes, hypertension, hypercholesterolemia, and a family history of CAD were present in 14%, 49%, 57%, and 46% of patients respectively and 30% were current smokers. The final diagnosis of significant CAD was established in 152 out of 500 patients (30%), based on CT-angiography in 90 patients and invasive coronary angiography in 62 patients.

Handheld echocardiography

Adequate HHE images were obtained in 500 out of 520 patients. In 10 patients (2,0%) echocardiographic abnormalities were found that could relate to CCP (Table 2). Eight (1,6%)

Table 2. Echocardiographic findings related to chest pain			
Cardiac abnormalities	Patients	Echo indicated	Echo not indicated
Number of patients	500	154	346
Abnormal wall motion (CAD)	8 (1,6%)	7 (4,5%)	1 (0,3%)
Mitral valve prolaps	0	0	0
Pericarditis	2 (0,4%)	0	2 (0,6%)
Hypertrophic cardiomyopathy	0	0	0
Severe aortic stenosis	0	0	0
Pulmonary embolism	0	0	0
Aortic dissection	0	0	0
All findings	10 (2,0%)	7 (4,5%)	3 (0,9%)

patients had regional wall motion abnormalities and 2 (0,4%) pericardial fluid. According to the current guidelines, only 154 patients (31%) had an appropriate indication for echocardiography. In 7 of these 154 patients (4,5%) a CCP related abnormality was found. In 346 patients without an indication for echocardiography 3 (0,9%) CCP related finding was found. When HHE was restricted to the 154 patients with an indication for echocardiography, 3 of 10 (30%) diagnoses would have been missed (Table 2).

Abnormalities not related to CCP but with an established indication for follow-up were found in 78 (15,6%) patients. In 154 patients with an indication for echocardiography 42 (27,3%) diagnosis not related to CCP were established As well as in 36 (10,4%) patients 346 without an indication. When HHE would be restricted to patients with a formal indication, 36 of 78 (46,0%) findings would have been missed, including 18 cases of mild valve insufficiency and 18 with left ventricular hypertrophy or impaired left ventricular function (Table 3).

Echocardiographic finding	Patients	Echo indicated	Echo not indicated
Number of patients	500	154	346
Impaired LV function (EF < 40%)	12 (2,4%)	5 (3,2%)	7 (2,0%)
Aortic stenosis			
- mild	9 (1,8%)	4 (2,6%)	5 (1,4%)
- moderate	0		
Aortic regurgitation			
- mild	10 (2,0%)	8 (5,2%)	2 (0,6%)
- moderate	1 (0,2%)	1 (0,6%)	0
- severe	0		0
Mitral regurgitation			
- mild	25 (5,0%)	14 (9,1%)	11 (3,2%)
- moderate	0		0
- severe	0		0
Left ventricular hypertrophy	21 (4,2%)	10 (6,5%)	11 (3,2%)
All findings (%)	78 (15,6%)	42 (27,3%)	36 (10,4%)

DISCUSSION

Patient with CCP are frequently referred to the cardiologist. The primary focus in these patients is to detect or exclude significant CAD, while also other causes for CCP should be investigated. Echocardiography is an important tool to detect or exclude most cardiac causes for CCP apart from coronary artery disease. Therefore, according to current guidelines, echo-

cardiography is recommended in the presence of symptoms of heart failure, murmurs or ECG abnormalities although prospective data to support this strategy are limited.⁵

In order to verify whether systematic or selective HHE provides a significant contribution to the diagnostic protocol, including stress ECG and CT-angiography, we evaluated 500 consecutive patients with CCP and sufficient quality HHE who were referred to our chest pain clinic. HHE yielded possible CCP-related findings in 10 patients, of which approximately one third would have been missed when echocardiography was used selectively, according to the guidelines: 2 patients with pericardial effusion and one patient with abnormal regional wall motion. No patients with severe aortic stenosis or hypertrophic cardiomyopathy were present in our study population. This may be explained by the low prevalence of hypertrophic cardiomyopathy in the overall population (estimated 1 in 500 patients)¹¹ and the relative young age of the referred patients, while severe aortic stenosis occurs more frequently in the elderly.³ Because of the absence of hypertrophic cardiomyopathy and severe aortic stenosis in our patients with chest pain we can not be certain whether we would have missed patients with such disease if we performed HHE in selected cases only. However, others have reported that only 6% of patients with hypertrophic cardiomyopathy present with a normal ECG. Furthermore, these patients had better cardiovascular outcome compared to patients with ECG abnormalities.¹² So it's very unlikely that patients with a clinically relevant severe hypertrophic cardiomyopathy would have been missed when HHE would have been performed according to the guideline. The same is true for patients with severe aortic stenosis. These patients usually present with a murmur or abnormal ECG. In our study of 27 patients with severe aortic stenosis all patients had a murmur and 26 of 27 (96,3%) an abnormal ECG and would not have been missed if HHE was performed according to the guideline.¹³ Taken together, these data confirm that HHE in selected patients with chest pain is an adequate and safe procedure indeed.

The relevance of detecting (or missing) regional wall motion abnormalities and pericardial effusion with echocardiography in this particular patient group is not clear. Pericardial effusion can readily be detected by computed tomography, as was the case in our patients. The relevance of detection of regional wall motion abnormalities may be questioned. These findings increase the probability of CAD, however, all patients in our chest pain protocol do undergo CT-angiography. Surprisingly, in our study only two out of eight patients with regional wall motion abnormalities actually had significant CAD, although it can not be excluded that these patients previously suffered from a thrombotic event in a non-significant coronary lesion. Five of these patients without significant CAD had isolated basal inferior and/or inferoseptal wall motion abnormalities which are known to be not specific for CAD.¹⁴

Findings that were not related to the symptoms but which may require (more intensive) prescription of medication according to the current guidelines were seen in 78 (15,6%) patients of whom 36 would have been missed when echocardiography was not performed systematically (Table 3). The question is whether these 36 abnormalities, find by echocardiography, are important to prevent structural and irreversible damage to the heart during

long time follow-up? This is only true if these unexpected findings would lead to treatment with medication or other relevant changes that could prevent cardiac damage and worse outcome in the future. Seven patients had impaired LV function and would have been missed if echocardiography would be performed according to the guidelines.⁵ Heart failure guidelines recommend starting ACE inhibition therapy in asymptomatic patients with LV ejection fraction of less than 40%. However, this recommendation is based on a single study in which had established cardiac disease such as a previous myocardial infarction.¹⁵ The 7 patients in our study without an indication for echocardiography but with impaired LV function had no coronary artery disease on CT-angiography and it's not clear if they would benefit from ACE inhibition. In 21 (4,2%) patients left ventricular hypertrophy was present on echocardiography. Eleven patients had normal ECG and blood pressure and would have been missed if echocardiography would have been restricted to patients with those characteristics. Since these 11 patients did not have hypertension its not clear if they would benefit from treatment with an ACE-inhibitor or other drugs in the same way as hypertensive patients.⁹

Another cardiac abnormality that was found is valve disease. In 45 (9,0%) patients valve disease was detected and in 18 (3,6%) this would have been missed if echocardiography was restricted to patients with heart murmurs or signs of heart failure. The latter included mild aortic stenosis in 5 (1,0%), mild aortic regurgitation in 2 (0,4%) and mild mitral regurgitation in 11 (2,2%) patients. None of these patients was symptomatic with respect to valve disease and no patient had an indication for valve surgery. The relevancy of finding mild native valve disease is low in particular since current guidelines state that prophylactic administration of antibiotics for prevention of endocarditis in such cases is no longer indicated.¹⁶ We should also consider the possibility that mild disease progresses to severe and the optimal moment of correcting this disease can be missed. Current ESC guidelines state that mild aortic regurgitation and mild aortic stenosis warrant follow up every 2 year, while follow up is not recommended in mild mitral regurgitation.⁷ Accordingly, in our 18 patients with unexpected valve disease only in 7 follow up would be indicated. Since it is known that the majority of patients with severe aortic stenosis and regurgitation develop symptoms before left ventricular dysfunction develops, it is unlikely that major damage would occur if these patients went undetected.⁷

As a limitation of our study it should be appreciated that HHE may be inferior to standard echocardiography. However, it has been shown in several studies that the agreement between these two modalities is excellent⁶, in particular when patients with poor image quality are excluded as was the case in 20 patients in this series.

In our study of 500 patients with CCP evaluated for coronary artery disease echocardiography was indicated according to current guidelines in 154 patients and yielded additional information compared with the other investigations in one third of the patients. In 346 patients without a clear indication for echocardiography no clinically relevant abnormalities were found with CCP. Therefore we do not recommend to perform systematic echocardiography in every patient with CCP, but rather to use this method selectively in accordance with current guidelines.

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Chapter 12

Comparison of the Value of Coronary Calcium Detection to Computed Tomographic Angiography and Exercise Testing in Patients with Chest Pain

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ABSTRACT

The aim of this study was to investigate the value of coronary calcium detection by computed tomography compared to computed tomographic angiography (CTA) and exercise testing to detect obstructive coronary artery disease (CAD) in patients with stable chest pain. A total of 471 consecutive patients with new stable chest complaints were scheduled to undergo dual-source multislice computed tomography (Siemens, Germany; coronary calcium score [CCS] and coronary CTA) and exercise electrocardiography (XECG). Clinically driven invasive quantitative angiography was performed in 98 patients. Only 3 of 175 patients (2%) with a negative CCS had significant CAD on CT angiogram, with only 1 confirmed by quantitative angiography. In patients with a high calcium score (Agatston score >400), CTA could exclude significant CAD in no more than 4 of 65 patients (6%). In patients with a low–intermediate CCS, CTA more often yielded diagnostic results compared to XECG and could rule out obstructive CAD in 56% of patients. For patients with CAD on CT angiogram, those with abnormal exercise electrocardiographic results more often showed severe CAD ($p < 0.034$). In patients with diagnostic results for all tests, the sensitivity and specificity to detect >50% quantitative angiographic diameter stenosis were 100% and 15% for CCS >0, 82% and 64% for CCS >100, 97% and 36% for CTA, and 70% and 76% for XECG, respectively. In conclusion, nonenhanced computed tomography for calcium detection is a reliable means to exclude obstructive CAD in stable, symptomatic patients. Contrast-enhanced CTA can exclude significant CAD in patients with a low–intermediate CCS but is of limited value in patients with a high CCS.

INTRODUCTION

Noninvasive computed tomographic angiography (CTA) is regarded as a diagnostic option to evaluate patients with chest pain, particularly when stress tests cannot be performed or fail to achieve conclusive results.^{1,2} Although mostly used for risk stratification, coronary calcium also yields diagnostic value to exclude obstructive coronary artery disease (CAD), which has been demonstrated in stable and acute chest pain, and unexplained heart failure.^{3,4} Recently, concerns about the radiation and contrast medium exposure of CTA have regenerated interest in calcium imaging in symptomatic patients. In this study we investigated the diagnostic value of calcium scanning compared to CTA, exercise electrocardiography (XECG), and catheter angiography in the diagnostic workup of stable angina.

METHODS

From September 2006 to December 2008, 471 consecutive patients with stable chest pain and no history of CAD were evaluated at our 1-day chest pain clinic. All patients with a pre-test probability >5% were planned to undergo cardiac computed tomography and XECG, in addition to clinical examination, blood analysis, and echocardiography.⁵ Information on risk factors was prospectively acquired. Chest pain was categorized as typical (retrosternal, precipitated by exercise or emotion, relieved <10 minutes after rest or nitroglycerin), atypical (with only 2 of the previous characteristics), or nonanginal (with none or only 1 characteristic of typical angina; Table 1). The study complied with the Declaration of Helsinki, the institutional ethical committee approved the study, and informed consent was obtained from all patients.

Dual-source multislice computed tomography (Siemens Definition, Forchheim, Germany; collimation 32×0.6 mm, 64-channel acquisition by z-axis focal spot alternation, rotation time 330 ms, temporal resolution 83 ms) was performed in the absence of pregnancy, contrast allergies, or renal dysfunction.

Nonenhanced computed tomography

Electrocardiographically triggered, sequential step-and-shoot acquisition mode, with 120-kV tube voltage, 78 ± 26 -mAs tube current, and 3-mm slice thickness, was performed for calcium detection and quantification by the Agatston method and a standard 130-HU attenuation threshold.⁶

Age (years)	56 ± 10
Women	227 (48%)
Nicotine abuse	138 (29%)
Hypertension	233 (50%)
Diabetes mellitus	68 (14%)
Dyslipidemia	280 (59%)
Family history of cardiovascular disease	214 (45%)
History of vascular disease	31 (7%)
Median cardiovascular risk (SCORE ²⁰ , %)	4 (2–11%)
Typical angina pectoris	146 (31%)
Atypical angina pectoris	251 (53%)
Nonanginal	74 (16%)
Pretest probability (%) ⁵	53 ± 28
CCS—performed	463 (98%)
Median calcium score ⁷	15 (0–145)
CTA—performed	455 (97%)
CT angiographic diameter stenosis <50%	312 (69%)
CT angiographic diameter stenosis ≥50%	140 (31%)
Nondiagnostic examinations	3 (1%)
Heart rate (min ⁻¹)	68 ± 12
Atrial fibrillation	3 (1%)
XECG—performed	423 (90%)
Normal result	190 (45%)
Abnormal result	93 (22%)
Nondiagnostic result	140 (33%)
Catheter angiography	98 (21%)
Quantitative coronary angiographic diameter stenosis <50%	41 (42%)
Quantitative coronary angiographic diameter stenosis ≥50%	57 (58%)
1-vessel disease	26 (27%)
2-vessel disease	19 (19%)
3-vessel disease	12 (12%)
≥70% diameter stenosis	29 (30%)
Revascularization	59 (13%)
Percutaneous intervention	46 (10)
Bypass graft surgery	13 (3%)
<p>Patient characteristics are presented as absolute numbers of patients (percentages) or means ± SDs, unless otherwise stated. Dyslipidemia defined as a total cholesterol level >5 mmol/L, low-density lipoprotein level >3 mmol/L, or on lipid-lowering medication. Estimated annual risk of cardiovascular death was done using SCORE.²⁵ Pretest probability used criteria of Diamond and Forrester.⁵</p> <p>SCORE = Systematic Coronary Risk Evaluation.</p>	

Contrast-enhanced CT angiographic parameters

Spiral acquisition consisted of 120-kV tube voltage, 380- to 412-mAs tube current depending on patient size, and variable pitch depending on heart rate. Prospectively electrocardiographically triggered tube modulation was applied in all patients with a regular heart rate.

Contrast medium

Iopromide 70 to 100 ml (Ultravist 370 mgI/ml, Schering AG, Berlin, Germany), followed by a 40-ml saline bolus chaser, was peripherally injected at 5.0 to 5.5 ml/s. A bolus tracking technique was used to synchronize data acquisition with contrast delivery. Patients received a sublingual dose of nitroglycerin just before the scan, but no additional β blockers. Retrospective electrocardiographically gated end-systolic and/or diastolic datasets (0.75-mm slice thickness, 0.4-mm reconstruction increment) were created depending on heart rate and tube modulation protocol. Effective radiation doses for CCS and CTA were 0.8 ± 0.2 mSv (range 0.4 to 1.6) and 11.0 ± 3.5 mSv (range 4.7 to 17.8).

The right coronary artery, left main branch, left anterior descending coronary artery, and left circumflex branch were evaluated on axial images, multiplanar reformations, and maximum intensity projections according to readers' preferences. Readers were not informed about patients' symptoms or exercise test results. Vessels were qualitatively scored as stenosed (>50% diameter narrowing), less than significantly stenosed (<50%), or normal.

Bicycle XECG was performed by standardized protocol, with established criteria for performance and exercise discontinuation. Criteria for myocardial ischemia included horizontal or downsloping ST-segment depression or elevation >0.1 mV during or after exercise, or typical, increasing angina during exercise. XECG was considered nondiagnostic if discontinued without evidence of myocardial ischemia before reaching the 85% target heart rate.

Clinically indicated quantitative coronary angiography (QCA) was performed using standard techniques, with assessment of the most severe obstruction from ≥ 2 orthogonal projections using quantitative software (CAAS, Pie Medical, Maastricht, The Netherlands). Maximum lumen diameter stenosis >50% was considered significant.

Summary data are presented as numbers (proportions), means \pm SDs, or medians (interquartile ranges) when indicated. Diagnostic performance parameters, sensitivity, specificity, positive predictive value, and negative predictive value, were calculated with 95% confidence intervals. Differences between groups were compared using 2-sided unpaired *t* test, chi-square test, or analysis of variance, as appropriate. A *p* value <0.05 was considered significant. Statistical analysis was performed using SPSS 15.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

Neither CCS nor CTA could be performed in 8 patients (1.7%), and CTA could not be performed in another 8 patients (1.7%) because of renal failure, contrast allergy, patient preference, Parkinson disease, patient nonco-operation, failed venous access, and severe obesity. All calcium scans were successful. Three CTAs (0.7%) failed because of patient movement

(2) and premature scan initiation (1). Mild to moderate allergic reactions were observed in 3 patients (0.7%).

XECG could not be performed in 48 patients (10.2%) because of orthopedic reasons (13), neurologic impairment (4), severe obesity (2), electrocardiographic abnormalities at rest (6), pulmonary disease (2), and a combination/unspecified (21). XECG was inconclusive in 140 of 423 patients (33%), mostly due to failure to reach the target heart rate.

Catheter angiography (QCA) was performed in 98 patients, of whom 57 showed >50% diameter obstruction. Percutaneous coronary intervention was performed in 46 patients; coronary artery bypass graft surgery was performed in 13. Another 32 patients with abnormal CT angiographic and exercise electrocardiographic results were treated medically without undergoing cardiac catheterization.

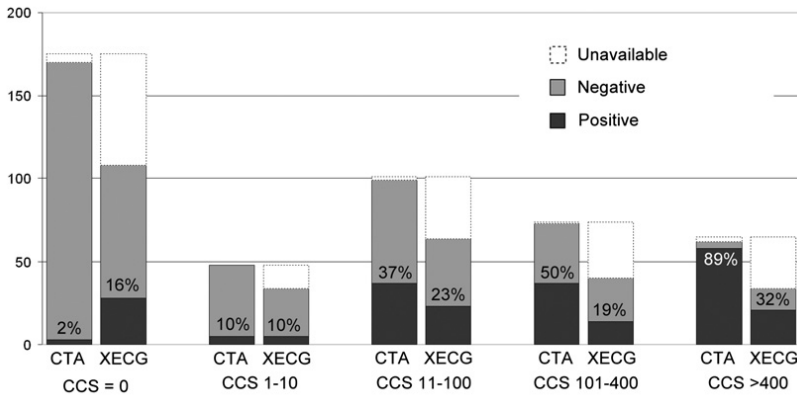
A high CCS was associated with older age, male gender, a less favorable risk profile, typical angina rather than nonanginal pain, and a higher pretest probability of obstructive CAD (Table 2).

	CCS					p Value*
	0 (n = 175)	0,1–10 (n = 48)	11–100 (n = 101)	101–400 (n = 74)	<400 (n = 65)	
Age (years)	51 ± 10	53 ± 10	58 ± 9	59 ± 8	63 ± 8	<0.001
Women	112 (64%)	26 (54%)	46 (46%)	25 (34%)	14 (22%)	<0.001
Nicotine abuse	44 (25%)	18 (38%)	23 (23%)	27 (36%)	25 (38%)	0.049
Hypertension	70 (40%)	21 (44%)	58 (57%)	31 (42%)	45 (69%)	<0.001
Diabetes mellitus	21 (12%)	3 (6%)	10 (10%)	10 (14%)	21 (32%)	<0.001
Dyslipidemia	76 (43%)	34 (71%)	65 (64%)	56 (74%)	44 (68%)	<0.001
Family history of cardiovascular disease	80 (46%)	28 (58%)	45 (45%)	35 (47%)	23 (35%)	0.20
History cardiovascular disease	10 (6%)	1 (2%)	6 (6%)	6 (8%)	8 (12%)	0.24
Cardiovascular risk (%) [†]	1 (1–3)	2 (1–5)	4 (2–7)	5.5 (3–9)	7 (4–12)	<0.001
Angina score [‡]	2.2 ± 0.6	1.8 ± 0.6	2.2 ± 0.6	2.0 ± 0.7	2.5 ± 0.7	<0.001
Pretest probability (%) [§]	45 ± 26	38 ± 26	57 ± 27	55 ± 26	74 ± 26	<0.001
Interpretable CT angiogram	170 (97%)	48 (100%)	99 (98%)	73 (99%)	62 (95%)	0.54
≥50% stenosis	3 (2%)	5 (10%)	37 (37%)	37 (51%)	58 (94%)	<0.001
Conclusive exercise electrocardiogram	108 (62%)	34 (71%)	64 (65%)	40 (55%)	34 (52%)	0.22
Abnormal result	28 (26%)	5 (15%)	23 (36%)	14 (35%)	21 (62%)	<0.001
Catheter angiogram	7 (4%)	4 (8%)	25 (25%)	22 (30%)	39 (60%)	<0.001
50–70% stenosis	0	0	5 (20%)	5 (23%)	18 (46%)	<0.001
≥70% stenosis	1 (14%)	1 (25%)	4 (16%)	6 (27%)	16 (41%)	0.23
Revascularization	2 (1%)	1 (2%)	10 (10%)	11 (15%)	35 (54%)	<0.001

Abbreviation as in Table 1.
* Analysis of variance.
[†] Estimated annual risk of cardiovascular death (SCORE²⁵).
[‡] Angina score: typical angina = 3, atypical angina = 2, nonanginal = 1.
[§] Pretest probability of obstructive CAD using criteria of Diamond and Forrester.⁵

No calcium was detected in 175 patients (37%), of whom only 3 of 170 diagnostic CT angiograms showed obstructive CAD (2%; Figure 1, Table 3). None of these 3 patients had diagnostic exercise electrocardiograms, and all underwent invasive angiography. Two patients underwent percutaneous coronary intervention of the left anterior descending coronary artery. One of these (43-year-old man) showed undisputable, severe stenosis (Figure 2), and the other (61-year-old man) had a borderline bifurcation lesion, without quantitative angiographically confirmed significance, and was treated on clinical grounds. The patient in whom CTA overestimated disease severity was a 79-years-old woman. In patients without

Figure 1: Number of patients with unavailable, negative (normal), and positive (abnormal) CT angiographic and exercise electrocardiographic results (percentage of total) stratified by CCS group.

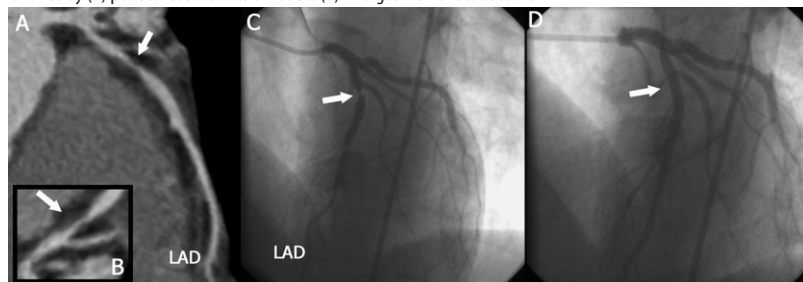


CCS	CTA	XECG	Quantitative Catheter Angiographic Diameter Stenosis >50%
0	0-49%	normal	0/2
		ischemia	0/2
		unavailable	0/2
0.1-10	0-49%	normal	1/3
		ischemia	0/2
		unavailable	0/1
11-100	0-49%	normal	1/1
		ischemia	0/1
		unavailable	0/1
101-400	0-49%	normal	1/4
		ischemia	2/8
		unavailable	3/5
>400	0-49%	normal	3/6
		ischemia	0/1
		unavailable	1/1
Total	0-49%	normal	1/7
		ischemia	4/5
		unavailable	5/7
Total	0-49%	normal	0/1
		ischemia	7/8
		unavailable	14/14
Total	0-49%	normal	12/15
		ischemia	55/96
		unavailable	452

Diagnostic results per test are presented as numbers of patients (percentages). Patients without diagnostic calcium scores or CT angiograms (n = 19) were in not included in this table. Quantitative catheter angiographic results are presented as number of patients with ≥50% stenosis/total catheterizations. Unavailable tests include tests not performed, not interpretable, or not conclusive.

obstructive CAD on CT angiogram, 28 patients (17%) had a positive exercise electrocardiogram, although quantitative coronary angiogram did not show significant stenosis in the few who underwent catheterization. A low CCS (<10) was found in 48 patients (10%), 5 of whom had obstructive CAD on CT angiogram. After a positive exercise electrocardiogram in 3, 1 had

Figure 2: Exceptional case of severe coronary obstruction without detectable calcium by computed tomography. This 45-year-old man with a positive family history for cardiovascular disease presented with recently progressive, typical, stress-induced chest pain. No exercise testing was performed because of precordial STT changes at rest. Although no calcium was detected, (A) CT angiogram showed severe (noncalcified) obstruction of the proximal left anterior descending coronary artery (LAD) (arrows), which was confirmed by (C) catheter angiogram, and then followed by (D) percutaneous revascularization. (B) Enlarged view of obstruction.



quantitative angiographic confirmation of severe obstructive disease. The others had relief of symptoms on medical treatment.

A CCS from 10 to 400 was found in 175 patients (37%). Obstructive CAD was found on CT angiogram in 74 patients (42%), and exercise electrocardiogram was positive in 37 patients (21%, 36% of conclusive tests), with poor agreement between tests ($\kappa = 0.10$).

A CCS >400 was found in 65 patients (14%). CTA could exclude obstructive CAD in no more than 4 (6%). In patients with a diagnostic exercise electrocardiogram, the test was normal in 13 of 34 (38%). By QCA 34 of 39 patients (87%) showed significant CAD.

For patients in whom all tests produced diagnostic results, overall diagnostic accuracy to assess significant coronary stenosis compared to QCA was comparable among CCS, CTA, and XECG (Table 4). CTA and CCS with a low threshold (>0) were more sensitive than XECG, whereas XECG and CCS with a high threshold (>400) were significantly more specific than CTA.

Analysis	TP	TN	FP	FN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
All (n = 58)									
CCS >0	33	4	21	0	100	16 (2–30)	61 (48–74)	100	64 (51–76)
CCS >100	27	16	9	6	82 (69–95)	64 (45–83)	75 (61–89)	73 (58–87)	74 (63–85)
CCS >400	21	24	1	12	64 (47–80)	96 (88–100)	96 (87–100)	67 (47–86)	78 (67–88)
CTA	32	9	16	1	97 (91–100)	36 (17–55)	67 (53–80)	90 (82–99)	71 (59–82)
XECG	23	19	6	10	70 (54–85)	76 (59–93)	79 (65–94)	66 (48–83)	72 (61–84)
CCS 1–400 (n = 32)									
CTA	11	5	15	1	92 (76–100)	25 (6–44)	42 (23–61)	83 (69–98)	50 (33–67)
XECG	9	16	4	3	75 (51–100)	80 (63–98)	69 (44–94)	84 (64–100)	78 (64–92)

Diagnostic performance of CCS based on consecutive cut-off values, CT angiogram, and exercise electrocardiogram to identify patients with ≥ 1 vessel with $\geq 50\%$ diameter stenosis by quantitative catheter angiography. Patients with unavailable test results (unavailable CT angiogram, n = 1; exercise electrocardiogram, n = 38; CT angiogram and exercise electrocardiogram, n = 1) were excluded. Subanalysis for patients with a CCS from 1 to 400. Sensitivity, specificity, PPV, NPV, and accuracy are presented with 95% confidence intervals.
FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.

DISCUSSION

Coronary CTA has emerged as a noninvasive angiographic alternative in patients with suspected CAD. Drawbacks of CTA are the substantial radiation dose and need for potentially nephrotoxic contrast medium. The large difference in radiation dose between CTA and CCS is becoming smaller but unlikely to completely disappear, despite new dose-saving acquisition techniques.⁷ In this large prospective registry we report the clinical value of low-dose, nonenhanced calcium imaging by computed tomography in the diagnostic workup of symptomatic patients. A negative CCS makes obstructive CAD very unlikely and is associated with an excellent prognosis.^{4, 8, 9 and 10} Also in our study the prevalence of significant coronary obstruction by CTA or QCA was very low in patients with a negative CCS. Of 175 patients only 3 showed coronary obstruction on CT angiogram, of whom only 1 case was confirmed by QCA. Few cases of obstructive disease were detected in patients with a low CCS (<10), despite undeniable evidence of atherosclerotic disease presenting in these patients. In a retrospective analysis of 554 patients (64% symptomatic), Cheng et al¹¹ showed that the prevalence of obstructive CAD in patients with a low calcium score is low (8.7% stenosis prevalence, CCS 1 to 50 for men, 1 to 10 for women), but significantly higher compared to those with a negative CCS (0.5%), which is in line with our findings.

In patients with a low–intermediate CCS (10 to 400), CTA could be performed with interpretable results in more patients compared to XECG and ruled out obstructive CAD in 56% of these patients. Our study confirmed the very modest agreement between functional tests and CTA.^{12, 13, 14, 15 and 16} Patients with a positive CT angiogram (42%) had significant stenosis on quantitative angiogram more often when exercise electrocardiogram was also positive ($p = 0.034$).

As expected, obstructive CAD was more frequent in patients with a high CCS. CTA is less accurate and tends to overestimate stenosis severity in patients with extensive calcifications.^{17 and 18} Indeed, CTA excluded obstructive CAD in no more than 4 patients (6%).

In patients with diagnostic test results CTA and CCS with a low threshold showed the highest sensitivity, although specificity was significantly better for XECG or CCS with a higher threshold.

The debate as to whether functional or anatomical tests are preferred for the workup of suspected CAD is ongoing. Although XECG is considered more cost effective, it has poor diagnostic performance.¹⁹ Similar to a negative stress test result, a negative CCS also has an excellent prognosis.^{7, 8, 9, 19 and 20} This suggests that a negative CCS could suffice to rule out obstructive CAD without the need for further testing. Whether this includes patients with a very low CCS (<10) is debatable.¹¹ Those with a low–moderate CCS (<400) could undergo CTA to rule out obstructive CAD. Stress testing would be reserved for patients with obstructive CAD on CT angiogram or a CCS >400. When prognostically important left main coronary artery, proximal left anterior descending coronary artery, or 3-vessel disease was absent on

CT angiogram, we found this increased our confidence to initiate and maintain medical treatment before referral to invasive angiography. Prospective trials will need to establish whether this or other implementations of cardiac computed tomography are effective and efficient in the workup of patients with chest pain.

Because cardiac catheterization was not performed in all patients, it is not possible to completely exclude angiographic CAD in all patients. Based on the reported good negative predictive value of CTA and the assumption that patients with borderline lesions and compelling, nonresolving symptoms would eventually be catheterized, we expect the number of missed lesions to be very small.²¹ A low disease prevalence, verification bias, and selective use of invasive angiography likely contributed to the low specificity of CTA compared to previous studies.^{22 and 23} Our findings should not yet be extrapolated to patients with unstable symptoms, in whom significant obstructive CAD without calcification may be more prevalent.²⁴

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Chapter 13

Computed Tomography versus exercise electrocardiography in Patients with stable Chest Complaints: real World Experience from a Fast-Track Chest Pain Clinic

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ABSTRACT

Objective: To compare the diagnostic performance of CT angiography (CTA) and exercise electrocardiography (XECG) in a symptomatic population with a low–intermediate prevalence of coronary artery disease (CAD).

Design: Prospective registry.

Setting: Tertiary university hospital.

Patients: 471 consecutive ambulatory patients with stable chest pain complaints, mean (SD) age 56 (10), female 227 (48%), pre-test probability for significant CAD >5%.

Intervention: All patients were intended to undergo both 64-slice, dual-source CTA and an XECG. Clinically driven quantitative catheter angiography was performed in 98 patients. Main outcome measures: Feasibility and interpretability of, and association between, CTA and XECG, and their diagnostic performance with invasive coronary angiography as reference.

Results: CTA and XECG could not be performed in 16 (3.4%) vs 48 (10.2%, $p<0.001$), and produced non-diagnostic results in 3 (0.7%) vs 140 (33%, $p<0.001$). CTA showed ≥ 1 coronary stenosis ($\geq 50\%$) in 140 patients (30%), XECG was abnormal in 93 patients (33%). Results by CTA and XECG matched for 185 patients (68%, $p=0.63$). Catheter angiography showed obstructive CAD in 57/98 patients (58%). Sensitivity, specificity, positive and negative predictive value of CTA to identify patients with $\geq 50\%$ stenosis was 96%, 37%, 67% and 88%, respectively; compared with XECG: 71%, 76%, 80% and 66%, respectively. Quantitative CTA slightly overestimated diameter stenosis: 6 (21%) ($R=0.71$), compared with QCA. Of the 312 patients (66%) with a negative CTA, 44 (14%) had a positive XECG, but only 2/17 who underwent catheter angiography had significant CAD.

Conclusion: CTA is feasible and diagnostic in more patients than XECG. For interpretable studies, CTA has a higher sensitivity, but lower specificity for detection of CAD.

INTRODUCTION

Exercise electrocardiography (XECG) is a well-established and inexpensive procedure to evaluate patients with suspected angina pectoris, and has been in widespread clinical use for decades. While considered cost effective, the test is also known for its modest diagnostic accuracy,¹ which in practice often leads to multiple testing. Multislice computed tomography allows non-invasive angiography of the coronary arteries, and has emerged as a diagnostic alternative in patients with suspected coronary artery disease (CAD).² However, recommendations for the use of CT angiography (CTA) are based on studies in populations often with high disease prevalence.^{3, 4, 5} Considering the Bayes' theorem, performance of CTA may not be comparable in low-risk populations—the group of patients in whom the test is most commonly used. In this study we explored the value of 64-slice, dual-source CTA in a large, real-world, symptomatic population with a low–intermediate disease prevalence, and compared it with XECG.

METHODS

Study population

Between September 2006 and December 2008, 471 consecutive patients with stable chest pain and no history of CAD were evaluated at our 1-day chest pain clinic. All patients with a pre-test probability $>5\%$ ⁶ were intended to undergo XECG and contrast-enhanced cardiac CT, in addition to a clinical examination, blood analysis and echocardiography. Angina was categorised as typical: retrosternal discomfort, precipitated by exercise or emotion, relieved within 10 min after rest or nitroglycerin; atypical: with only two of the previous characteristics; or non-anginal: with none or only a single characteristic (Table 1). The study was approved by the institutional ethical committee and informed consent was obtained from all patients.

Computed tomography

Contraindications to CTA were pregnancy, known allergy to iodine contrast media, impaired kidney function. Contrast-enhanced, 64-slice dual-source CT (Siemens Definition, Forchheim, Germany) was performed with the following parameters: spiral mode, collimation 32×0.6 mm, 64-channel acquisition using Z-axis alternation of the focal spot, rotation time 330 ms, temporal resolution 83 ms, tube voltage 120 kV, tube current 380–412 mA depending on the patient size, variable pitch depending on the heart rate. Prospectively ECG-triggered tube modulation was used in all patients with a regular heart rate. A 70–100 ml bolus was injected at 5.0–5.5 ml/s through a peripheral vein in the arm, followed by 40 ml of saline

Table 1 Patient characteristics (n = 471)	
Characteristics	Value
Age (years), mean (SD)	56 (10)
Female: male	227: 244 (0.48:0.52)
Risk profile	
Nicotine abuse	138 (0.29)
Hypertension	233 (0.49)
Diabetes	68 (0.14)
Dyslipidaemia	280 (0.59)
Family history of CVD	214 (0.45)
History of vascular disease	31 (0.07)
Chest pain	
Typical angina	146 (0.31)
Atypical angina	251 (0.53)
Non-anginal chest pain	74 (0.16)
Pre-test probability (%), mean (SD) ⁶	52 (28)
Heart rate (min ⁻¹), mean (SD)	68 (13)
Catheter angiography	
>50% Stenosis, any vessel	98 (0.21)
Single-vessel disease	57/98 (0.58)
Two-vessel disease	26/98 (0.27)
Three-vessel disease	19/98 (0.19)
	12/98 (0.12)
>70% Stenosis, any vessel	29/98 (0.30)
Percutaneous or surgical management	59 (0.13)
Percutaneous intervention	46 (0.10)
Bypass graft surgery	13 (0.03)
Results are shown as number (proportion of the total) unless stated otherwise. CVD, cardiovascular disease.	

at the same injection rate. A bolus tracking technique was used to synchronise the data acquisition with contrast enhancement. Patients received a sublingual dose of nitroglycerin just before the scan. No additional β blockers were administered. Retrospective ECG-gated image reconstruction was performed using a slice thickness of 0.75 mm, with an overlap of 0.4 mm. End-systolic and/or diastolic datasets were created depending on the heart rate and the ECG-triggered tube modulation protocol.

The coronary arteries, the right coronary artery, left main stem, left anterior descending coronary artery and left circumflex branch, were assessed using the axial images, multiplanar reformations and maximum intensity projections. Vessels were qualitatively scored as significantly stenosed (>50% diameter narrowing), less than significantly stenosed (<50%) or normal.

Exercise ECG

XECG on a bicycle ergometer was performed by standardised protocol. XECG was not performed if the patient was technically or physically unable to perform the test, or in patients with a significantly abnormal resting ECG. During continuous ECG registration and 12-lead prints at 1 min intervals, the workload was increased from 40 W by 20 W increments at 2 min intervals. Blood pressure was measured every 2 min. Criteria for discontinuation were systolic blood pressure >230 mm Hg, diastolic blood pressure >130 mm Hg, a >10 mm Hg systolic blood pressure drop, ST depression >0.3 mV, ST elevation >0.1 mV, sustained ventricular tachycardia, increasing frequency of polymorphic ventricular complexes, altered atrioventricular or intraventricular conduction, exhaustion, severe dyspnoea, angina or other discomfort. Criteria for myocardial ischaemia included horizontal or downsloping ST depression or elevation >0.1 mV measured at 80 ms from the J point during or after exercise, or typical, increasing angina during exercise. The XECG was considered non-diagnostic if the test was discontinued without evidence of myocardial ischaemia before the 85% target heart rate was reached.

Invasive angiography

Clinically indicated cardiac catheterisation was performed in 98 patients using standard techniques. Semiautomatic quantification angiography (QCA) of luminal obstruction was performed by an independent, blinded observer. Maximum lumen diameter stenosis $\geq 50\%$ was considered moderate, $\geq 70\%$ was considered severely stenosed.

Quantitative coronary angiography

For patients who underwent invasive coronary angiography, coronary obstructions were also quantitatively assessed on CTA, using validated semiautomatic quantification software (Circulation; Siemens, Forchheim, Germany).^{7,8} After vessel segmentation and centre-lumen line reconstruction, short-axis images of the vessel at submillimetre increments were reconstructed. The lumen area was automatically quantified based on attenuation thresholds, with the option for manual adjustments. The diameter stenosis was calculated from the minimal lumen area and the average of the proximal and distal reference area, with the assumption of a circular shape of the respective lumen areas.

For the quantitative comparison of CTA and QCA all vessels were included, and the most severe lesion for each vessel was used in the analysis. Both for CTA and QCA normal vessels and vessels with minor wall irregularities or mildly obstructive plaque were visually scored as 0% and 20% stenosis, respectively. Severely calcified obstructions that could not be processed automatically, required qualitative assessment, classified as moderately stenosed (50–70%),

severely stenosed (>70–99%), or completely obstructed (100%), and were recorded as 60%, 80% and 100%, respectively, in comparison with quantitative invasive angiography. Quantitative analysis was possible for CTA in 150, and for QCA in 143 vessels.

Statistical analysis

Summary data are presented as numbers (proportions) or means (SD), unless otherwise indicated. Diagnostic performance is expressed as sensitivity, specificity, positive predictive value and negative predictive value, with 95% confidence intervals. Association between quantitative CT and catheter angiography measurements were analysed using the Pearson coefficient. Differences between groups were compared using a two-sided unpaired t test, a χ^2 test or analysis of variance test. p Values <0.05 were considered significant. For lesions where quantitative CT analysis could not be applied (inferior image quality, extensive calcification) visually moderate and severe stenosis were classified as 60% or 80% diameter stenosis. Segments with wall irregularities on QCA or non-obstructive plaque on CT were semiquantified as 20% stenosis. Statistical analysis was performed using SPSS, version 15.0 (SPSS, Chicago, USA).

RESULTS

CTA could not be performed in 16 patients (3.4%), for reasons of renal failure, known contrast allergies, patient preferences, Parkinson's disease, patient non-cooperation, lack of venous access and severe obesity. Three scans (0.7%) failed because of patient movement (two) and premature scan initiation (one). Interpretable CT scans were available in 452/471 (96%) patients (Table 2). Three patients (0.7%) had mild to moderate allergic reactions.

XECG could not be performed in 48 (10.2%) patients because of orthopaedic restraints (13), neurological restraints (four), severe obesity (two), resting ECG abnormalities (six), pulmonary disease (two), combination/unspecified (21). For the 423 XECGs performed the mean (SD) maximum workload was 143 (47) W (1.00 (24)% of the predicted workload), and the maximum heart rate was 87 (13)% of the target heart rate. Results were considered inconclusive in 140/423 (33%) patients, mostly because the target heart rate was not reached.

CTA and XECG test agreement

The percentage of CT angiograms with >50% stenosis in at least one vessel: 30% (140/452), was comparable to the proportion of abnormal X-ECGs: 33% (93/283, P=0.63)(Table 2). CTA and XECG results matched in 185/274 (68%) patients with interpretable results (Figure 1).

	XECG not performed (n = 178)	Negative agreement (n = 138)	Disagreement (n = 89)	Positive agreement (n = 47)	p Value*
Gender (female)	91 (0.51)	79 (0.57)	40 (0.45)	7 (0.15)	<0.001
Age (years), mean (SD)	57 (10)	52 (9)	56 (10)	59 (9)	<0.001
Heart rate (min ⁻¹), mean (SD)	68 (12)	70 (13)	68 (10)	64 (12)	0.02
Pre-test probability (%), mean (SD)	57 (27)	45 (25)	52 (28)	68 (32)	<0.001
Risk profile					
Nicotine abuse	59 (0.33)	40 (0.29)	23 (0.26)	14 (0.30)	0.65
Hypertension	98 (0.55)	52 (0.38)	43 (0.48)	27 (0.57)	0.01
Dyslipidaemia	102 (0.57)	78 (0.57)	55 (0.62)	36 (0.77)	0.08
Diabetes	27 (0.15)	12 (0.09)	16 (0.18)	8 (0.17)	0.18
Family history of CVD	72 (0.40)	75 (0.54)	39 (0.44)	20 (0.43)	0.09
History of vascular disease	20 (0.11)	4 (0.03)	3 (0.03)	5 (0.11)	0.01
Chest pain symptoms					
Typical	60 (0.34)	26 (0.19)	28 (0.31)	27 (0.57)	0.003
Atypical	97 (0.54)	90 (0.65)	43 (0.48)	12 (0.26)	
Non-anginal	21 (0.12)	22 (0.16)	18 (0.20)	8 (0.17)	
CT angiography					
>50% Stenosis, any vessel	48 (0.27)	0	45 (0.51)	47 (1.0)	<0.001
Single-vessel disease	19 (0.11)	0	26 (0.29)	16 (0.34)	<0.001
Two-vessel disease	16 (0.09)	0	10 (0.11)	13 (0.28)	<0.001
Three-vessel disease	13 (0.07)	0	9 (0.10)	18 (0.38)	<0.001
Catheter angiography					
>50% Stenosis, any vessel	38 (0.21)	6 (0.04)	27 (0.30)	25 (0.53)	<0.001
Single-vessel disease	22 (0.12)	0	11 (0.12)	22 (0.47)	
Two-vessel disease	8 (0.04)	0	7 (0.08)	8 (0.17)	
Three-vessel disease	9 (0.05)	0	3 (0.03)	8 (0.17)	
Revascularisation	5 (0.03)	0	1 (0.01)	6 (0.13)	<0.001
Revascularisation					
Bypass graft surgery	25 (0.14)	0	11 (0.12)	22 (0.47)	<0.001
Percutaneous intervention	5 (0.03)	0	1 (0.01)	7 (0.15)	0.05
	20 (0.11)	0	10 (0.11)	15 (0.32)	0.03

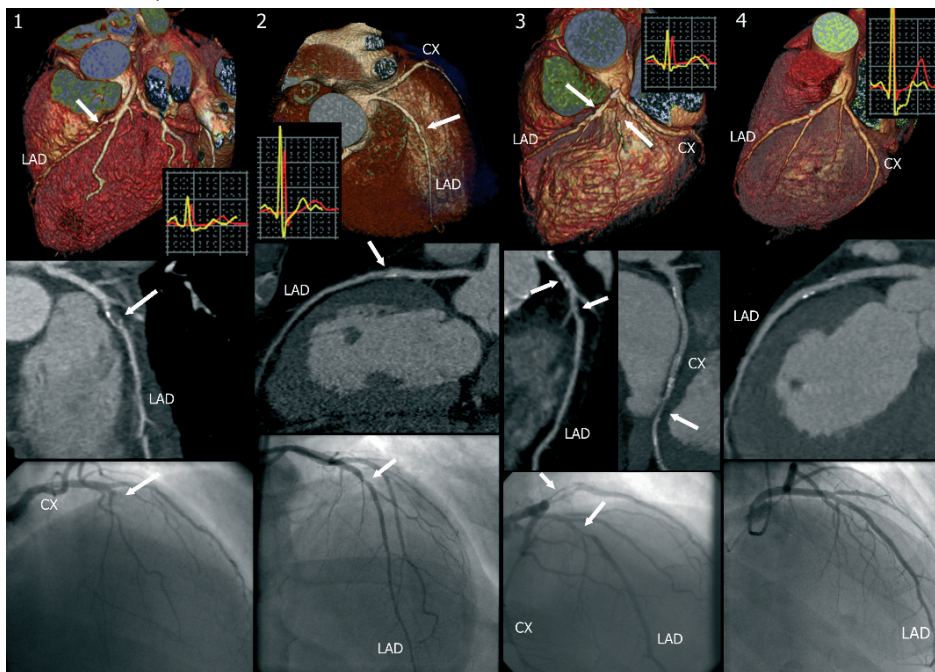
Results are shown as number (proportion of the total) unless stated otherwise.
 *Analysis of variance test. Excluding 19 patients with unavailable CT angiography results.
 CVD, cardiovascular disease.

Diagnostic performance compared with quantitative coronary angiography

Clinically driven invasive angiography was performed in 98 patients (21%), which showed significant CAD in 57 (58%). Including patients with both positive XECG and CTA, without invasive angiography for confirmation, the total number of patients with significant CAD was 89 (19%). Only 59 (13%) patients underwent percutaneous (46) or surgical revascularisation (13).

The sensitivity of CTA to identify patients with any >50% CAD was significantly better than XECG (Table 3): 96% (95% CI 86% to 99%) compared with 71% (52% to 84%), respectively. After exclusion of non-diagnostic cases specificity was significantly better for XECG than for CTA: 76% (54% to 90%) versus 37% (23% to 53%), respectively. When an intention-to-

Figure 1: CT angiography (CTA; three-dimensional volume rendered and curved reconstructions), invasive coronary angiography (QCA), and maximum ST depression on exercise ECG (XECG, insert) of four patients: (1) A 54-year old woman with a symptomatic exercise test, though modest ST depression (insert), and severe obstructive disease in the left anterior descending coronary artery (LAD) on both CTA and QCA. (2) A 62-year-old man with atypical complaints, a negative XECG, a moderate stenosis with calcification on CTA, but less than significant QCA. (3) A 55-year-old man with atypical angina, a negative XECG, but three-vessel disease on CTA and QCA, including the LAD, the intermediate branch, a marginal branch and the left circumflex branch (CX). (4) A 47-year-old man with atypical angina and a positive XECG, but without significant obstruction on CTA or QCA.



diagnose approach was used, which includes non-diagnostic tests as positive results, the specificity of XECG decreased to the same level as CTA. Combined CTA and XECG (positive results for both) improved specificity, at a loss of sensitivity. CTA was not significantly more sensitive in patients with a diagnostic exercise test than in those who could not perform XECG or had an inconclusive result.

Quantitatively CTA correlated fairly with QCA, with a slight overestimation of diameter stenosis severity (per vessel): 6 (21%) ($R=0.71$). Quantitative measurements between CT and QCA correlated best for the right coronary artery ($R=0.79$) and least for the left main coronary artery ($R=0.22$).

Potential value of complementary imaging

CTA did not show significant stenosis in 312 patients (66%), of whom 44 (14%) had a positive XECG. Seventeen patients (5%) had a clinical need for invasive angiography, which was positive in two patients (0.6%), of whom only one had a positive XECG. XECG was negative in

Table 3 Diagnostic performance of CT angiography (CTA) and exercise electrocardiography (XECG) for detection of (invasive) angiographic significant coronary artery disease, per patient (n = 98)

Analysis	Excl	TP	TN	FP	FN	Sensitivity (%) Mean (95% CI)	Specificity (%) Mean (95% CI)	Positive PV (%) Mean (95% CI)	Negative PV (%) Mean (95% CI)
<i>Per patient analysis, ≥50% QCA stenosis</i>									
CTA (≥50% stenosis)	2	53	15	26	2	96 (86 to 99)	37 (23 to 53)	67 (55 to 77)	88 (62 to 98)
XECG	39	24	19	6	10	71 (52 to 84)	76 (54 to 90)	80 (61 to 92)	66 (46 to 81)
CTA + XECG	40	22	22	3	11	67 (51 to 83)	88 (75 to 100)	88 (75 to 100)	67 (48 to 85)
<i>Per patient analysis, ≥50% QCA stenosis, intention to diagnose</i>									
CTA (≥50% stenosis)	–	55	15	26	2	96 (87 to 99)	37 (23 to 53)	68 (56 to 78)	88 (62 to 98)
XECG	–	47	19	22	10	82 (70 to 91)	46 (31 to 62)	68 (56 to 79)	66 (46 to 81)
<i>Per patient analysis, ≥70% QCA stenosis</i>									
CTA (≥50% stenosis)	2	27	16	52	1	96 (80 to 100)	24 (14 to 36)	34 (24 to 46)	94 (69 to 100)
XECG	39	16	25	14	4	80 (56 to 93)	64 (47 to 78)	53 (35 to 71)	86 (67 to 95)
CTA + XECG	40	15	29	10	4	79 (61 to 97)	74 (61 to 88)	60 (41 to 79)	88 (75 to 100)
<i>Per patient analysis, ≥70% QCA stenosis, intention to diagnose</i>									
CTA (≥50% stenosis)	–	28	17	52	1	97 (80 to 100)	25 (15 to 37)	35 (25 to 47)	94 (71 to 100)
XECG	–	25	25	44	4	86 (67 to 95)	36 (25 to 49)	36 (25 to 49)	86 (67 to 95)
<i>Per vessel analysis, CT angiography (≥50% stenosis)</i>									
>50% QCA stenosis	8	83	218	68	15	85 (78 to 92)	76 (71 to 81)	55 (47 to 63)	94 (90 to 98)
Diagnostic XECG	4	52	133	41	6	90 (82 to 98)	76 (70 to 83)	56 (46 to 66)	96 (92 to 100)
Non-diagnostic XECG	4	31	85	27	9	78 (65 to 90)	76 (68 to 84)	53 (41 to 66)	90 (83 to 98)
>70% QCA stenosis	8	27	229	124	4	87 (75 to 99)	65 (60 to 70)	18 (12 to 24)	98 (96 to 100)

Diagnostic performance of (CTA), exercise ECG (XECG), or combined (with both tests required positive), by per patient or per vessel analysis, using either a >50% or >70% quantitative catheter angiography (QCA) threshold as reference. Unavailable data were excluded, or assumed positive in the intention-to-diagnose analysis. Subanalysis in patients with diagnostic or non-diagnostic XECG results (including XECGs not performed). FN, false negative; FP, false positive; PV, predictive value; TN, true negative; TP, true positive.

190 patients (40%), of whom 45 (24%) had a positive CTA. Of the 29 patients who underwent QCA, 10 had significantly obstructive coronary disease, all with positive CTAs (figure 2).

Among patients with a positive CTA (140), for those with a positive XECG (47, 34%) QCA showed more, and more severe CAD: 22/25 significant, 15/25 severe stenosis; compared with those with a negative XECG (45, 32%): 10/23 significant ($p=0.001$), 4/23 severe CAD ($p<0.003$).

Within the group of patients without interpretable XECGs, CAD was ruled out by CTA in 30/188 (69%) patients, contradicted by QCA in only a single patient out of seven catheterised.

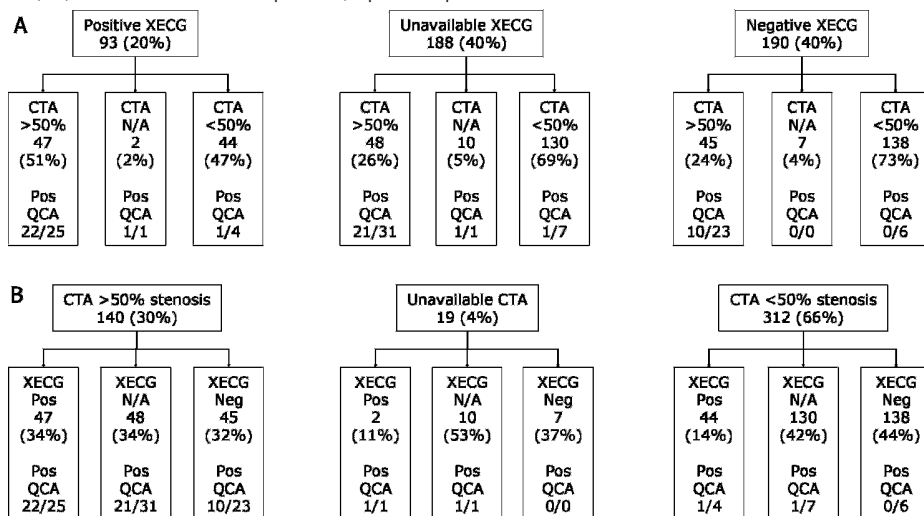
Most patients with a non-diagnostic XECG and positive CTA underwent QCA (31/48, 65%), which confirmed significant disease in 21 (68%).

DISCUSSION

Diagnostic evaluation of chest pain of recent onset

Chest pain is a common symptom, and a potential manifestation of coronary heart disease. Despite a modest diagnostic accuracy of merely 70%, combined with a thorough clinical assessment, XECG remains the most widely used test to assess the presence of ischaemic heart disease.¹ Rapid-access chest pain clinics, which have emerged over the past decade, appear effective to assess patients early after the onset of symptoms and to identify patients at increased risk for adverse cardiac events.^{8,9} In patients diagnosed with angina, based on

Figure 2: Virtual flow chart of exercise ECG (XECG) followed by coronary CT angiography (CTA) (A), and CTA followed by XECG (B). Unavailable tests (N/A) include tests that could not be performed, or produced equivocal results.



clinical assessment, resting ECG and XECG, death to coronary heart disease or acute coronary syndrome was reported in 16.5% at 3 years' follow-up, compared with 2.7% in patients with non-cardiac complaints.¹⁰ Nevertheless, nearly one-third of all major adverse coronary events occurred in the (larger) group of patients thought not to have coronary related complaints, which is explained by the fact that luminal obstruction is not required before these acute events. Furthermore, Sekhri, *et al*, demonstrated that after clinical evaluation, the XECG contributed only modestly to the prediction of outcome.¹¹ Taylor *et al*, reported that patients who were unable to perform an exercise test, or produced uninterpretable results, experienced major adverse events at a rate similar to that of patients classified as having stable angina pectoris.⁹ Considering these observations, XECG may be insufficient to stratify patients with undifferentiated chest pain according to risk. Stress imaging, which may be more accurate for myocardial ischaemia detection, shares the limitation of XECG with respect to the detection of less obstructive atherosclerotic disease.

Coronary CTA can be used to rule out (obstructive) coronary artery disease, particularly in patients at intermediate risk with non-conclusive stress test results.² Additional prognostic value may be found in the detection of coronary atherosclerosis by CT, whether obstructive or not.^{12 13}

Performance of CTA versus XECG

In this prospective registry of real-world, symptomatic patients with a low–intermediate prevalence of ischaemic heart disease, CT could be performed in more patients ($p < 0.001$), and interpretable results were more often achieved ($p < 0.001$). Using strict criteria, the num-

ber of non-diagnostic XECGs was 33%, which is high in comparison with previous reports (18–31%).^{14, 15} With quantitative invasive angiography as reference, the sensitivity of CTA to detect significant CAD was higher than XECG. Only after exclusion of non-diagnostic tests did XECG showed better specificity than CTA. Sensitivity and specificity of XECG for the detection of significant CAD on QCA was 71% and 76%, comparable to a large meta-analysis that reported a sensitivity and specificity of 68% and 77%.¹ Differentiation between severe stenosis and total occlusion can be difficult by CTA.¹⁶ Catheterisation showed 14 occluded vessels, which CTA assessed as occluded in eight, severely stenosed in three, moderately stenosed in two, and less than significantly stenosed in one patient (CT diameter stenosis 41%). There were no false-positive occlusions by CTA.

To date, two studies in populations of moderate size and high disease prevalence have compared the diagnostic performance of 16-slice CTA and XECG. Using an intention-to-diagnose approach Dewey *et al* found that CTA outperformed XECG for both sensitivity: 91% vs 73%, and specificity: 83% vs 31%, and a substantial number of non-assessable XECGs, as well as CTAs.¹⁷ In a population with a 74% disease prevalence Mollet *et al*, found a sensitivity and specificity of 100% and 87% for CTA, compared with 78% and 67% for XECG.¹⁸ Verification bias is assumed at least partially responsible for the lower specificity of CTA in our study—that is, patients with perceived stenosis (as a result of excessive calcification) were more likely to undergo clinically driven invasive investigation.

This study further confirmed earlier reported discrepancies between angiographic CTA and myocardial perfusion imaging.^{19,20,21} Some authors reported better agreement between CTA and nuclear imaging using a 70% stenosis cut-off point.²²

Clinical use of CTA in stable angina

CT could be performed with diagnostic quality in nearly all patients and could rule out obstructive CAD in 66% of patients, compared with 40% by XECG. Based on these results CT may be considered as initial test in patients with chest pain and reason to suspect CAD. A negative CTA virtually rules out ischaemic heart disease, requiring no further testing. In patients with obstructive CAD on CT, functional testing would be required to assess haemodynamic significance, localise ischaemia and determine the need for revascularisation. In our study not all patients with an abnormal exercise test were catheterised. In the absence of severe inducible ischaemia and prognostically important CAD—that is, left main or three-vessel disease, the caring doctors were more confident initiating and continuing medical treatment instead of referral for revascularisation.

Drawbacks of cardiac CTA include the lack of prognostic information from the patient's aerobic performance, the vulnerability of the technique to cardiac arrhythmia and the need for potentially nephrotoxic contrast media and radiation (10–15 mSv). Over the past few years a number of robust techniques have been (re-)introduced to decrease the radiation dose

associated with cardiac CT, including optimised ECG-triggered tube modulation for spiral acquisition protocols, variable table speed, ECG-triggered sequential acquisition protocols, anatomy-based dose modulation, lower tube output settings in smaller patients, tighter scan ranges, etc. Awareness of increased radiation dose by doctors, combined with contemporary technology, allows for routine cardiac CT at an effective dose below 5 mSv.^{23 24}

Study limitations

Referral to cardiac catheterisation and coronary angiography was clinically driven and not available in the majority of patients without non-invasive evidence of (severe) CAD. Many patients with positive CTAs and/or XECGs were treated medically, at least initially. Selective referral to invasive angiography probably had a positive effect on sensitivity and a negative effect on the specificity of CTA, in comparison with QCA. The results of this study have generated hypotheses for the use of CTA in patients with stable chest pain, which require testing in prospective, randomised trials.

CONCLUSION

Contrary to XECG, CT can nearly always be performed with diagnostic results. CTA was normal or showed less than significantly obstructive coronary disease in the majority of patients, in which case an abnormal exercise test or catheter angiogram was unlikely. With invasive angiography as a reference, CTA is more sensitive but less specific than XECG for the detection of significant CAD. Randomised trials are needed to define how CTA might be used (cost-) effectively in real-world patients with stable angina.

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Part V

General Discussion and Summary of the Thesis



Chapter 14

Summary and Conclusions



SUMMARY

In **chapter 2** we describe our experience during a three-year period with SonoVue, a second-generation contrast agent. SonoVue was used in 241 patients to improve endocardial border delineation, which in turn makes the assessment of segmental wall motion analysis, left ventricular ejection fraction and volumes calculations more reliable. SonoVue also improves the assessment of the right ventricular function, which is especially important in patients with congenital heart disease. In patients with non-compaction cardiomyopathy and hypertrophic cardiomyopathy during septal ablation echocardiographic images with SonoVue added important information to standard images. Another potentially important indication of contrast agents is the assessment of myocardial perfusion in patients with coronary artery disease. Although many publications report increase in diagnostic accuracy when contrast agents are added to routine echocardiography this has not yet led to widespread use of these agents in general cardiac practice. Probably issues like costs, safety and complexity are reasons for many cardiologists not to use contrast agents in routine practice. In conclusion we think that the use of SonoVue is helpful in providing detailed morphological and/or quantitative information of the heart. Although perfusion is a very attractive application of SonoVue we think its not yet applicable for routine practice.

In **chapter 3** we studied the effect of second harmonic imaging (SHI) on the image quality of a newly developed trans esophageal transducer (TEE). Although SHI was developed for the use of contrast echocardiography it was already known that SHI without the use of contrast improved image quality in trans thoracic echocardiography (TTE). In 14 patients, who underwent bypass surgery, images were made in 4 chamber view and the transgastric short-axis view. Endocardial border detection was scored in both fundamental and SHI mode in all 168 segments. Compared to fundamental imaging endocardial border delineation improved in 26% but worsened in 2% of 108 segments. Improvement was more evident in the short-axis view compared to 4-chamber view (37% vv 18%). It seems that the lower the quality of the fundamental image the greater the improvement when SHI is used.

In conclusion, although fundamental TEE shows good quality images, SHI further improves endocardial delineation.

In **chapter 4** we described whether adding a second-generation contrast agent could decrease the intra- and inter-observer variability for assessment of left ventricular ejection fraction (LV-EF). The assessment of LV-EF after acute myocardial infarction (AMI) is a marker of prognosis and used for selecting patients who benefit from an internal cardiac defibrillator. Although echocardiography is the most used imaging modality to assess LV-EF the high variability is a disadvantage of this technique. We studied 48 patients with AMI and measured

LV-EF in second harmonic mode with SonoVue (LVO), and in second harmonic mode without SonoVue (SHI). With LVO the intra-observer variability decreased from

12.5±11.5% to 7.0±7.0% ($p<0.001$) and inter-observer variability decreased from 16.9±9.9% to 7.0±6.2% ($p<0.001$). The improvement was found in patients both with good and moderate-to-poor image quality.

This study shows that assessment of LV-EF is more reliable with LVO as there is better intra- and inter-observer variability. If clinical decision making on LV-EF is made, we recommend using LVO in patients with good and moderate-to-poor quality images.

In **chapter 5** we studied the interobserver agreement for wall motion and wall motion score index (WMSI) in 100 patients who underwent both two-dimensional second harmonic (SH) and contrast left ventricular(LVO) echocardiography and to study the correlation between the LVO-imaged WMSI and left ventricular ejection fraction (LV-EF). Two independent observers' assessed LV segmental quality and wall motion both for SH and LVO studies according to a 17-segment model. Wall motion was defined as normokinesia, hypokinesia, akinesia and dyskinesia. LV-EF was assessed from the LVO images according to the biplane modified Simpson's method. Of the 1,700 analyzed segments, 453 (26,6%) were poorly visualized with SH imaging, and 173 (10,2%) with LVO imaging ($P<0.0001$). The two observers agreed on segmental wall motion in 1,299 segments (76%, Kappa 0.60) in SH imaging and in 1,491 segments (88%, Kappa 0.78) in LVO imaging. Interobserver correlation (r_2) was 0.86 for the SH-imaged WMSI and 0.93 for the LVO-imaged WMSI. The LVO- imaged WMSI correlated well with LV-EF ($r_2=0.71$). The conclusion of this study was that echo contrast improves interobserver agreement for wall motion scoring and the WMSI. The LVO-imaged WMSI correlates well with LV-EF.

In **chapter 7** myocardial contrast echocardiography (MCE) is used to visualize perfusion in 30 patients 2 days after Q-wave myocardial infarction (MI). Twenty patients were treated with thrombolytic therapy and 10 didn't receive reperfusion therapy. All patients underwent coronary angiography and 18 patients SPECT scintigraphy. MCE was performed using second harmonic imaging (SHI) and power Doppler imaging with an intravenous infusion of perfluorocarbon-exposed sonicated dextrose-albumin (PESDA). A 16-segment left ventricular model was used to relate perfusion to coronary artery territories. Sensitivity and specificity for MCE detecting segments supplied by the infarct-related artery were 82% and 95% respectively. These results were comparable with SPECT. Concordance between MCE and SPECT for detecting abnormal perfusion in a segment-by-segment analysis was 93%. A 6-week follow-up echocardiography was made to assess wall motion. Dysfunctional segment with hypo- or normal perfusion with power Doppler imaging at baseline had significant more recovery of function after 6- weeks than dysfunctional segments without perfusion.

Conclusion of this study is that power Doppler imaging with intravenous infusion of PESDA can detect reperfusion after acute MI. Also this non-invasive technique can predict late recovery of ventricular function.

In **chapter 8** we studied whether end-diastolic wall thickness (EDWT) can predict recovery of regional left ventricular contractile function after percutaneous coronary intervention (PCI).

Regional contractile function does not recover in all patients after PCI for acute myocardial infarction (AMI). Prediction of functional recovery after AMI may help in clinical decision making. Forty consecutive patients with AMI were studied with left ventricular contrast echocardiography for accurate wall thickness and function measurement and myocardial perfusion immediately after and two months following PCI.

Out of 640 segments, 175 (27%) dysfunctional segments in the infarct territory were analyzed for EDWT, wall function, and perfusion. One hundred and three (59%) dysfunctional segments presented with an EDWT <11 mm and 72 (41%) presented with an EDWT \geq 11 mm. Perfusion (partial or complete) was present in 63 segments with an EDWT <11 mm (61%) and 71 segments with an EDWT \geq 11 mm (99%) ($p < 0.001$). At two months' follow-up, 66 of 72 segments with an EDWT \geq 11 mm (92%) improved, whereas only 35 of 103 of the dysfunctional segments with an EDWT <11 mm (34%) improved ($p < 0.0001$).

Wall thickness is an easy parameter to predict recovery of function after revascularization. Moreover, combining EDWT and perfusion, segments with an EDWT \geq 11 mm, and presence of perfusion have the highest chance of recovery; segments with an EDWT <11 mm and perfusion have an intermediate chance of recovery. In segments with an EDWT <11 mm and no perfusion, chances of recovery are very low.

In **chapter 9** 29 patients with symptomatic severe aortic stenosis (AS) were studied and compared to control subjects with respect to left ventricular (LV) function. LV function is most commonly assessed as LV ejection fraction (LV-EF) by the modified Simpson's biplane disc method. Doppler tissue imaging (DTI) has shown to be more sensitive to identify subtle changes in both systolic and diastolic function in several conditions. We performed DTI measurements in 29 patients with severe AS and 17 age-matched control subjects with both normal LV-EF. AS patients had significant lower systolic- and diastolic DTI values compared to control subjects. Also, LV filling pressure expressed by the E/Em ratio was significantly higher in AS patients. DTI-derived variables were correlated with NT-proBNP levels. Conclusion of this study was that DTI derived variables showed systolic and diastolic dysfunction in patients with symptomatic severe AS while conventional echo parameters, as LV-EF, were normal.

In **chapter 10** 27 patients with severe aortic stenosis (AS) were followed one-year after aortic valve replacement (AVR). All had normal left ventricular ejection fraction (LV-EF) pre-operative and decreased Doppler tissue measurements (DTI) of both systolic- and diastolic function.

The aim of the study was to investigate if, and to which extent, the long-axis DTI depressed LV function was reversible after AVR. Echocardiography was performed 3 weeks, 6 months and 12 months after AVR. Values were compared with age-matched controls without cardiac disease. Long-axis systolic LV function measured on the lateral mitral annulus (Sm) improved 3 weeks after AVR and sustained in the follow up. Post-operative improved Sm were not different compared to the control group. Diastolic function expressed as the ratio of peak early filling mitral inflow by pulsed Doppler and early diastolic peak velocity lateral mitral annulus (E/Em) also improved but did not reach normal values compared to the control group. Conclusion of this observational study was that long-axis DTI systolic LV dysfunction was reversible in patients with severe AS and normal LV-EF after AVR. Diastolic DTI dysfunction improved but still remained abnormal one-year after AVR.

In **chapter 11** we studied the value of performing echocardiography in 500 consecutive patients evaluated for chronic chest pain (CCP). Cardiac investigations in patients CCP are focused on the detection of ischemia. In addition to stress tests, current guidelines recommend rest echocardiography in patients referred for the evaluation of CCP with an abnormal ECG, suspicion of heart failure and in the presence of murmurs. However, there are no prospective studies supporting this strategy. In 500 consecutive patients with intermediate and high risk for coronary artery disease (CAD) we performed a diagnostic protocol that consists of physical examination, ECG, bicycle exercise test and CT angiography. Also we performed handheld echocardiography (HHE) in all patients and compared these results with the final diagnosis made by the other exams. Abnormal HHE results were found in 15,6% of all patients. In 346 patients with normal blood pressure, no murmurs or signs of heart failure and a normal ECG only 10,4% had abnormal HHE. The majority of the findings by HHE had no implications for patient management. In contrast, abnormal findings were detected in 49 out of 154 patients (32%) with a guideline indication for HHE. Although systematic echocardiography in patients with chronic chest pain yields unexpected abnormalities in 10,4% of patients without abnormal findings by other investigations, the clinical relevance of these findings is limited. Our finding supports the current guideline to perform echocardiography in selected cases only.

In **chapter 12** we investigated the value of coronary calcium detection by computed tomography, in comparison with CT angiography and exercise testing, to detect obstructive coronary artery disease (CAD) in patients with stable chest pain. A total of 471 consecutive patients with new stable chest complaints were scheduled to undergo both dual-source multislice CT (Siemens, Germany): coronary calcium score (CCS) and CT coronary angiography (CTA), and exercise electrocardiography (XECG). Clinically driven invasive quantitative angiography (QCA) was performed in 98 patients. Only 3/175 (2%) of patients with a negative CCS had significant CAD on CTA, with only one confirmed by QCA. In patients with a high calcium score (Agatston score >400), CTA could exclude significant

CAD in no more than 4/65 patients (6%). Patients with a low-intermediate CCS, CTA more often yielded diagnostic results compared to XECG, and could rule out obstructive CAD in 56% of patients. For patients with CAD on CTA, those with abnormal XECG results more often showed severe CAD ($P<0.034$). In patients with diagnostic results for all tests the sensitivity and specificity to detect $>50\%$ QCA diameter stenosis was 100% and 15% for $CCS>0$, 82% and 64% for $CCS>100$, 97% and 36% for CTA, and 70% and 76% for XECG, respectively. In conclusion, non-enhanced CT for calcium detection is a reliable means to exclude obstructive CAD in stable, symptomatic patients. Contrast-enhanced CTA can exclude significant CAD in patients with a low-intermediate CCS, but is of limited value in patients with high CCS.

In **chapter 13** we compared the diagnostic performance of CT coronary angiography (CTCA) and exercise electrocardiography (X-ECG) in a symptomatic population with a low-intermediate prevalence of coronary artery disease (CAD). In this prospective registry we studied 471 ambulatory patients with complaints of stable chest pain, age 56 (SD 10), female 227 (48%) and pre-test probability for significant CAD $>5\%$. All patients had to undergo both 64-slice dual-source CTCA and an X-ECG. Clinically driven quantitative catheter angiography (QCA) was performed in 98 patients. The main outcome measures were the feasibility and interpretability of, and the association between CTCA and X-ECG, and their diagnostic performance using invasive coronary angiography as reference. CTCA and X-ECG could not be performed in 16 (3.4%) vs. 48 (10%, $P<0.001$), and produced non-diagnostic results in 3 (0.7%) vs. 140 (33%, $P<0.001$). CTCA showed ≥ 1 coronary stenosis ($\geq 50\%$) in 140 patients (30%), X-ECG was abnormal in 93 patients (33%). Results by CTCA and X-ECG matched for 185 patients (68%, $P=0.63$). Catheter angiography showed obstructive CAD in 57/98 patients (58%). Sensitivity, specificity, positive and negative predictive value of CTCA to identify patients with $\geq 50\%$ stenosis: 96%, 37%, 67% and 88%; compared to X-ECG: 71%, 76%, 80% and 66%. Quantitative CTCA slightly overestimated diameter stenosis: $6\pm 21\%$ ($R=0.71$), compared to QCA. Of the 312 patients (66%) with a negative CTCA, 44 (14%) had a positive X-ECG, but only 2/17 that underwent catheter angiography had significant CAD.

The conclusion of the study was that CTCA is feasible and diagnostic in more patients compared to X-ECG. For interpretable studies, CTCA has a higher sensitivity, but lower specificity for detection of CAD.

Conclusions

In the majority of patients referred to a cardiologist for diagnostic or therapeutic reasons cardiac imaging is needed. Several imaging techniques are available and each has its own advantages and disadvantages. In this thesis the value of some new modalities of echocardiography and computer tomographic angiography (CT-angiography) are evaluated in patients assessed by cardiologists at the Thoraxcenter.

Echocardiography is by far the most widely used imaging modality in clinical practice to obtain information about the structure and function of the heart and heart valves. Several patient characteristics, as obesity and chronic obstructive pulmonary disease, may decrease image quality and make reliable judgement of the cardiac structures sometimes difficult. In **chapter 2** we describe how the use of echo contrast improves the image quality. For many years qualitative description of left ventricular function as either severely, moderately or mildly impaired was sufficient for clinical purposes. Subsequently quantitative assessment of left ventricular ejection fraction was introduced for example to start medication after myocardial infarction and to decide which patients would benefit by implanting a cardioverter-defibrillator (ICD) to prevent sudden cardiac death. In most studies echocardiography was the imaging technique used to measure ejection fraction despite its high intra- and inter-observer variability. In **chapter 3, 4 and 5** we used second harmonic imaging and echo contrast to assess wall motion, wall motion score index and left ventricular ejection fraction. We showed improvement of endocardial border alignment resulting in reduced intra-observer variability and inter-observer variability for assessment of left ventricular ejection fraction. Also, more segments could be analysed with echo contrast. The wall motion score index, assessed with contrast, correlated well with ejection fraction. Therefore, we recommend using echo contrast agents when quantitative measurement of left ventricular wall motion, wall motion score index or ejection fraction is important.

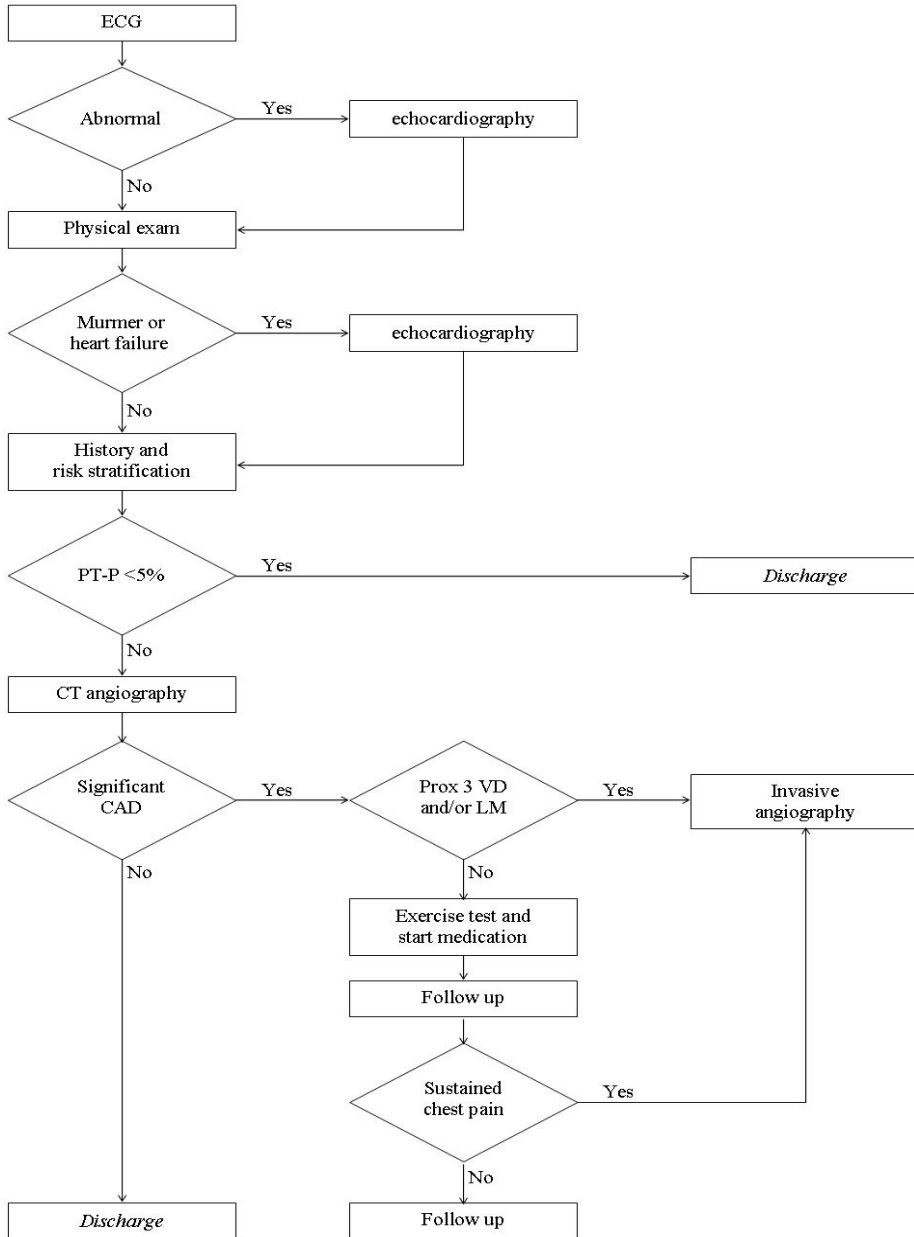
Myocardial contrast echocardiography is also used to detect myocardial ischemia caused by coronary artery disease and to predict recovery of function after myocardial infarction. In **chapter 7 and 8** we showed that myocardial perfusion and wall thickness as assessed by contrast echocardiography predict recovery of left ventricular function several weeks after myocardial infarction. Thus definite assessment of left ventricular function after a myocardial infarction has to take place at least several weeks after the acute event.

In many experimental and clinical studies including patients with hypertension, diabetes, valve disease and cardiomyopathy, Doppler tissue imaging is able to detect impaired longitudinal left ventricular function while ejection fraction is normal. Ejection fraction is relatively insensitive to detect these subtle changes in left ventricular systolic function. Patients with cardiac disease and impaired left ventricular ejection fraction have a worse outcome than those with normal ejection fraction. Therefore we studied the longitudinal systolic function assessed by Doppler tissue imaging as a possible early marker of left ventricular dysfunction in

patients with severe aortic stenosis and normal left ventricular ejection fraction (**chapter 9**). Longitudinal function was reduced compared to controls and appeared to be related to NT-ProBNP levels as independent sign of abnormal cardiac function. Interestingly, these Doppler tissue parameters improved after aortic valve replacement as shown in **chapter 10**. Because patients with severe aortic stenosis and abnormal ejection fraction have worse outcome after valve replacement compared to patients with normal ejection fraction earlier surgery might be considered. We propose that patients with reduced longitudinal systolic function, as an early sign of left ventricular impairment, should be considered for valve surgery to improve prognosis, even though left ventricular ejection fraction is still within the normal range. Further prospective and observational studies are needed to determine whether these measurements can be used indeed to select the optimal moment for valve replacement in asymptomatic patients with severe aortic stenosis and normal ejection fraction.

Chest pain can be caused by coronary artery disease and also by other cardiac and non-cardiac causes. In the study presented in **chapter 11** we investigated the clinical value of echocardiography when performed in all patients with chest pain. The yield of chest pain related cardiac diseases was very low. Although substantial other, not related to chest pain, cardiac abnormalities were found, these had no implications for the treatment or prognosis of the patients. Therefore we recommend performing echocardiography only in selected patients with chronic chest pain in the presence of heart murmurs, ECG abnormalities or signs of heart failure.

Another cardiovascular imaging technique that has been introduced in the last decade is CT-angiography. CT-angiography evaluated very rapidly and can now be used in the out-patient clinic. In **chapter 12 and 13** we studied the value of coronary calcium detection, CT-angiography and exercise testing. Patients without calcium had a 2% incidence, while patients with very high calcium-score had a 94% incidence of significant coronary artery disease. Exercise testing could not be performed or showed inconclusive results in 40% of patients. CT-angiography was superior to diagnose significant coronary artery disease compared to exercise testing. Further technical improvement and decreased radiation dose below 1 mSv allows a more liberal use of this technique in patients evaluated for chest pain. Implementation of CT-angiography will change our diagnostic protocol in these patients from an ischemia, to an anatomically approach. The following figure illustrates a possible future approach in patients with chronic chest pain:



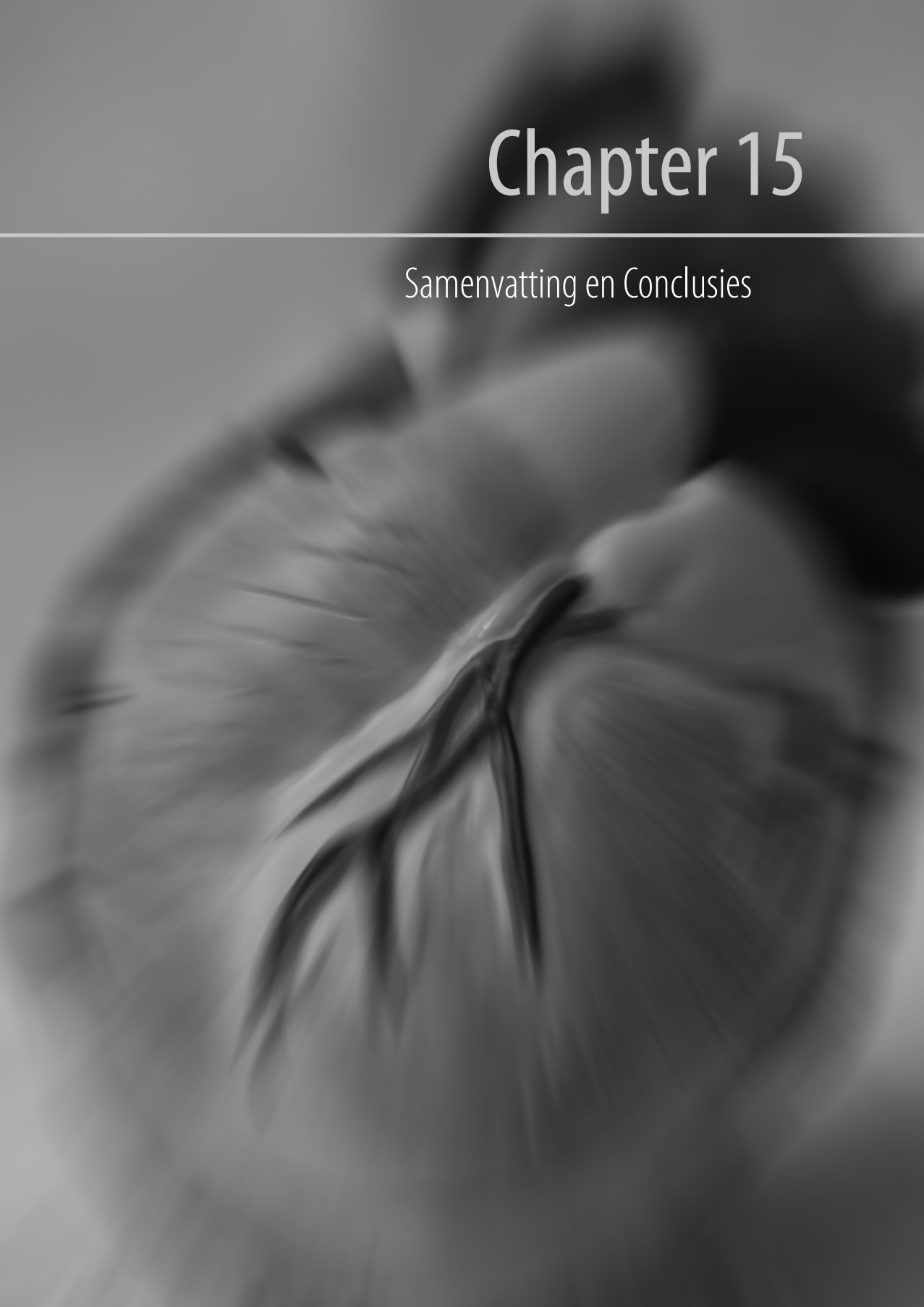
Abbreviations: PT-T, pre-test probability; 3 VD, 3 vessel disease; LM, left main; CAD, coronary artery disease.

Cardiovascular imaging in the future

At this moment not only echocardiography is becoming more complex with 3-dimensional echocardiography, speckle tracking, Doppler tissue imaging and strain imaging, which requires special expertise for recording and interpretation of the images, but also magnetic resonance imaging, positron emission tomography and multi-slice computer tomography evolve rapidly. The imaging modality chosen to answer a specific clinical question is currently based on limited individual experience as well as on availability and on the experience with the different techniques in each hospital. To optimize the use of these modalities in clinical practice we need to develop non-invasive cardiovascular imaging departments with access to all imaging modalities and cardiologists with extensive knowledge of all these techniques. They should decide which technique will be used for answering specific questions in patients. The studies presented in this thesis provide new information for positioning contrast echocardiography, Doppler tissue imaging and cardiac CT.

Chapter 15

Samenvatting en Conclusies



SAMENVATTING

In **hoofdstuk 2** beschrijven we onze ervaring opgedaan met het gebruik van SonoVue, een tweede generatie contrast middel, gedurende een periode van 3 jaar. SonoVue werd gebruikt bij 241 patiënten waarbij een verbetering werd gevonden van de afscheiding tussen myocard en bloed; de endocardial afscheiding. Dit vertaalde zich in een betere en nauwkeurige beoordeling van de ejectie fractie, volumina en analyse van wandbewegingen. Tevens werd een betere beoordeling van de rechter ventrikel gevonden wat vooral bij patiënten met een congenitale hartaandoening van grote waarde is. SonoVue werd verder gebruikt in cardiale aandoeningen als non-compaction cardiomyopathie en hypertrofische cardiomyopathie tijdens een alcoholablatie van het septum. Een potentieel belangrijke indicatie voor het gebruik van echocontrast middelen is het beoordelen van myocardperfusie, en dus ischeemie, in patiënten met coronair lijden. Hoewel vele publicaties aantonen dat het goed mogelijk is met echocontrast middelen myocard ischeemie aan te tonen heeft dit niet geleid tot grootschalig gebruik hiervan in de algemene cardiologisch praktijk. Waarschijnlijk spelen kosten van het contrastmiddel, veiligheids issues en complexiteit van het gebruik en techniek hierin een rol. Wij concluderen dat het gebruik van SonoVue additionele waarde heeft t.o.v. conventionele echocardiografie als gedetailleerde morfologisch en/of kwantitatieve informatie van het hart gevraagd wordt. Voor routine gebruik van echocontrast voor het aantonen van myocardperfusie defecten als uiting van coronair lijden in de algemene cardiologisch praktijk is deze techniek nog niet geschikt.

In **hoofdstuk 3** bestuderen we de invloed van second harmonic imaging (SHI) op de kwaliteit van de beelden verkregen met een nieuw ontwikkelde trans oesophageale transducer (TEE). Aanvankelijk was SHI ontwikkeld voor het gebruik van echocontrast maar gebruik bij trans thoracale echocardiografie (TTE) liet zien dat SHI ook zonder contrast de beeldkwaliteit belangrijk verbeterde. In 14 patiënten die een coronaire bypass operatie ondergingen werden vanuit de 4-kamer en de trans gastrische korte as opname beelden gemaakt. Door middel van een visuele score werd de endocardiale afscheiding beschreven in zowel de fundamentele als de SHI modus in 168 segmenten. Met SHI was de gescoorde kwaliteit in 26% van de segmenten beter en in 2% slechter dan in de fundamentele modus. De verbetering was het meest uitgesproken in de transgastrische korte as opname (37% vs. 18%). Anderen studies

lieten zien dat SHI t.o.v. fundamentele mode bij TTE beelden de verbetering nog sterker was. Waarschijnlijk is dat hoe lager de kwaliteit van de verkregen fundamentele beelden is hoe groter de verbetering wanneer SHI wordt gebruikt. Deze studie laat zien dat ondanks het feit dat de kwaliteit van beelden verkregen met TEE van goede kwaliteit zijn, het gebruik van SHI de endocardiale afscheiding verder verbetert.

In **hoofdstuk 4** beschrijven we een studie waarbij wordt onderzocht of toevoeging van een tweede generatie echocontrast middel de intra- en inter-observer variabiliteit van bepaling van de linker ventrikel ejectiefractie (LV-EF) kan verbeteren. De LV-EF na een acuut myocardinfarct (AMI) geeft een indruk over de prognose van de patiënt en wordt gebruikt als een selectie criterium voor patiënten die in aanmerking komen voor een interne defibrillator.

Hoewel echocardiografie de meest gebruikte imaging methode is weten we dat de grote variatie in metingen een nadeel is van deze techniek. In deze studie werden 48 patiënten bestudeerd die een AMI doormaakte. LV-EF werd in de second harmonic mode zowel zonder (SHI) als met contrast (LVO) bepaald. LVO verbeterde de intra-observer variabiliteit van $12.5 \pm 11.5\%$ naar $7.0 \pm 7.0\%$ ($p < 0.001$) en de inter-observer variabiliteit van $16.9 \pm 9.9\%$ naar $7.0 \pm 6.2\%$ ($p < 0.001$). Deze verbetering werd zowel in de goede als in de matige tot slechte kwaliteit echo's gezien. Conclusie van deze studie was dat wanneer LV-EF nodig is om klinische beslissingen te nemen bij patiënten na een AMI een echocontrast middel moet worden gebruikt. Dit geldt zowel bij goede als matig tot slechte kwaliteit echocardiografieën.

In **hoofdstuk 5** onderzoeken we de interobserver overeenstemming bij de beoordeling van wandbewegingen en de wandbewegingscore index (WBSI) bij 100 patiënten die een echocardiogram met zowel 2-dimensionale 'second harmonic' (SH) als linker ventrikel contrast (LVO) ondergingen. Tevens werd de correlatie bestudeerd tussen de met LVO verkregen WBSI en de linker ventrikel ejectie fractie (LVEF). Twee onafhankelijk beoordelaars bepaalden wandbewegingen en WBSI zowel in SH als in LVO beelden in het 17-segmenten model. Wandbeweging werd beoordeeld als normokinetisch, hypokinetisch, akinetisch en diskinetisch. LVEF werd berekend d.m.v. de biplane, gemodificeerde Simpson's methode. Van de 1700 beoordeelde segmenten waren de wandbewegingen van 453 (26,6%) slecht te beoordelen in de met SH verkregen beelden tegen 173 (10,2%) in de met LVO verkregen beelden ($p < 0.0001$). Beide beoordelaars hadden overeenstemming over wandbewegingen in 1299 segmenten (76%, Kappa 0.60) in de met SH verkregen beelden en in 1491 segmenten (88%, Kappa 0.78) in de met LVO verkregen beelden. De interobserver correlatie (r^2) van de WBSI was 0.86 met de door SH verkregen beelden en 0.93 met de door LVO verkregen beelden. De WBSI verkregen door de LVO beelden correleerde goed met LVEF ($r^2 = 0.71$). Conclusie van dit onderzoek was dat het gebruik van echo contrast de interobserver overeenstemming voor wandbewegingen en WBSI verbeterde en dat de LVO WBSI goed correleerde met LVEF.

In **hoofdstuk 7** wordt myocard contrast echocardiografie (MCE) gebruikt om naar myocard perfusie te kijken bij 30 patiënten 2 dagen na een acuut Q-wave myocardinfarct (AMI). 20 patiënten kregen thrombolysen en 10 geen reperfusie therapie. Alle patiënten ondergingen na 2 dagen coronair angiografie en 18 kregen voor ontslag een SPECT scintigrafie. MCE werd verricht met second harmonic imaging (SHI) en power Doppler waarbij perfluorocarbon-exposed sonicated dextrose-albumin (PESDA) als contrast middel werd gebruikt. Sensitiviteit

en specificiteit voor het vaststellen welke segmenten door het infarct gerelateerde vat van bloed werden voorzien waren respectievelijk 82% en 95%. Overeenkomst tussen SPECT en MCE in het vaststellen van abnormale perfusie op segment basis was 93%. Na 6 weken werd een follow-up echocardiogram gemaakt om een segmentale wandbeweging score te maken. Disfunctionele segmenten met hypo- of normoperfusie bij MCE tijdens baseline vertoonden significant meer herstel in functie dan disfunctionele segmenten zonder perfusie met MCE.

Concluderend toont deze studie aan dat Power Doppler imaging met intraveneus toegevend PESDA in staat is om reperfusie na AMI aan te tonen. Tevens kan met deze non-invasieve techniek voorspeld worden bij welke segmenten herstel van functie optreedt.

In **hoofdstuk 8** bestuderen we of de einddiastolische wanddikte (EDWD) verbetering van de segmentale contractiele functie voorspelt na primaire percutane coronaire interventie (PCI). Hiervoor werd de EDWD gemeten in 175 disfunctionele uit een totaal van 640 segmenten (27%) bij 40 patiënten met een acuut myocardiinfarct (AMI) die behandeld waren met een PCI. Om de EDWD beter te bepalen werd een echocontrast middel gebruikt tijdens het echocardiogram. Tevens werd met behulp van power Doppler methode gekeken naar myocardiale perfusie (MCE) en werden deze op een semi-kwantitatieve methode gescoord.

Na 2 maanden werd opnieuw een echocardiogram gemaakt om EDWD, perfusie en functie te beoordelen. De 175 disfunctionele segmenten werden onderverdeeld in segmenten met een EDWD <11mm (103) en een EDWD ≥11mm (72). MCE liet in 11 van de 103 segmenten met EDWD <11mm normale, in 52 gedeeltelijke en in 40 geen perfusie zien. In de 72 disfunctionele segmenten met EDWD ≥11mm hadden 33 normale, 38 gedeeltelijke en 1 geen perfusie. Bij de follow-up echo vertoonden 66 van de 72 segmenten met EDWD ≥11mm verbetering in functie terwijl slechts 35 van de 103 segmenten met EDWD <11mm verbeterden ($p < 0.001$). De segmenten met de combinatie van EDWD ≥11mm en aanwezigheid van perfusie hadden de grootste kans om in functie te verbeteren terwijl segmenten met EDWD <11mm zonder perfusie zelden verbetering in functie gaven na 2 maanden.

In **hoofdstuk 9** wordt de linker ventrikel (LV) functie bij patiënten met een symptomatische ernstige aorta stenose (AS) onderzocht en vergeleken met die van een controle groep. De LV functie wordt in het algemeen weergegeven als de LV ejectie fractie (LV-EF) en bepaald met echocardiografie en de Simpson's biplane disc methode. Doppler tissue imaging (DTI) heeft bij verschillende cardiale ziekten aangetoond dat ze meer subtiele veranderingen in zowel systolische als diastolische LV functie kan aantonen. Metingen werden verricht met DTI in 29 patiënten met AS en vergeleken met waarden bij 17, voor leeftijd gecorrigeerde, personen zonder AS. AS patiënten bleken significant lagere DTI waarden te hebben vergeleken met de controles. Ook was de LV vullingsdruk gemeten door de E/Em ratio significant hoger in AS patiënten. DTI variabelen waren gecorreleerd met NT-proBNP waarden. Geconcludeerd werd uit deze studie dat DTI variabelen LV systolische en diastolische disfunctie aantonen in

patiënten met symptomatische ernstige AS terwijl conventionele echo parameters als LV-EF normaal waren.

In **hoofdstuk 10** worden 27 patiënten met een ernstige aorta stenose (AS) vervolgd tot één jaar na aortaklep vervanging (AVR). Alle patiënten hadden een normale linker ventrikel ejectie fractie (LV-EF) en abnormale systolische en diastolische linker ventrikel functie gemeten met Doppler tissue imaging (DTI). Het doel van deze studie was om de eventuele reversibiliteit, en de mate waarin, te onderzoeken van deze abnormale lange-as DTI LV functie. Drie weken, 6 en 12 maanden na AVR werd een echocardiogram gemaakt en de gemeten waarden werden ook vergeleken met een voor leeftijd gecorrigeerde controle groep zonder hartziekte. Lange-as systolische LV functie van de laterale mitralis annulus verbeterde al 3 weken na de klepvervanging en persisteerde na 1 jaar. Deze verschilde niet van de controle groep. De diastolische functie uitgedrukt als ratio van de piek vroege diastolische mitralis flow gemeten met pulsed Doppler en de vroege diastolische piek snelheid van de laterale mitralis annulus verbeterde weliswaar na AVR maar bereikte niet de waarden van de controle groep en bleef dus verminderd. De conclusie van deze studie is dat lange-as systolische LV disfunctie bij patiënten met ernstige AS en normale LV-EF reversibel is maar dat diastolische LV disfunctie wel verbeterd maar niet normaliseert 1 jaar na de aortaklep vervanging.

In **hoofdstuk 11** bestuderen we de waarde van het maken van een echocardiogram bij 500 patiënten met thoracale pijn klachten. Bij deze patiënten richt het onderzoek zich met name op het diagnosticeren van eventueel aanwezig significant coronair lijden. De huidige richtlijnen adviseren een echocardiogram als er sprake is van een abnormaal ECG, hoge bloeddruk, verdenking op hartfalen of de aanwezigheid van een hartgeruis. Prospectieve data om deze werkwijze te ondersteunen ontbreken grotendeels. Bij 500 patiënten met een intermediair tot hoog risico op het hebben van coronair lijden verrichten we een diagnostisch protocol bestaande uit lichamelijk onderzoek, ECG, fiets ergometrie en een CT angiografie. Daarnaast werd bij iedereen een handheld echocardiogram (HHE) verricht en we vergeleken de bevindingen hiervan met de uiteindelijke diagnose die d.m.v. de andere onderzoeken werd gesteld. Abnormale HHE bevindingen werden gevonden in 15,6% van alle patiënten. Bij 346 patiënten met normale bloeddruk, zonder hartgeruis, geen tekenen van hartfalen en een normaal ECG 10,4% hadden een abnormale bevinding bij HHE. Het merendeel van deze bevindingen had geen implicaties voor de behandeling van de patiënten. Bij 49 van de 154 (32%) patiënten met een, volgend de richtlijnen, indicatie voor een HHE werden abnormale HHE diagnoses gevonden. De conclusie van deze prospectieve analyse is dat met het verrichten van een echocardiogram bij alle patiënten met thoracale pijn klachten in 10,4% een onverwachte diagnose werd gevonden the relevantie hiervan zeer beperkt is. Dit ondersteunt de richtlijnen om een echocardiogram alleen te verrichten in een selecte groep van patiënten.

In **hoofdstuk 12** wordt de waarde van de d.m.v. computer tomografie bepaalde calciumscore vergeleken met de CT coronaire angiografie (CTA) en inspanningstest (XECG) om significant coronairlijden (CAD) te diagnosticeren bij patiënten met pijn op de borst klachten. In totaal ondergingen 471 patiënten met thoracale pijn klachten een dual-source multislice CT coronaire calcium score (CCS) en CTA en een XECG. Invasieve kwantitatieve angiografie (QCA) werd op klinische gronden verricht bij 98 patiënten. Slechts 3/175 (2%) van alle patiënten met een negatieve CCS hadden significant CAD bij de CTA, waarvan er een werd bevestigd bij QCA. Bij patiënten met een hoge calcium score (Agatston score >400) werd slechts bij 4/65 patiënten (6%) CAD uitgesloten door QCA. Bij patiënten met een laag tot intermediaire CCS van had een CTA meer diagnostische waarde dan de XECG voor het aantonen van CAD. Patiënten met CAD bij CTA en abnormale XECG hadden vaker ernstig CAD ($P < 0.034$). Bij patiënten die alle diagnostische testen ondergingen de sensitiviteit en specificiteit voor het diagnosticeren van >50% QCA diameter stenose was 100% en 15% voor een CCS>0, 82% en 64% voor een CCS>100, 97% en 36% voor CTA, en 70% en 76% voor XECG. Conclusie van deze studie is dat calciumscore detectie door CT een betrouwbare techniek is om significant coronairlijden uit te sluiten bij patiënten met pijn op de borst klachten. CT-angiografie is in staat om significant coronairlijden uit te sluiten bij patiënten met een laag tot intermediair risico maar heeft beperkte waarde bij een hoge calciumscore.

In **hoofdstuk 13** vergelijken we de diagnostisch waarde van CT angiografie (CTA) en inspanning elektrocardiografie (X-ECG) bij symptomatisch patiënten met een laag tot intermediaire vooraf kans op het hebben van coronaire hartziekte (CAD). In deze prospectieve registratie warden 471 poliklinische patiënten bestudeerd met stabiele pijn op de borst klachten met een gemiddelde leeftijd van 56 jaar, 48% vrouwen en een pre-test probability op het hebben van CAD van >5%. Alle patiënten ondergingen i.p. een 64-slice dual-source CTA en een X-ECG. Invasieve kwantitatieve coronair angiografie (QCA) werd verricht in 98 patiënten wanneer daar een klinische indicatie voor was. Belangrijkste eindpunten waren de uitvoerbaarheid, betrouwbaarheid en de relatie tussen CTA en X-ECG van beide onderzoeken waarbij de referentie methode de QCA was.

CTA en X-ECG konden niet worden verricht in 16 (3.4%) resp. 48 (10%, $P < 0.001$), en waren niet diagnostisch in 3 (0.7%) resp. 140 (33%, $P < 0.001$). CTA ≥ 1 coronair stenose ($\geq 50\%$) in 140 patiënten (30%), X-ECG was abnormaal in 93 patiënten (33%). Resultaten van CTA en X-ECG kwamen overeen in 185 patiënten (68%, $P = 0.63$). Met QCA werd in 57/98 (58%) obstructief CAD gevonden. Sensitiviteit, specificiteit, positief en negatief voorspellende waarde van CTA om patiënten te identificeren met $\geq 50\%$ stenose waren respectievelijk: 96%, 37%, 67% and 88%; vergeleken met X-ECG: 71%, 76%, 80% en 66%. Kwantitatieve CTA overschatte de diameter stenose: $6 \pm 21\%$ ($R = 0.71$), vergeleken met QCA. Van de 312 patiënten (66%) met een negatieve CTA hadden er 44 (14%) een positieve X-ECG, maar slechts 2/17 die een CAG ondergingen hadden significant CAD.

De conclusie van dit onderzoek is dat CTA uitvoerbaar en diagnostisch is in een groter aantal patiënten dan een X-ECG. In goed interpreteerbare studies heeft CTA een hogere sensitiviteit maar een lagere specificiteit voor de detectie van CAD.

Conclusies

Bij de meeste patiënten die naar een cardioloog worden verwezen is een vorm van cardiale beeldvorming noodzakelijk om een diagnose te stellen en/of om de juiste therapie in te stellen. Verschillende technieken zijn hiervoor beschikbaar en iedere techniek heeft voor- en nadelen. In dit proefschrift worden verschillende nieuwe modaliteiten van echocardiografie en coronair angiografie door middel van computer tomografie (CT) geëvalueerd in patiënten die verwezen zijn naar de cardiologen van het Thoraxcentrum.

Echocardiografie is zonder twijfel de meest gebruikte beeldvormende techniek in de klinische praktijk om informatie te verkrijgen over de structuur en functie van het hart en de hartkleppen. Echter de kwaliteit van de beelden kan negatief worden beïnvloed door verschillende patiënten kenmerken zoals obesitas en chronisch obstructief longlijden. In **hoofdstuk 2** beschrijven wij hoe met behulp van echocontrast de beeldkwaliteit verbetert.

Gedurende lange tijd was kwalitatieve beoordeling van de linker ventrikel functie als "normaal", "licht verminderd", "matig verminderd" of "ernstig verminderd" voldoende voor de klinische praktijk. De laatste jaren wordt kwantitatieve beoordeling van de linker ventrikel ejectiefractie steeds meer gebruikt om te beslissen of patiënten behandeld moeten worden met bepaalde medicamenten en of zij in aanmerking komen voor een implanteerbare cardioverter-defibrillator (ICD). In veel studies werd echocardiografie gebruikt om deze ejectiefractie te bepalen hoewel er een grote intra- en inter-observer variabiliteit bestaat bij deze methode. In **hoofdstuk 3, 4 en 5** maken wij gebruik van 'second harmonic imaging' en echocontrast voor bepaling van wandbewegingen, de wandbeweging score index en de linker ventrikel ejectiefractie. Wij laten zien dat verbeterde endocard afgrenzing leidt tot verminderde intra- en inter-observer variabiliteit voor de bepaling van de linker ventrikel ejectiefractie. Tevens konden wij meer segmenten beoordelen met behulp van echocontrast. De wandbeweging score index correleerde goed met de ejectiefractie. Wij concluderen dan ook dat echocontrast gebruikt zou moeten worden als kwantitatieve beoordeling van wandbewegingen, wandbeweging score index of ejectiefractie essentieel is.

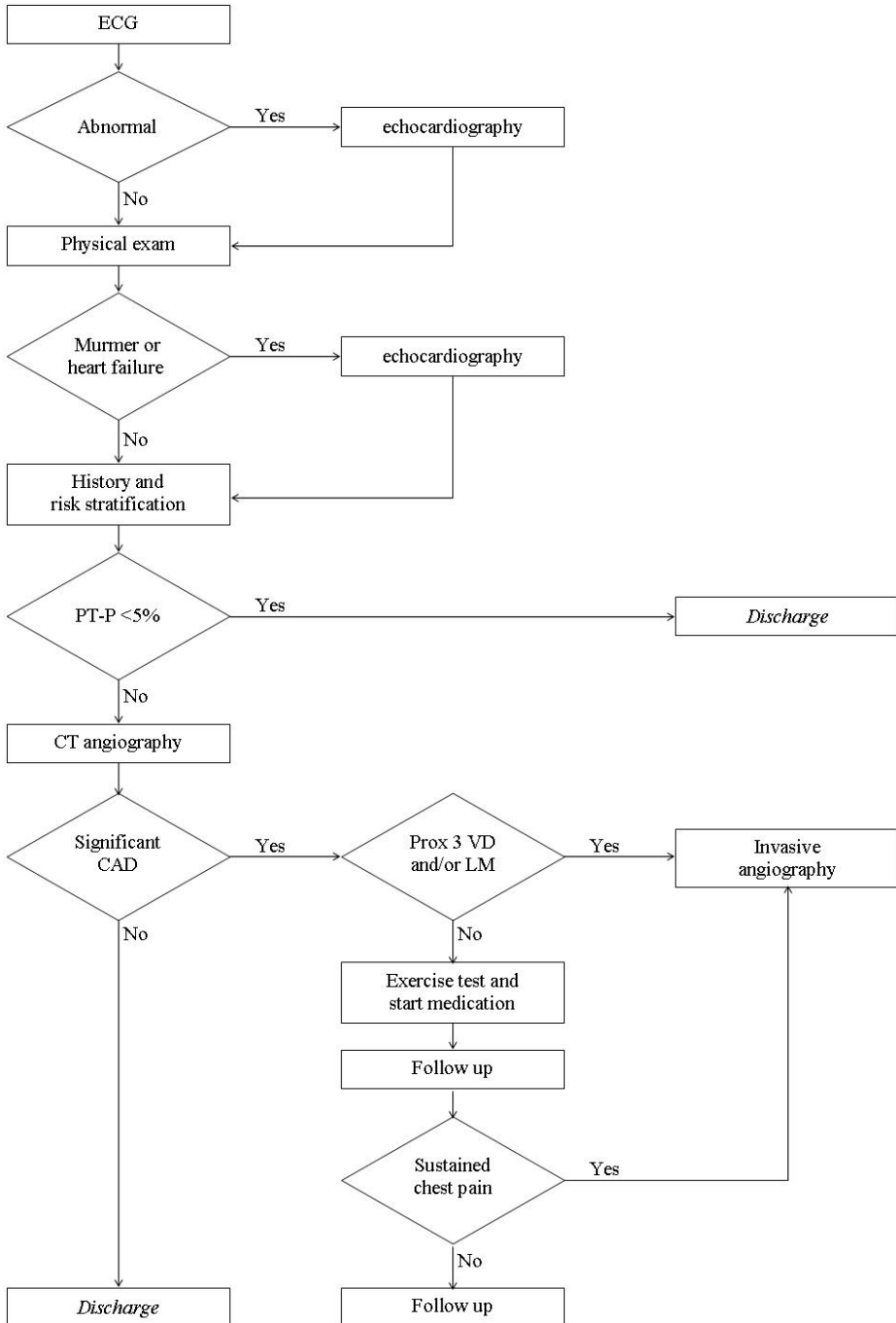
Myocard contrast echocardiografie wordt gebruikt voor het aantonen van ischemie als gevolg van significant coronairlijden en om verbetering van de linker ventrikel functie te voorspellen in de herstelfase na een myocardinfarct. In **hoofdstuk 7 en 8** tonen we aan dat myocard perfusie en wanddikte gemeten met behulp van echocontrast een voorspellende waarde heeft voor verbetering van linker ventrikel functie een aantal weken na een acute cardiale gebeurtenis.

In vele experimentele en klinisch studies bij patiënten met hypertensie, diabetes mellitus, kleplijden en cardiomyopathie kan met Doppler tissue imaging (DTI) discrete vermindering van de longitudinale linker ventrikel functie worden gedetecteerd terwijl de ejectiefractie normaal is. De ejectiefractie is een relatief ongevoelige maat om een subtiele achteruitgang van de linker ventrikel functie te diagnosticeren. Patiënten met een hartziekte en een ver-

minderde ejectiefraction hebben een slechtere prognose dan patiënten waarbij deze normaal is. Wij bestudeerden de longitudinale systolische functie met Doppler tissue imaging bij patiënten met een ernstige aortastenose en een normale ejectiefraction (**hoofdstuk 9**). In vergelijking met een controlegroep was de longitudinale functie verminderd bij deze patiënten en bleek deze gerelateerd aan NT-ProBNP gehalte als een onafhankelijke maat voor een verminderde hart functie. In **hoofdstuk 10** beschrijven wij dat deze functie herstelt na aortaklep vervanging. Omdat patiënten met een ernstige aortastenose en een abnormale ejectiefraction een slechtere prognose hebben dan diegenen met een normale ejectiefraction moet chirurgie plaatsvinden voor die achteruitgang. Wij stellen voor om klepvervanging te overwegen bij patiënten met een verminderde longitudinale linker ventrikel functie, als teken van vroege linker ventrikel disfunctie, en een normale ejectiefraction om hun prognose te verbeteren. Toekomstige prospectieve en observationele studies zijn nodig om vast te stellen of dit soort metingen gebruikt kunnen worden om het optimale moment voor klepvervanging vast te stellen bij patiënten met een ernstige aortastenose en een normale ejectiefraction.

Pijn op de borst kan veroorzaakt worden door significant coronairlijden maar ook door andere cardiale en niet cardiale oorzaken. In **hoofdstuk 11** beschrijven wij de waarde van het maken van een echocardiogram bij alle patiënten die zich presenteren met pijn op de borst klachten. Het percentage andere cardiale oorzaken van pijn op de borst wat wordt gevonden door middel van een echocardiogram bleek laag te zijn. Wel werden soms andere, niet aan de klachten gerelateerde cardiale afwijkingen gevonden maar deze hadden weinig of geen invloed op de behandeling of prognose van de patiënten. Wij concluderen dan ook dat een echocardiogram bij patiënten met pijn op de borst klachten alleen geïndiceerd is bij patiënten met hart geruisen, ECG afwijkingen of tekenen van hartfalen.

Een andere cardiovasculaire beeldvormende techniek die de laatste jaren is geïntroduceerd is de CT-coronair angiografie. Deze techniek is snel geëvalueerd en nu toepasbaar in de poliklinische situatie. In **hoofdstuk 12 en 13** bestuderen wij de waarde van de calciumscore, CT-coronair angiografie en de fietsergeometrie bij patiënten met pijn op de borst klachten. Patiënten zonder calcium in de coronairvaten hadden een kans van 2% en patiënten met een hoge calcium score een kans van 94% op het hebben van significant coronairlijden. In 40% van de patiënten kon fietsergeometrie niet worden verricht of gaf dit onderzoek geen duidelijke diagnostische resultaten. CT-coronair angiografie was beter om significant coronairlijden te diagnosticeren dan fietsergeometrie. Toekomstige technische verbeteringen en verlaging van de stralingbelasting tot minder dan 1 mSv maakt een meer liberale toepassing van deze techniek mogelijk bij patiënten met pijn op de borst klachten. Implementatie van CT-coronair angiografie zal het diagnostisch protocol in deze patiënten categorie van een op ischemie gerichte naar een meer anatomische benadering veranderen. Wij stellen het onderstaande schema voor als benadering voor patiënten met pijn op de borst klachten:



Afkorting: PT-P = pre-test probability; 3 VD = 3 vessel disease; LM = left main; CAD = coronary artery disease.

Cardiovasculaire beeldvorming in de toekomst

Echocardiografie wordt steeds meer complex met 3-dimensionele echocardiografie, speckle tracking, Doppler tissue en strain imaging. Daarnaast zijn nu ook magnetic resonantie imaging, positron emissie tomografie en multi-slice computer tomografie beschikbaar in vele ziekenhuizen. De beeldvormende techniek die wordt gekozen om een specifieke vraag te beantwoorden is veelal gebaseerd op beperkte individuele ervaring maar ook op de beschikbaarheid van en ervaring met deze technieken in het betreffende ziekenhuis. Om het gebruik van al deze technieken te optimaliseren zijn niet-invasieve, cardiovasculaire imaging afdelingen nodig met cardiologen die uitgebreide ervaring hebben met al deze technieken. Zij bepalen welke techniek wordt gebruikt om een specifieke vraag te beantwoorden. De in dit proefschrift beschreven studies geven informatie over het positioneren van contrast echocardiografie, Doppler tissue imaging en CT-coronair angiografie bij verschillende groepen patiënten.

Part VI

Epilogue



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CURRICULUM VITAE

Tjebbe Wilhelmus Galema werd op 28 november 1960 geboren te Roermond. Na het eindexamen te hebben afgelegd in 1978 aan het Triniteitlyceum te Haarlem, studeerde hij geneeskunde aan de VU Medisch Centrum Amsterdam van 1978-1987. In 1989 begon hij in het Isala kliniek te Zwolle met de vooropleiding Interne Geneeskunde (*opleider: J.A. ten Bokkel Huinink*). In 1991 startte hij met de opleiding Cardiologie in de VU Medisch Centrum Amsterdam (*opleiders: Prof.dr. F.W.A. Verheugt en Prof.dr. C.A. Visser †*). Op 01 maart 1995 werd hij geregistreerd als Cardioloog.

Van 1995-1997 werkte hij in de Isala ziekenhuis te Zwolle. Na zijn verhuizing naar Rotterdam heeft hij van 1997-1998 gewerkt in het Maasstad ziekenhuis, waarna hij stafid werd in het Erasmus Medisch Centrum waar hij vanaf 2005 Medisch Coördinator van de Polikliniek Cardiologie is. Specifieke aandachtsgebieden zijn: non-invasieve cardiale imaging en in het bijzonder echocardiografie en MSCT van de coronairen.

Hij is getrouwd met Annette Galema-Boers en zij hebben drie zonen: Hidde (1994), Jouke (1996) en Geert (1998).

PHD PORTFOLIO SUMMARY

Name PhD student: T.W. Galema

Erasmus MC: Cardiology

Research School: COEUR

	Year	Workload (Hours)
1. PhD TRAINING		
General academic skills		
- Medische Statistiek	2006, 2007	26
- Teach-the-Teacher	2007	26
Research skills		
- Cardiac CT course Level A, Maastricht	2009	25
- Masterclass: financiering binnen de gezondheidszorg	2009	4
- Cardiologie & sport: van sport-ECG naar pathologie	2009	6
In-depth COEUR courses		
- COEUR Research seminars (Friday afternoon)	2005-2009	17.5
Other courses		
- Cardiology and Vascular Medicine update and perspective, Rotterdam	2005-2009	75
- Voorjaarscongres Nederlandse Vereniging voor Cardiologie	2005-2009	62
- Najaarscongres Nederlandse Vereniging voor Cardiologie	2005-2009	22
- CV risico begrijpen	2009	6
- Symposium: Cardiale CT en MRI in de praktijk	2008	4
- Symposium: Academie & Periferie: "best of both worlds"	2008	2
- First Cardiovascular Imaging Symposium, Rotterdam	2008	5
- Post ACC symposium 2008, ASS in perspective	2008	2
- Leiden Cardiology Course	2007, 2008	19
- Cardiovasculair Risicomanagement	2007	5
- POST ASS symposium	2006	4
- Haagse cursus Echocardiografie	2005	12

International Conferences

- Euro Echo	2007, 2008	39
- Cardiovascular exchange summit, Madrid	2008	14
- European Society of Cardiology	2008	24
- Cardiovascular exchange summit, Montreal	2006, 2007	23
- Cardiac MRI en CT	2007	16
- ACC (Fuster), New York	2006	8

2. TEACHING ACTIVITIES**Lecturing**

- Keuzeonderwijs begeleiding voor studenten	2005-2009	1
- Journal Club	2005-2009	4
- Assistentenonderwijs	2005-2009	5