



FACULTY OF MEDICINE AND HEALTH SCIENCES

**NONINVASIVE EVALUATION OF PATIENTS
WITH CORONARY ARTERY DISEASE AND HEART FAILURE**

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THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF 'DOCTOR IN MEDICAL SCIENCES' (PHD)

D/2006/11.061/1

ISBN-10: 90-9021224-8

ISBN-13: 978-90-9021224-1

2006

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BELGIUM

Logistic support by Roche Belgium for the publication of this thesis is gratefully acknowledged

Painting on the cover:

*“Twee overliden van het chirurgijns-gilde te Amsterdam”
by Jurriaen Pool, 1699, Amsterdams Historisch Museum,
exhibited at Boerhaave Museum, Leiden, The Netherlands*

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General Introduction and Outline of the Thesis

General Introduction

Over the past 50 years, the cardiologic landscape underwent a fundamental transformation. Before the Second World War, acute myocardial infarction, secondary to acute thrombotic coronary occlusion was regarded as a rare condition not compatible with survival. In the fifties and sixties an alarming rise in coronary artery disease (CAD) mortality was observed in the industrialised world. At that time, therapeutic modalities for patients presenting with myocardial infarction provided little benefit, other than relieving pain. Consequently mortality rates, even in hospital setting, were high. (1) The introduction of coronary care units in the sixties, providing a better control of life threatening arrhythmias, was the first step to improve survival. (1) In most Western European countries the age standardised CAD death rates started to decline since the seventies. (2-5) This encouraging decline of – predominantly in-hospital - death rate can be explained by an improved treatment of patients with myocardial infarction and unstable angina through the use of both cardiac medication and coronary reperfusion strategies. (2) In many countries, efforts to improve primary prevention of CAD, by reducing traditional risk factors such as smoking, hypertension, hypercholesterolemia, diabetes mellitus and obesity, have made an important contribution to declining CAD death rates. (6) Also changes in diet and lifestyle modifications play a central role in this positive evolution. (5)

Anno 2006, CAD is still an important cause of death in Flanders, Belgium, accounting for almost 14 percent of total mortality; ischemic heart disease is one of the main causes of potential life years lost and is the first cause of death in the age category between 70 and 80 years. (7) Among CAD patients, acute myocardial infarctions are responsible for two thirds of all deaths, followed by ischemic cardiomyopathy. (7) In-

hospital mortality rates of acute myocardial infarction have declined, but data from the MONICA project show that a large group of patients die from myocardial infarction, before reaching the hospital. (8)

Moreover, despite a slow but significant decrease in age-standardized mortality due to acute coronary syndromes, the (absolute) mortality due to chronic heart failure continues to increase worldwide. (9) The decrease in cardiovascular mortality and the increase in admission rates for chronic conditions such as heart failure, chronic coronary syndromes, and diseases of the arteries, support the hypothesis that longer survival of many patients with heart diseases is leading to a growing pool of patients at increased risk for subsequent cardiovascular complications in Western countries. (10) In Flanders, chronic ischemic heart disease is the most important reason for hospitalization for men between 50 and 79 years and the second most important reason for women between 70 and 79 years old. (7) For men, aged 85 or more, heart failure is the most important hospital admission reason; for women aged 80 years or more, heart failure is the second most important hospitalization reason. (7)

As a result, general practitioners and cardiologists are facing increasingly frail, mostly elderly CAD patients who survived myocardial infarction but developed a chronic ischemic cardiomyopathy, often causing signs and symptoms of heart failure. (11) Several treatment options, both medical and non-pharmacologic, are available for these patients. (12) Large, randomized trials have proven the efficacy of new and old drugs such as ACE-inhibitors, AT2-receptor blockers, aldosteron antagonists and beta-blockers. (13) Cardiac rehabilitation therapy, first introduced in post myocardial

infarction patients, is now successfully applied in heart failure patients. (14) Device therapy, including implantable defibrillators and biventricular pacemakers is also being increasingly used. (15)

Heart failure is not the sole privilege of patients with a poor left ventricular ejection fraction. Recent reports show that a large proportion of patients admitted to the hospital with a diagnosis of heart failure have a preserved ejection fraction. (16,17) Moreover the proportion of patients with the diagnosis of heart failure with preserved ejection fraction increased over a period of 15 years. (16) The survival of patients with heart failure with preserved ejection fraction was similar to that of patients with reduced ejection fraction. (17) In this thesis, several chapters are devoted to this important group of patients.

In order to select the best therapeutic option for a specific patient, the cardiologist needs additional information concerning the present status and prognosis of the patient. As we are dealing with elderly, less mobile and fragile patients, these techniques should be easily accessible, noninvasive and if possible, bedside.

The goal of the clinical research projects presented in this thesis is to investigate the potential value of some recently introduced noninvasive techniques, including tissue Doppler imaging, nuclear imaging, multi slice computed tomography and biomarkers to provide diagnostic, therapeutic and decision-making information in CAD patients with heart failure. The patients studied in this thesis are mainly elderly patients with a documented history of coronary artery disease, recruited from the outpatient clinics and wards of the University Hospital Ghent and Leiden University Medical Center.

Both patients with heart failure and poor left ventricular systolic function and patients with heart failure and preserved left ventricular systolic function were included.

The most recent guidelines of the European Society of Cardiology emphasize the role of several noninvasive techniques in the diagnostic work-out of heart failure patients. (18) These guidelines explicitly mention the use of echocardiography and more specifically tissue Doppler imaging to evaluate diastolic function and left ventricular filling pressures. In the first part of the thesis we study the effects of aging on these parameters and try to provide age-specific reference values. Furthermore we will apply these parameters in a population of CAD patients with a wide range of left ventricular ejection fraction, that developed ischemic mitral regurgitation.

As already mentioned previously, cardiac resynchronization therapy (CRT) is an exciting new treatment option for heart failure patients. The CARE-HF trial showed that CRT improves symptoms and the quality of life and reduces complications and the risk of death. (19) Not all patients however respond favorably to this invasive and expensive treatment. (20) An improved selection of potential responders is mandatory. The second chapter will integrate multi modality imaging to address several issues related to the selection of CRT candidates.

When dealing with a potentially fatal disease such as heart failure, it becomes extremely important for patient management and decision making, to determine the prognosis of an individual patient. Several prognosticators and prognostic models have been proposed to stratify patients. (21) In the last chapter we will investigate the

prognostic value of a simple biochemical marker: fasting blood glucose in patients with poor left ventricular systolic function. Since the landmark publication by Mancini et al (22), exercise capacity, as evaluated with spiroergometry has become a widely accepted prognosticator. The underlying mechanisms, contributing to or limiting functional capacity, are not completely understood. In the last part of this thesis we will investigate the association between echocardiographic tissue Doppler imaging parameters, novel biomarkers and maximal oxygen uptake during a bicycle exercise test in CAD patients with heart failure and a preserved left ventricular systolic function.

Outline of the thesis

Part 1: Echocardiography and filling pressures

History taking and clinical examination are the cornerstones of diagnostic work-up. Advanced technology is increasingly used by physicians to confirm or revoke the clinicians' original hypothesis and findings. Echocardiography is a fine example of a bedside diagnostic technique used daily by cardiologists. (23) Novel technological advances developed within the last decade have expanded the accuracy and potential applications of echocardiography. Even the art of measuring filling pressures, previously a privilege of the invasive techniques, nowadays belongs to the diagnostic array of the cardiac sonographer. (24) The advantages of echocardiographic evaluation of filling pressure are numerous: it can be performed bedside, it is safe and noninvasive, is available at every time in every part of the hospital and it is nonexpensive.

The first part of this thesis is entirely devoted to the echocardiographic assessment of filling pressures. In the mid eighties several authors validated the estimation of right ventricular end-systolic pressure by measuring the peak systolic pressure gradient across a regurgitant tricuspid valve and assessing inferior caval size and its respiratory variation. (25,26,27) A clinical example of this measurement is depicted in Figure 1.

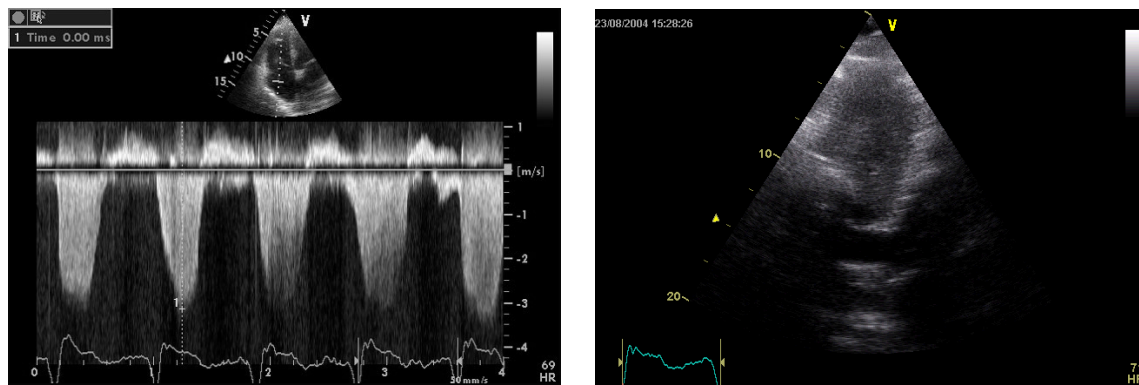


Figure 1: Example of estimation of right ventricular systolic pressure in a patient with an ischemic cardiomyopathy. **Left panel:** The peak systolic pressure gradient across the regurgitant tricuspid valve in this patient is 40 mmHg. **Right panel:** the right atrial pressure is estimated at 10 mmHg (inferior vena cava diameter between 1.5 and 2 cm). Right ventricular pressure estimation: 40 mmHg + 10 mmHg = 50 mmHg;

More recently the E/E' value was introduced. This simple value, derived from the early mitral inflow and early diastolic mitral annulus velocity was validated almost a decade ago and has become a reliable estimation of left ventricular end-diastolic pressure. (28,29)

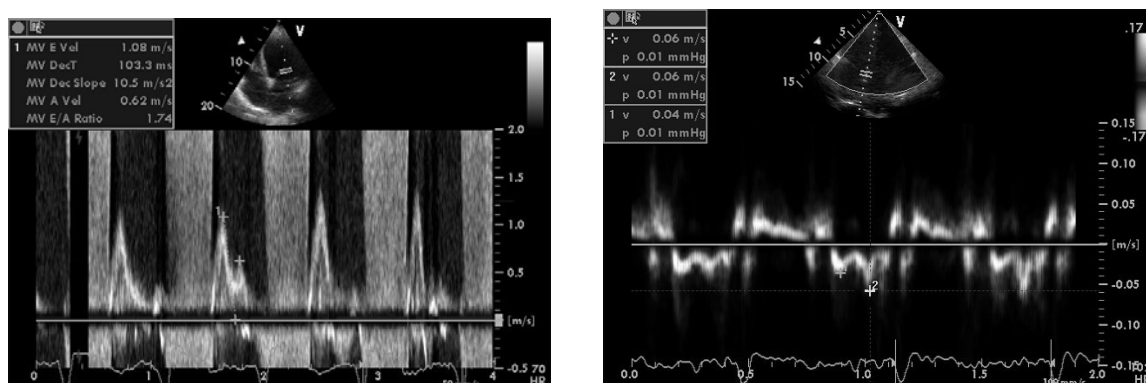


Figure 2: Example of assessment of the E/E' value in a patient with ischemic cardiomyopathy. **Left panel:** Transmitral flow is evaluated by placing the sample volume of the pulsed wave Doppler at the tips of the mitral valve leaflets. E: 108. **Right panel:** The E' value is evaluated by placing the sample volume of the pulsed wave Tissue Doppler Imaging modality at the septal side of the mitral valve annulus. E': 4. E/E': 27, indicating elevated left ventricular end-systolic pressures.

As aging is accompanied with several structural and functional cardiac changes, it was our hypothesis that these changes are reflected by echocardiographic parameters including estimated right and left ventricular filling pressures. This hypothesis was tested in healthy individuals without a history of hypertension and with normotensive blood pressure during the echocardiographic examination.

In the second chapter of Part 1 we studied effects of age and gender on E/E' and the effect of increased left ventricular mass as many CAD patients develop hypertrophy as a result of arterial hypertension.

The last chapter of Part 1 is devoted to the noninvasive assessment of left ventricular end-diastolic pressure and its relation with severity of mitral regurgitation. Many CAD patients develop some degree of mitral regurgitation, that is not related to primary structural valvular abnormalities. Among CAD patients, changes in ventricular structure and function related to ischemia and remodelling can lead to mitral regurgitation. (30) In this part of the thesis we investigated the prevalence of ischemic mitral regurgitation in patients with established CAD referred for echocardiography. In the same population we investigated the relation between severity of ischemic mitral regurgitation and E/E'.

Part 2: Selection of potential candidates for Cardiac Resynchronization Therapy.

Although the treatment of heart failure patients improved tremendously over the last decade (12), following the introduction of drugs such as ACE-inhibitors, AT2-receptor blockers, aldosteron antagonists and beta-blockers, clinical trials involving novel medical treatments focusing on the immune system produced rather disappointing results. As a consequence non-medical treatment options such as cardiac rehabilitation, surgery and device therapy gained interest. (18) In highly symptomatic heart failure patients on optimal medical treatment, with a left bundle branch block on the surface electrocardiogram and poor left ventricular systolic function, the implantation of a biventricular pacemaker has become an attractive treatment option. (31,32,33) The rationale behind Cardiac Resynchronization Therapy (CRT) is that these patients have an inefficient coordination of the contraction between the left and right ventricle (interventricular dyssynchrony) and/or between the various segments of the left ventricle (intraventricular dyssynchrony). (34) Stimulating both right ventricle and left ventricle has acute hemodynamic effects reducing mitral regurgitation and improving systolic function. On the long run it will lead to reverse remodeling, improvement of symptoms and exercise capacity. The CARE-HF trial has even shown beneficial effects on morbidity and mortality. (19) However, 30 % of patients treated with CRT do not respond favorably to this expensive and invasive therapy. (20,35,36) The reasons for failure of biventricular pacing are numerous: infection, lead dislodgment, programming errors, ... A better selection of potential candidates for biventricular pacing is imperative and the second part of this thesis is devoted to patient selection by means of noninvasive imaging modalities.

Cardiologists have always evaluated time intervals, intrinsically related to the cardiac cyclus, either by auscultating the heart with a stethoscope or by interpreting the surface electrocardiogram. In the early years of echocardiography M-mode and Doppler were used to quantify intervals and they are still used today to evaluate left ventricular function or to measure interventricular delay. The difference in activation between the right and left ventricular activation – interventricular dyssynchrony – can be measured by evaluating the difference between onset QRS – Doppler flow in the aorta and onset QRS – Doppler flow in the pulmonary artery.

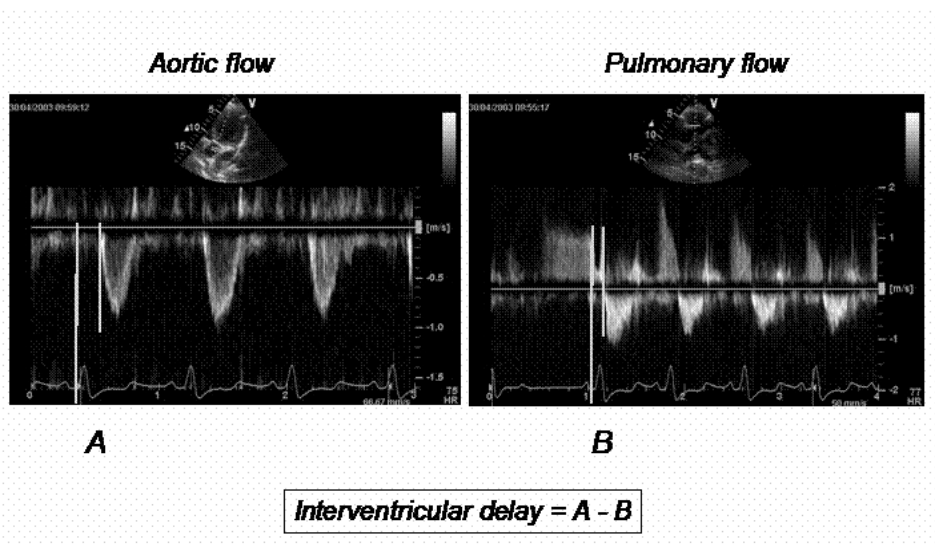


Figure 3: Interventricular delay. Start with measuring the time interval between onset of QRS and onset aortic flow (A). Then the time interval between the onset of QRS and the pulmonary flow is measured (B). Interventricular delay is the difference between A and B

Recently Tissue Doppler Imaging (TDI) expanded the clinical applications of measuring time intervals. Colour TDI graphically depicts myocardial velocities, measured at a specific sampling position, in function of time. Using the QRS-complex as a reference it becomes possible to measure the time interval between the onset of QRS and the time to peak systolic myocardial velocity.

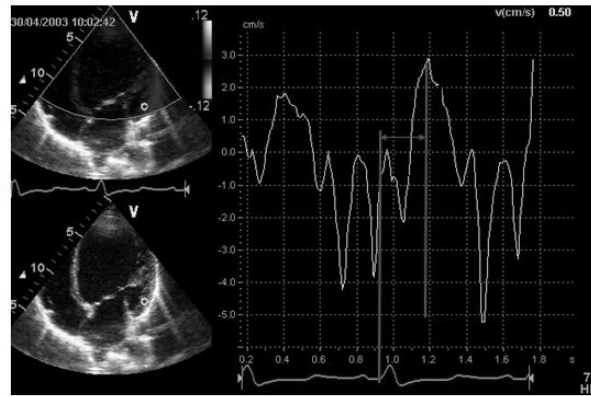


Figure 4: Example of a Colour Tissue Doppler Imaging myocardial velocity curve at the basal left ventricular lateral segment. The time interval between the onset of QRS and peak systolic myocardial velocity is measured and expressed in ms.

If sample volumes are placed at different left ventricular segments it is possible to identify the area of latest mechanical activation and to quantify differences in activation delays between these left ventricular segments. Several authors have proposed different parameters to quantify the degree of dyssynchrony. (37) Several observational studies have shown that the larger the intraventricular dyssynchrony the more likely that these patients will respond favorably to biventricular pacemaker implantation.

During 2003, the Belgian Working Group on Echocardiography and Cardiac Doppler set up a Multicenter Registry on Dyssynchrony and the results are presented in the first and second chapters of Part 2. First we studied potential differences between patients with ischemic cardiomyopathy and patients with idiopathic dilated cardiomyopathy. We used Colour TDI to assess global and regional mechanical dyssynchrony in these patients groups. We particularly focused on potential differences regarding the area of latest activation as this could have practical

implications regarding left ventricular lead implantation. The second paper of the Belgian Multicenter Registry on Dyssynchrony describes the prevalence of dyssynchrony, using conventional Doppler and TDI, in patients with heart failure but with a preserved left ventricular systolic function.

In the 3th chapter of Part 2 we investigated another important issue in patient selection of CRT candidates: viability. We used myocardial perfusion imaging to assess viability of the different LV segments in patients with a poor left ventricular systolic function and broad QRS complex.

Finally, in the fourth chapter of Part 2 we focused on the cardiac venous system. The left ventricular lead of a biventricular pacemaker should ideally be positioned in a tributary of the coronary sinus that is draining the area of latest mechanical activation (evaluated with TDI) and containing viable myocardial tissue. Knowledge on the anatomy of the cardiac veins before the CRT implantation would add to the success ratio of this procedure. We retrospectively analysed 100 patients with a noninvasive imaging technique: 64 slice Computed Tomography. The study aims were to evaluate the feasibility of analysing the cardiac venous system with CT and to study possible differences in coronary venous anatomy between patients without CAD, patients with significant CAD and patients with a history of myocardial infarction.

Part 3: Noninvasive markers of prognosis in heart failure patients

Exercise testing is being used in daily practice to detect myocardial ischemia. (38) The treadmill (USA) and the bicycle (Europe), in combination with a 12 lead standard electrocardiogram and blood pressure measurements, have been used for decades for this purpose. The sensitivity and specificity of exercise testing to detect myocardial ischemia can be enhanced if combined with myocardial perfusion imaging. (38) Exercise testing also provides information on the physical condition of a patient: the watts reached at peak exercise are a measurement of physical status. More objective information is available for the physician if the exercise test is combined with spiroergometry. Using this technique, the minute ventilation, carbon dioxide production and oxygen consumption are measured on a breath by breath basis. By analyzing these curves it is possible to conclude if the patients really reached a maximal effort. The oxygen consumption at peak exercise offers important prognostic information, especially in patients with heart failure. (39)

Exercise capacity is the resultant of a complex interaction between the circulatory, respiratory and musculoskeletal system. Many factors contributing to exercise capacity are not fully understood. In the last chapter of Part 3 we studied the possible role of Brain Natriuretic Peptide, blood fasting glucose (also a prognosticator) and inflammatory markers on top of longitudinal myocardial function and diastolic function, evaluated with TDI.

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**Application of Tissue Doppler Imaging techniques
for the noninvasive assessment of filling pressures**

CHAPTER 1.1

Echocardiographically estimated left ventricular end-diastolic and right ventricular systolic pressure in normotensive healthy individuals

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September 2005, Stockholm

ABSTRACT

Aim

To study the effect of aging on and the relationship between echocardiographically estimated left ventricular (LV) filling pressure and estimated right ventricular (RV) systolic pressure among healthy normotensive individuals.

Methods

We analyzed 249 healthy individuals (aged 18-82 years, 52% men) with normal echocardiographic findings and reliably measurable tricuspid regurgitation gradients. Subjects with blood pressure > 140/90 mmHg and/or LV hypertrophy were excluded. LV & RV dimensions and LV mass were measured with M-mode echocardiography. Atrial (A) volumes were determined with the area-length method. Diastolic function was assessed with transmitral Doppler and mitral annulus tissue Doppler. The ratio of transmitral early peak velocity to early diastolic mitral annulus velocity (E/E') was used as estimation of LV filling pressure. The transtricuspid Doppler gradient was used to estimate RV end-systolic pressure.

Results

Even in normotensive individuals aging was accompanied by an increase in LV mass and LA dimensions and an increase in relaxation abnormalities. E/E' increased with every decade: from 7.8 for age 18-35 years to 10.9 for age \geq 75 years ($p < 0.0001$) as did the transtricuspid gradient: from 18.3 mmHg for age 18-35 years to 25.8 mmHg for age \geq 75 years ($p < 0.0001$). Linear regression showed that estimated RV systolic

pressure was independently predicted by age, LA volume, LV systolic function and E/E'.

Conclusion

Among normotensive healthy individuals both E/E' and tricuspid regurgitation gradients increase significantly with aging. Moreover the E/E' ratio was independently predicting the tricuspid regurgitation gradient. These findings support the need for further studies defining age specific normal values.

ABBREVIATIONS

A: late transmitral flow velocity

DT: deceleration time

E: transmitral early peak velocity

E': early diastolic mitral annulus velocity

FS: fractional shortening

IVSD: end-diastolic interventricular septum wall thickness

L: left

LA: left atrial

LAD: left atrial diameter

LAV: left atrial volume

LV: left ventricular

LVEDD: left ventricular end-diastolic diameter

LVESD: left ventricular end-systolic diameter

PWD: end-diastolic posterior wall thickness

R: right

RA: right atrial

RAV: right atrial volume

RV: right ventricular

RVEDD: right ventricular end-diastolic diameter

TAPSE: tricuspid annular plane systolic excursion

INTRODUCTION

In daily clinical practice transthoracic echocardiography is frequently used as a noninvasive tool to evaluate left (L) and right (R) ventricular (V) pressures. (1) The first papers demonstrating that RV systolic pressure could be accurately estimated by measuring the peak systolic pressure gradient across a regurgitant tricuspid valve were published in the mid eighties. (2-4) This method became a standard part of any routine echocardiographic study. More recently a novel echocardiographic parameter was introduced, allowing physicians to evaluate LV filling pressures noninvasively: the ratio of transmitral early peak velocity (E) over early diastolic mitral annulus velocity (E') or E/E'. In order to identify patients with elevated left ventricular end-diastolic pressures different cut-off values have been proposed for E/E'. Nagueh et al suggested a cut-off of 10 (5) and this value was used in a large epidemiologic study evaluating the prevalence of systolic and diastolic LV dysfunction (6). Ommen et al suggested a higher cut-off of 15 for E/E' which is now increasingly used (7).

Increased LV wall thickness and alterations in diastolic filling patterns are the most dramatic changes in cardiac function that occur with aging in healthy adults (8). It is therefore logical to assume that physiological aging of the heart is reflected by changes in echocardiographic parameters such as estimated filling pressures. Published normal values, including individuals of all ages, for RV and LV pressures, as estimated by echocardiography, are however scarce. Some earlier studies suggested that age should be taken into account when interpreting RV systolic pressure values but these reports were limited by the small number of included subjects (9,10,11).

McQuillan et al evaluated 3790 echocardiographic normal subjects and established an age-adjusted reference range for pulmonary artery systolic pressure (12). McQuillan et al also report a correlation between LV wall thickness and pulmonary artery systolic pressure, even within the normal range of wall thickness considered in their study (12). The authors suggest that LV wall thickness may relate to pulmonary artery systolic pressure through diastolic dysfunction and the effects of decreased LV compliance and increased LV end-diastolic pressure with aging and in conditions as systemic hypertension. In that study however no data were available regarding diastolic function including estimated LV filling pressures (E/E').

The aims of the present study were 1) to evaluate estimated LV filling pressure (E/E') and estimated RV systolic pressure (tricuspid regurgitation gradient) among apparently healthy individuals with a broad age range; 2) to evaluate whether RV systolic pressure is independently predicted by E/E' in a healthy normotensive population without echocardiographic evidence of LV hypertrophy.

METHODS

Between January and June 2004 we prospectively screened all presumed healthy individuals, referred to our institution for a cardiovascular check-up, who underwent a transthoracic echocardiography. For analysis we selected individuals, aged 18 years or older, without a cardiovascular history and in sinus rhythm, with a normal transthoracic echocardiogram, without structural heart disease and with a reliably measurable tricuspid regurgitation gradient. Excluded were subjects in whom abnormalities, such as significant valvular disease, hypertrophic cardiomyopathy, LV wall motion abnormalities or pericardial effusion were found during the

echocardiographic examination. Also subjects with echocardiographic evidence of LV hypertrophy, defined as a LV mass index $> 134 \text{ g/m}^2$ for men and a LV mass index $> 110 \text{ g/m}^2$ for women, were excluded (13, 14). Individuals with a history of hypertension or with resting systolic blood pressure $> 140 \text{ mmHg}$ and/or diastolic blood pressure $> 90 \text{ mmHg}$ were excluded. Subjects with a history of pulmonary hypertension, echocardiographic evidence of pulmonary hypertension, chronic obstructive pulmonary disease or pulmonary embolism were also excluded. The 249 healthy individuals (130 men and 119 woman) who met the strict inclusion criteria and had a reliably measurable tricuspid regurgitation gradient were divided in 6 age categories: 67 subjects between 18 and 34 years, 45 individuals between 35 and 44 years, 53 subjects between 45 and 54 years, 46 between 55 and 64 years, 27 between 65 and 74 years and finally 11 subjects aged 75 years or more.

Echocardiographic examination

After 5 minutes resting, arterial blood pressure was measured at the right brachial artery. All patients underwent a standard echocardiographic examination with a VIVID 7 (Vingmed Ultrasound, GE, Horten, Norway) commercially available scanner. The examinations were performed by cardiologists or cardiologists in training. All studies were supervised by an experienced echocardiographer (level III, American Society of Echocardiography). Patients were examined in the left lateral recumbent position using standard parasternal short- and long-axis and apical views. Left ventricular dimensions were measured by 2-dimensional guided M-mode in the parasternal long-axis view. LV end-diastolic and end-systolic diameters (LVEDD and LVESD) as well as interventricular septum (IVSD) and posterior (PWD) end-diastolic

wall thickness were measured from leading edge to leading edge using the ASE convention (13). To assess global left ventricular systolic function the fractional shortening (FS) was calculated using the formula: $(LVEDD-LVESD)/LVEDD * 100$. RV end-diastolic diameter (RVEDD) was measured in parasternal long axis. Left atrial diameter (LAD) was measured in M-mode at the end of systole as the largest distance between the posterior aortic wall and the centre of the line denoting the posterior LA wall. Left and right atrial (RA) volumes were measured using the single plane area-length method in the apical 4 chamber view. Average LV wall thickness was calculated as the sum of IVSD and PWD divided by 2. LV mass was calculated using the Penn formula: $(1.04 [(LVEDD + \text{posterior wall thickness} + \text{septal wall thickness})^3 - (LVEDD)^3]) - 14 \text{ g}$ and was indexed for body surface (13, 14). LVEDD, LVESD, IVSD, PWD, RVEDD, LAD, LA and RA volumes were also indexed for body surface. RV function was evaluated by measuring the systolic displacement of the lateral portion of the tricuspid annular plane systolic excursion (TAPSE). TAPSE was recorded on the M-mode format under 2-dimensional echocardiographic guidance (15).

Tricuspid regurgitation was graded as trace (grade 1) or mild (grade 2) by assessment of the colour-flow jet in relation to the RA in multiple orthogonal views. With continuous-wave Doppler, the maximum peak tricuspid regurgitation recorded from any view was used to determine the RV systolic pressure with the simplified Bernoulli equation ($RV \text{ systolic pressure} = 4V^2 + RA \text{ pressure}$). Pulmonary artery systolic pressure was assumed to equate the RV systolic pressure in the absence of pulmonic stenosis and RV outflow tract obstruction.

A 2-mm sized sample volume of the pulsed wave Doppler was placed between the tips of the mitral leaflets in the apical 4-chamber view. Early (E) and late (A) transmitral flow velocities, the ratio of early to late flow velocities (E/A), and deceleration time (DT) of E velocity were obtained. Pulse-wave tissue Doppler imaging was performed by activating the Doppler tissue imaging function in the same machine. Sample volume was located at the medial side of the mitral annulus. Early (E') diastolic mitral annulus velocities and the ratio of E/E' were obtained. The mean values of ≥ 2 different cycles were obtained.

Statistical analysis

Data were analyzed with the software program SPSS 11.5 (SPSS Inc, Chicago, IL, USA). Data in the tables are presented as mean \pm standard deviation. Differences between age categories were studied with Analysis of Variance (ANOVA). Determinants of LV dimensions, LA diameters and E/E' were evaluated with linear regression analysis. Spearman correlations were used to test the association of continuous variables with mean tricuspid regurgitation gradient. Multiple linear regression analysis was used to determine the slope of the association between tricuspid regurgitation gradients and continuous variables. Significance level p was set at 0.05.

RESULTS

The 249 included healthy individuals had mean systolic and diastolic blood pressure values of 123 ± 11 and 66 ± 12 mmHg; blood pressures were comparable between

Table 1: Ventricular and atrial dimensions according to age category

Dimension	AGE (years)						Overall P
	18-34 N = 67	35-44 N = 45	45-54 N = 53	55-64 N = 46	65-74 N = 27	≥ 75 N = 11	
SBP (mmHg)	123 ± 11	123 ± 10	122 ± 10	123 ± 14	124 ± 10	125 ± 8	NS
DBP (mmHg)	68 ± 9	69 ± 9	67 ± 10	68 ± 11	68 ± 9	66 ± 12	NS
LVEDD (mm)	44.3 ± 4.2	45.0 ± 4.7	44.9 ± 4.7	44.4 ± 5.0	42.7 ± 5.2	43.4 ± 5.9	NS
LVEDDind (mm/m ²)	24.9 ± 2.8	25.0 ± 2.4	24.1 ± 2.9	24.4 ± 3.0	23.7 ± 1.6	24.4 ± 2.9	NS
LVESD (mm)	28.8 ± 4.1	28.6 ± 5.3	28.4 ± 4.0	28.4 ± 5.3	26.8 ± 4.9	27.1 ± 6.7	NS
LVESDind (mm/m ²)	16.2 ± 2.4	15.9 ± 2.7	15.2 ± 2.4	15.6 ± 3.1	14.9 ± 2.5	15.3 ± 3.8	NS
FS (%)	35 ± 7	37 ± 9	37 ± 7	36 ± 8	37 ± 9	38 ± 9	NS
IVSD (mm)	8.3 ± 1.5	9.1 ± 1.3	9.5 ± 1.6	9.8 ± 1.3	10.0 ± 1.3	9.6 ± 1.3	< 0.0001
IVSDind (mm/m ²)	4.6 ± 0.8	5.0 ± 0.7	5.1 ± 0.8	5.3 ± 0.7	5.6 ± 1	5.5 ± 0.9	< 0.0001
PWD (mm)	8.6 ± 1.6	9.0 ± 1.4	9.6 ± 1.4	9.4 ± 1.3	9.8 ± 1.2	10.2 ± 1.5	< 0.0001
PWDind (mm/m ²)	4.8 ± 0.8	5.0 ± 0.7	5.1 ± 0.8	5.1 ± 0.6	5.5 ± 0.8	5.7 ± 0.7	< 0.0001
RVEDD ¹ (mm)	28.2 ± 4.9	30.4 ± 5.2	30.2 ± 5.3	31.3 ± 5.2	31 ± 5.8	34.0 ± 2.7	0.04
RVEDDind ¹ (mm/m ²)	15.6 ± 2.6	16.5 ± 2.3	15.9 ± 2.6	17.2 ± 2.4	17.2 ± 3.7	18.9 ± 3.1	0.01
TAPSE (mm)	25.1 ± 4.1	24.6 ± 4.6	25.9 ± 4.7	25.6 ± 4.0	25.3 ± 3.0	22.7 ± 4.7	NS
LAD (mm)	31.3 ± 4.2	32.8 ± 4.9	34.9 ± 6.0	37.0 ± 4.8	36.0 ± 4.2	37.5 ± 5.5	< 0.0001
LADind (mm)	17.4 ± 2.3	18.1 ± 1.9	18.5 ± 2.7	20.3 ± 2.8	20.1 ± 2.5	21.0 ± 2.7	< 0.0001
LA vol ² (ml)	37 ± 14	40 ± 14	43 ± 17	49 ± 20	50 ± 39	58 ± 39	0.004
LA vol ² ind (ml/m ²)	20 ± 7	22 ± 7	23 ± 7	27 ± 9	26 ± 11	32 ± 18	< 0.0001
RA vol ¹ (ml)	37 ± 13	36 ± 12	43 ± 16	40 ± 16	42 ± 17	43 ± 24	NS
RA vol ¹ ind (ml/m ²)	20 ± 7	20 ± 6	22 ± 7	22 ± 8	22 ± 7	24 ± 12	NS

Data are presented as mean \pm standard deviation. ¹Data available in 185 subjects. ²Data available in 186 subjects.

Abbreviations: SBP: systolic blood pressure, DBP: diastolic blood pressure, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, FS: fractional shortening, IVSD: interventricular septum end-diastolic thickness, PWD: posterior wall end-diastolic thickness, ind: indexed for body surface, RVEDD: right ventricular end-diastolic diameter. TAPSE: tricuspid annulus plane systolic excursion, LAD: left atrium diameter, LA vol: left atrium volume, RA vol: right atrial volume.

the age categories (table 1). The mean BMI was 24 ± 3 kg/m² and mean body surface area 1.82 ± 0.20 m². The percentage male participants was slightly higher (52%) but with an even distribution over the age categories.

LV and LA dimensions and LV mass according to age categories

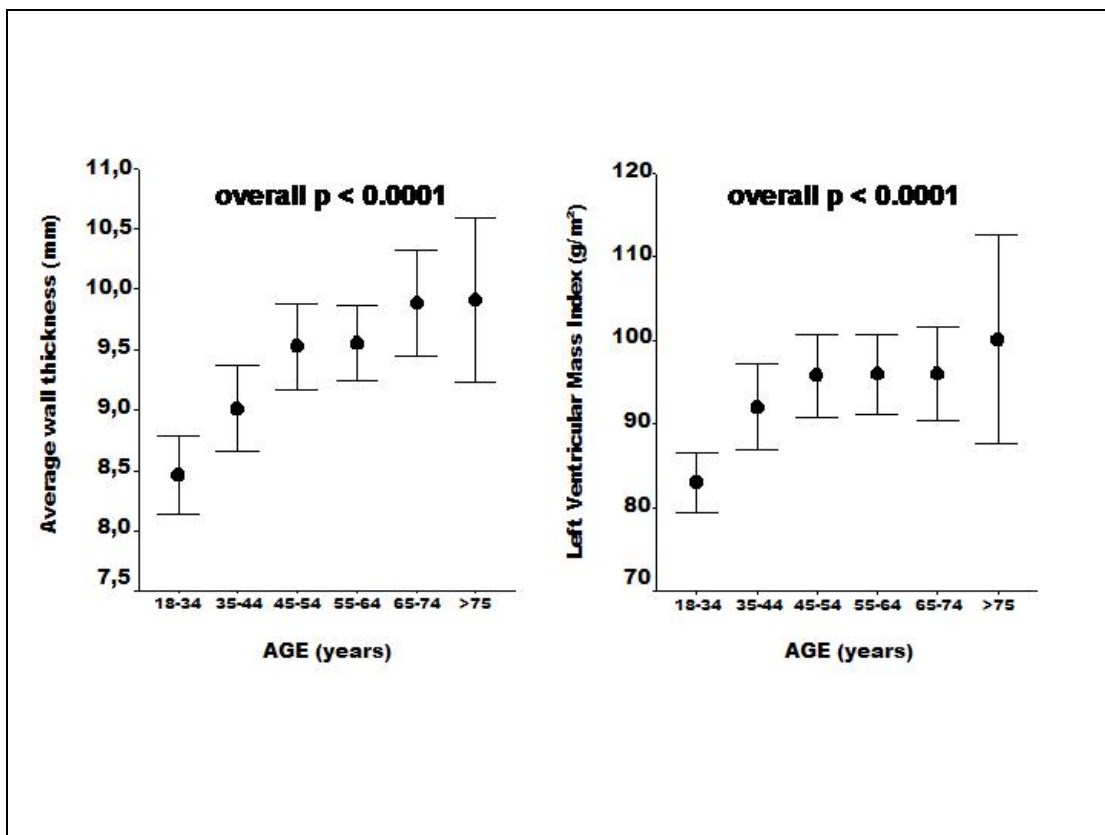
Mean LVEDD was 44 ± 5 mm, mean LVESD was 28 ± 5 mm and all subjects had a normal global LV systolic function (mean FS: 36 ± 8 %). Table 1 shows no significant differences between the age categories regarding LV dimensions and this holds true when the dimensions are indexed for body surface. With linear regression analysis LV diameters were predicted by body surface but not by age or gender.

Mean IVSD was 9 ± 2 mm, mean PWD was 9 ± 1 mm and mean LV mass index was 92 ± 17 g/m². In multivariate linear regression analysis LV mass index was predicted by age and gender. Table 1 shows that IVSD and PWD increased as subjects got older resulting in an increased average wall thickness and LV mass index (Figure 1). It is also apparent from table 1 that the LA diameters and LA volumes (available in

186 subjects) increased with age. With linear regression analysis LA dimensions were predicted by age and body surface but not by gender.

Figure 1

Mean values \pm 95 % confidence intervals according to age categories of average wall thickness (left panel) and left ventricular mass indexed for body surface (right panel)



RV and RA dimensions according to age categories

RV end-diastolic diameters (available in 185 subjects) were higher in older subjects (table 1) and this was confirmed after indexation for body surface. Age, gender and body surface were independent predictors of RVEDD in multivariate linear regression analysis. RV function as assessed with TAPSE was normal and comparable between

the age categories. No significant differences were observed between the age categories regarding RA volumes. RA volumes were independently predicted by body surface area but not by age or gender.

Diastolic parameters and estimated left ventricular end-diastolic pressure according to age categories (table 2)

Mean E was 75 ± 17 cm/s, mean A 64 ± 17 cm/s, mean DT 202 ± 54 ms and mean E/A 1.3 ± 0.4 . All these parameters were predicted by age (linear regression analysis); when subjects became older E decreased, A increased, DT prolonged and E/A decreased. Mitral annulus velocities (E') measured at the medial annulus decreased with age (table 2). In multivariate analysis E/E' was predicted by age (Table 2, Fig 2) and gender.

Table 2: Diastolic function, and estimated left and right ventricular pressures

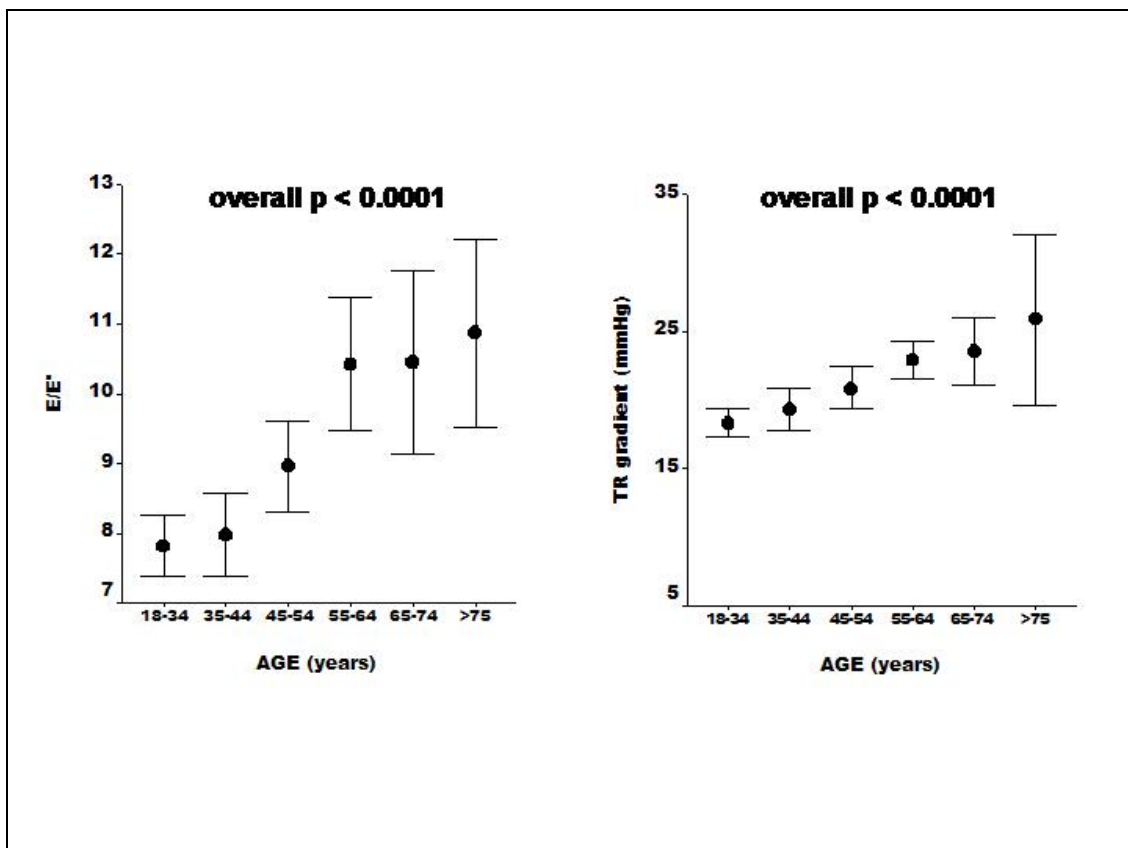
Dimension	AGE (years)						Overall P
	< 35 N = 67	35-44 N = 45	45-54 N = 53	55-64 N = 46	65-74 N = 27	≥ 75 N = 11	
E (cm/s)	84 ± 14	77 ± 16	74 ± 20	73 ± 13	65 ± 17	62 ± 16	< 0.0001
A (cm/s)	56 ± 10	56 ± 11	63 ± 16	75 ± 20	76 ± 18	76 ± 19	< 0.0001
DT (ms)	186 ± 39	187 ± 45	210 ± 57	201 ± 50	232 ± 63	251 ± 87	< 0.0001
E/A	1.5 ± 0.3	1.4 ± 0.3	1.2 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.9 ± 0.4	< 0.0001
E' (cm/s)	11 ± 2	10 ± 2	9 ± 2	8 ± 3	7 ± 2	6 ± 1	< 0.0001
E/E'	7.8 ± 1.8	8.0 ± 2.0	9.0 ± 2.3	10.4 ± 3.2	10.5 ± 3.2	10.9 ± 2.0	< 0.0001
TR grad (mmHg)	18.3 ± 4.1	19.3 ± 5	20.8 ± 5.6	22.9 ± 4.7	23.5 ± 6.1	25.8 ± 9.3	< 0.0001

Data are presented as mean \pm standard deviation.

Abbreviations: E: early peak mitral flow velocity, A: late mitral flow velocity, DT: deceleration time, E/A: ratio of early and late mitral flow velocity, E': early mitral annulus diastolic velocity, medial: E' measured at the medial side of the mitral annulus, E/E': ratio of early mitral flow velocity and mitral annulus velocity, TR grad: tricuspid regurgitation gradient.

Figure 2

Mean values \pm 95% confidence intervals according to age categories of the ratio of early peak mitral flow velocity E and early diastolic mitral annulus velocity E' (E/E') (left panel) and maximum peak tricuspid regurgitation gradient (right panel). Overall p was derived with analysis of variance (ANOVA).



Tricuspid regurgitation according to age categories

The mean tricuspid regurgitation gradient was 20.8 ± 6 mmHg (range 4 to 44 mmHg). The transvalvular gradient increased according to age (table 2, Figure 2). The parameters that correlated significantly with the tricuspid regurgitation gradients were age, BMI, systolic blood pressure, diastolic blood pressure, LA volume, IVSD, PWD, average wall thickness, LV mass index, FS, A, E' (inverse correlation), E/A (inverse correlation) and E/E' with r values ranging from 0.15 to 0.36 (p ranging from < 0.0001 to < 0.05). The following variables were entered into a multiple linear regression model to predict tricuspid regurgitation gradients: age, BMI, systolic blood pressure, LA volume, LV mass index, fractional shortening and E/E'. Age ($\beta=0.1$, $p=0.003$), LA volume ($\beta=0.05$, $p=0.01$), fractional shortening ($\beta=0.22$, $p<0.0001$) and E/E' ($\beta=0.32$, $p=0.04$) independently predicted right ventricular systolic pressure as estimated by the tricuspid regurgitation gradient (model $R^2= 0.32$, $p<0.0001$).

DISCUSSION

This study shows that among carefully selected normotensive healthy individuals with a broad age range, both E/E' and tricuspid regurgitation gradients increase significantly with aging. Moreover the E/E' ratio was independently predicting the tricuspid regurgitation gradient.

Aging is associated with several changes and adaptations in the cardiovascular system. There is controversy, however, about to what extent these adaptations are part of a natural aging process, or a response to environmental factors. (16) Many of

these age related structural and functional changes in the heart are reflected by changes in echocardiographic parameters. LV wall thickness, measured via M-mode echocardiography, increases progressively with age. (17) This is most likely caused by increased vascular loading on the heart. An age dependent increase in LV mass increases the stiffness of the left ventricle and promotes an increase in end-diastolic filling pressure. (8) Structural and functional changes within the LV myocardium are responsible for a reduced early diastolic LV filling rate reflected by smaller E waves on the transmitral flow pattern. Despite the slowing of LV filling early in diastole, more filling occurs in late diastole, due to a more vigorous atrial contraction, which produces an exaggerated A wave. (8) The augmented atrial contraction and the increased diastolic filling pressure result in left atrial enlargement which is reflected by increased LA dimensions. The prolonged DT slope reflects decreased LV compliance, as it takes longer for LA and LV pressures to equilibrate.

All of these changes can also occur in hypertensive subjects. In the present study we did not only exclude subjects with a history of hypertension but blood pressure was actually measured, thereby guaranteeing that non-detected hypertensive subjects were also excluded. Even when applying these strict inclusion criteria, the present study confirms the findings of previous reports (18,19, 20): LA dimensions, LV wall thickness and LV mass index increased with aging; E decreased, A increased, DT prolonged, E/A decreased and the E/E' ratio increased. The upper limit of LA diameter was 25 mm/m² in our study. One study reports an upper limit of 24 mm/m² (based on a reference population aged 18-60 years) but this likely ignores age-related increases in LA dimensions. (21)

Right ventricular systolic pressure can be assessed noninvasively by measuring the tricuspid regurgitation gradient plus right atrial pressure. Unfortunately various studies have used various estimates for the right atrial pressure, ranging from 5 (22, 23) to 10 mmHg (10, 12). However, since 10 mmHg may be an overestimation in healthy individuals, we report tricuspid regurgitation gradients without adding an estimation of right atrial pressure. In clinical practice evaluation of the jugular vein or respiratory echographic changes of the inferior vena cava diameter can be used for the estimation of right atrial pressure.

Tricuspid regurgitation gradients increased with age as reported in previous studies. Dib et al studied 134 echocardiographic normals (including 37 hypertensive patients), aged 20 to 85 years and found systolic pulmonary artery pressure increasing progressively with age with values up to 32 ± 6 mmHg in 80 years old or more. (10) Aessopos et al studied 53 healthy persons; the tricuspid gradient ranged from 12.6 to 29.3 mmHg. (11) They found no correlation with age but had deliberately excluded individuals aged 55 or more. Gradients ≥ 20 mmHg were found in 36% and they considered a gradient of 30 mmHg as the upper normal limit. (11) Dokainish et al studied 33 echocardiographically normal individuals, aged 90 to 100 years. (23) Mean pulmonary artery pressure was $31 \text{ mmHg} \pm 6$. The authors concluded that, in the elderly, a pulmonary artery pressure ≤ 40 mmHg by echocardiography could be considered normal. McQuillan et al determined pulmonary artery systolic pressure (PASP) in 3790 echocardiographically normal subjects. (12) To calculate PASP the authors assumed that right atrial pressure was 10 mmHg in all cases. The mean tricuspid regurgitation gradient in their study was 18.3 ± 4.9 mmHg. This is 2.5 mmHg lower than the mean gradient in the present study but this could be explained by the

lower mean age in McQuillan's study: 33 years versus 47 years in the present study. Age was found to be the strongest predictor of pulmonary artery pressure with an increase of approximately 1 mmHg per decade.

Interestingly, McQuillan and co-workers found LV PWD and IVSD to be independently associated with pulmonary artery systolic pressure. They suggested that LV wall thickness might relate to pulmonary artery systolic pressure through diastolic dysfunction and the effects of decreased LV compliance and increased LV end-diastolic pressure with aging and in such conditions as systemic hypertension. However, McQuillan et al had no information available on diastolic function or left ventricular filling pressures, 3% of their patients had a history of arterial hypertension, blood pressure was not measured and it was not detailed whether increased LVMI was an exclusion criterion. McQuillan et al report significant univariate correlations between tricuspid regurgitation gradient and age, BMI, LV wall thickness, LA dimension and LV systolic function. All of these correlations were also found in the present study next to LV mass index, diastolic function parameters (A, E/A, E/E') and blood pressure. In multivariate linear regression analysis the tricuspid regurgitation gradient was independently predicted by age, LA volume, LV function and E/E'. This suggests but does not prove that the age related LV changes with increased wall thickness, diastolic dysfunction and increased left ventricular filling pressures could, at least in part, be responsible for the equivalent increase of the right ventricular systolic pressure at older age. Other factors could be a decrease in the pulmonary blood flow, an increase in the mean pulmonary pressure and an increase in pulmonary resistance, presumed related to reduced compliance of the pulmonary vascular bed. (22) Moreover, not only the cardiovascular but also the pulmonary

system, is subject to aging and these structural and functional changes of the lungs could also explain higher right ventricular systolic pressures at older age. (25)

Our findings support the need for age adjusted cut-off values for echocardiographic estimated ventricular pressures. As E/E' ratios and tricuspid regurgitation gradients are increasingly used in clinical decision making and patient follow-up, age specific normal values of these parameters should be available, especially in the old and very old.

LIMITATIONS

The reported data are limited to adults, aged 18 years or more. The subjects included in this study were “presumed healthy” individuals undergoing a check-up. Although we took great care in selecting these normals it is possible that some of the subjects could have occult cardiovascular disease. However, all subjects had normal cavity dimensions and normal wall motion making severe coronary artery disease less likely. Doppler measurement of tricuspid systolic pressure gradient is applicable only in a proportion of healthy subjects, characterized by a clearly definable tricuspid regurgitation Doppler signal. Persons with mild to moderate tricuspid regurgitation were considered healthy, though the presence of tricuspid regurgitation might be related to mild pulmonary abnormalities. Although patients with a history of pulmonary disease were excluded, the lack of objective evaluation of pulmonary status with spirometry is an important limitation of this study. The early diastolic mitral annulus velocities were recorded at the medial mitral annulus; values recorded at the lateral side are mostly higher resulting in a lower E/E' . (23)

CONCLUSION

The present study demonstrates in 249 healthy, normotensive individuals, aged 18 to 82 years that aging is accompanied by an increase of LV wall thickness and LV mass index. These changes probably reduce LV compliance which induces elevated LV filling pressures as reflected by higher E/E' values. The equivalent elevation of right ventricular systolic pressure as reflected by the increased tricuspid regurgitation gradient might be related to the increased LVMI through diastolic dysfunction. These data support the need for age adjusted normal values for echocardiographic estimated ventricular pressures, especially in the old and very old.

ACKNOWLEDGEMENTS

Nico Van de Veire is a research assistant and Johan De Sutter a senior clinical investigator of the Fund for Scientific Research Flanders – Belgium (F.W.O.-Vlaanderen). Julie De Backer is a recipient of a BOF mandate at Ghent University, Belgium. The authors would like to thank Krista Van Vlaenderen (M.Eng) for her technical assistance.

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CHAPTER 1.2

Effects of age, gender and left ventricular mass on septal mitral annulus velocity (E') and the ratio of transmitral early peak velocity to E' (E/E')

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Am J Cardiol 2005; 95:1020-1023

Oral presentation at the Belgian Society of Cardiology Congress,
February 2004, Brussels

AIMS

The aims of this study are to evaluate the effects of age, gender and left ventricular (LV) hypertrophy on the early diastolic mitral annulus velocity (E') evaluated by tissue Doppler imaging and the ratio of the transmitral early peak velocity (E) evaluated by conventional Doppler over E' (E/E') in a wide age range of normal individuals and in patients with LV hypertrophy due to hypertension (1-6).

METHODS

Study population

From January 2002 until December 2002 we evaluated all asymptomatic individuals without a history of cardiovascular or pulmonary disease who were referred for routine echocardiography at our department. Subjects with atrial fibrillation as well as subjects in whom significant abnormalities (such as significant valvular disease, hypertrophic cardiomyopathy, LV systolic dysfunction, pericardial effusion, LV hypertrophy or pulmonary hypertension) were found during the echocardiographic examination were excluded. In total, 174 individuals were included in the study. This study population represents 3% of all transthoracic echocardiographies performed during the study period at our department.

To study the effect of LV mass on annular velocities, an additional 86 patients with a history of hypertension (defined as a blood pressure > 140/90 mmHg or taking antihypertensive medication) and previously documented LV hypertrophy on

echocardiography were evaluated. All these patients were asymptomatic and exclusion criteria were similar as for the normal individuals.

Echocardiographic examination

All patients underwent a standard echocardiographic examination, using a VIVID 7 (Vingmed, GE, Horten, Norway) scanner. Patients were examined in the left lateral recumbent position using standard parasternal short- and long-axis and apical views. The LV dimensions and ejection fraction were measured by two-dimension guided M-mode in the parasternal long-axis view. Left ventricular end diastolic and end systolic diameters (LVEDD and LVESD) as well as septal and posterior enddiastolic wall thickness were measured using the Penn convention. Left ventricular mass was calculated using the Penn formula: $1.04 ((LVEDD + \text{posterior wall thickness} + \text{septal wall thickness})^3 - (LVEDD)^3) - 14 \text{ g}$ and was indexed for body surface area. LV hypertrophy was defined as a LV mass index $> 134 \text{ g/m}^2$ for men and a LV mass index $> 110 \text{ g/m}^2$ for women (7,8).

Sample volume (size 2 mm) of the pulsed wave Doppler was placed between the tips of the mitral leaflets in the apical four-chamber view. Early (E) and late (A) transmitral flow velocities, the ratio of early to late peak velocities (E/A) and deceleration time of E velocity were obtained. Pulsed wave tissue Doppler imaging was performed by activating the Doppler tissue imaging function in the same machine. Sample volume was located at the septal side of the mitral annulus. Early (E') mitral annulus velocities and the ratio of E/E' were obtained. The mean values of at least two different cycles were obtained.

Statistical analysis

Data are expressed as mean \pm standard deviation. Differences between the normal individuals and patients with LV hypertrophy were evaluated with the unpaired Student's t test. Determinants of E' and E/E' were evaluated by multiple linear regression analysis. Differences across age groups were assessed by analysis of variance (ANOVA). A p-value < 0.05 was considered as statistically significant.

RESULTS

In total 174 normal individuals were included (age 56 ± 14 years, range 21-87 years, 108 men). Mean LVEDD was 47 ± 6 mm and mean LVESD 30 ± 6 mm with a calculated mean LV ejection fraction of $59\pm 10\%$ and mean LV mass index of 98 ± 20 g/m². Mean E was 77 ± 19 cm/s, mean A 69 ± 19 cm/s, mean E/A 1.2 ± 0.5 , mean deceleration time 204 ± 51 ms, mean E' 8.2 ± 2.5 cm/s and mean E/E' 10.0 ± 3.2 . Table 1 shows the results of the different diastolic parameters in the normal population according to 5 age groups: < 45 years (n=39, age 36 ± 7 years), age 45-54 years (n=43, age 50 ± 3 years), 55-64 years (n=40, age 59 ± 3 years), 65-74 years (n=35, age 69 ± 3 years) and age > 74 years (n=17, age 78 ± 4 years).

TABLE 1 Diastolic Transmitral and Mitral Annulus Recordings in Normal Subjects and Patients With LV Hypertrophy Due to Hypertension

Age (yrs)	No.	E (cm/s)	A (cm/s)	E/A	Deceleration Time (ms)	E' (cm/s)	E/E'
Normals							
<45	39	79 ± 17	57 ± 10	1.44 ± 0.41	197 ± 49	10.1 ± 2.6	8.2 ± 2.2
45-54	43	77 ± 17	63 ± 14	1.25 ± 0.39	200 ± 41	8.9 ± 1.8	9.1 ± 2.9
55-64	40	74 ± 21	73 ± 22	1.11 ± 0.47	197 ± 50	7.6 ± 2.3	10.4 ± 3.3
65-74	35	77 ± 21	76 ± 21	1.08 ± 0.43	210 ± 49	7 ± 2.1	11.5 ± 3.1
>74	17	74 ± 20	83 ± 22	0.98 ± 0.58	215 ± 71	6.2 ± 1.7	12.4 ± 3.3
LV hypertrophy							
<45	11	83 ± 14	64 ± 14	1.36 ± 0.44	204 ± 45	9.5 ± 3.1	9.3 ± 2.3
45-54	13	77 ± 10	63 ± 10	1.23 ± 0.21	198 ± 59	7.6 ± 1.8	10.5 ± 2.2
55-64	22	85 ± 25	75 ± 21	1.21 ± 0.55	204 ± 46	8 ± 2.6	11.1 ± 3.1
65-74	23	84 ± 17	76 ± 27	1.3 ± 0.72	219 ± 50	7.3 ± 2.6	12.6 ± 3.9
>74	17	74 ± 15	74 ± 18	1.1 ± 0.34	220 ± 70	5.7 ± 1.3	13.6 ± 3.9

Data are presented as mean ± SD.

Multiple linear regression analysis, including age, gender and LV mass index, showed that E' was only predicted by age ($\beta = -0.54$, $p < 0.001$). Figure 1 shows the values for E' in the 5 age groups. It can be noticed that E' shows a step decrease with age ($p < 0.005$ in ANOVA).

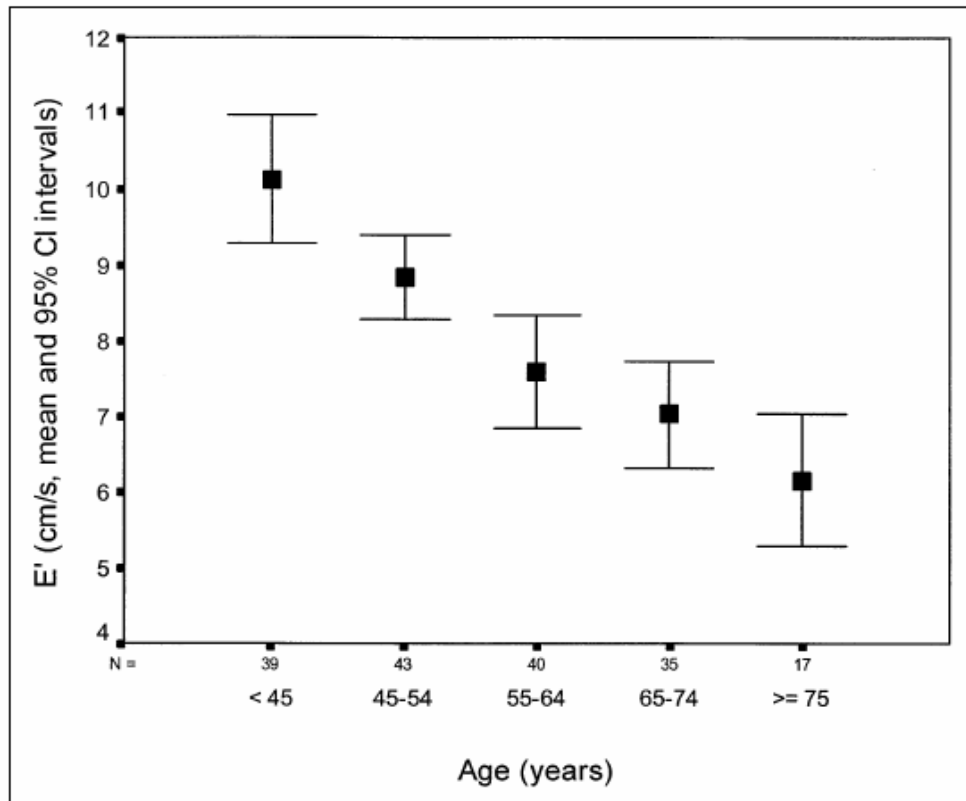


FIGURE 1. Values for E' in normal patients across 5 age groups. Data are expressed as mean and 95% confidence intervals (CI).

In contrast, E/E' was predicted by age ($\beta=0.44$, $p<0.001$) and gender ($\beta=-0.22$, $p<0.01$) but not by LV mass index. Figure 2 shows the values for E/E' in the different age groups according to gender. For both men and women, E/E' showed a significant increase with age ($p<0.001$ in ANOVA). Moreover, women had in general slightly higher values ($p<0.05$) for E/E' compared to men.

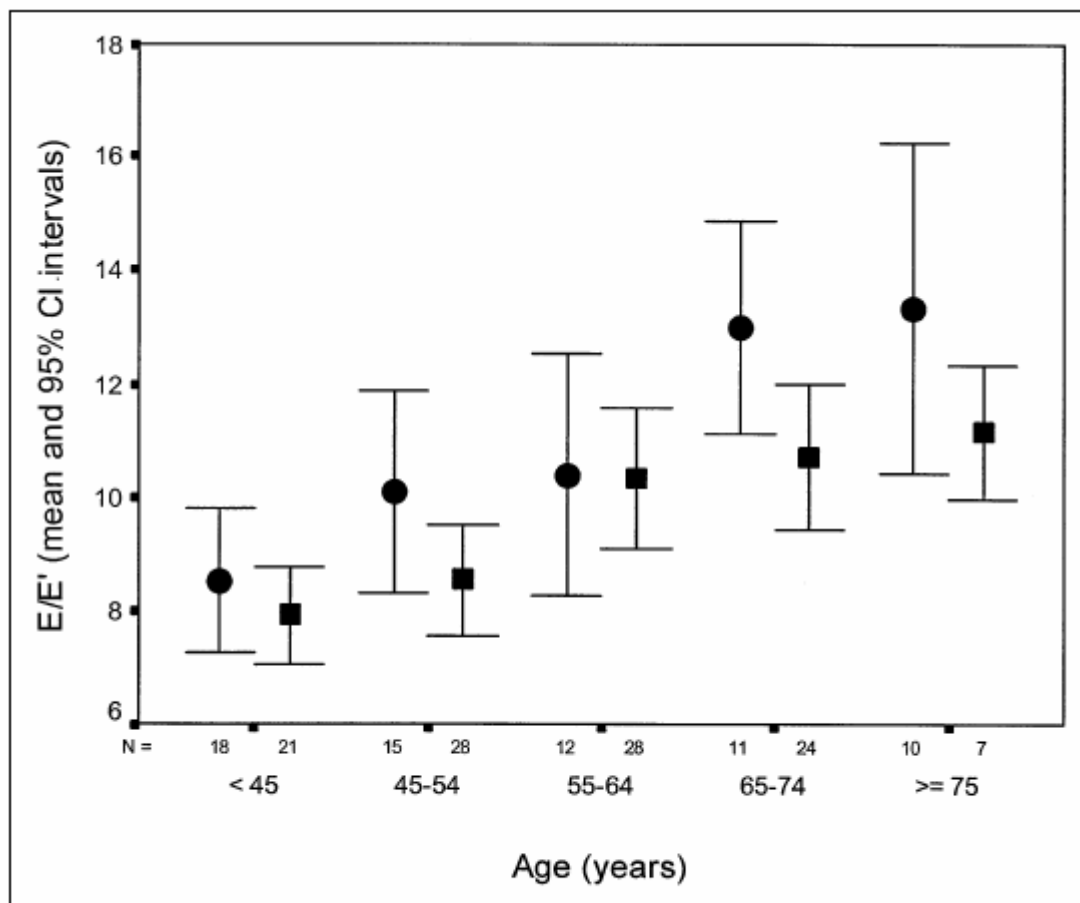


FIGURE 2. Values for E/E' in normal patients across 5 age groups according to gender (circles, women; squares, men). Data are expressed as mean and 95% CI. Abbreviation as in Figure 1.

In total 86 patients with hypertension and previously documented LV hypertrophy were included (age 62 ± 14 years, range 24-88 years, 50 men). Mean LVEDD was 52 ± 5 mm and mean LVESD 31 ± 6 mm with a calculated mean LVEF of $62\pm 10\%$ and mean LV mass index of 151 ± 22 g/m² ($p < 0.01$ compared to normal individuals). Mean E was 81 ± 18 cm/s, mean A 72 ± 20 cm/s, mean E/A 1.2 ± 0.5 , mean deceleration time 203 ± 53 ms, mean E' 7.5 ± 2.5 cm/s ($p < 0.01$ compared to normal individuals) and mean E/E' 11.7 ± 3.5 ($p < 0.01$ compared to normal individuals). Table 1 shows the results of the different diastolic parameters in this population according to 5 age groups: < 45 years (n=11, age 37 ± 6 years), age 45-54 years (n=13, age 52 ± 3 years), 55-64 years (n=22, age 60 ± 3 years), 65-74 years (n=23, age 69 ± 3 years) and age > 74 years (n=17, age 80 ± 4 years). Stepwise multiple linear regression analysis, including age, gender and LV mass index, showed that E' was only predicted by age ($\beta = -0.41$, $p < 0.001$). Also E/E' was only predicted by age ($\beta = 0.35$, $p < 0.001$) and not by gender or LV mass index.

Figure 3 shows the values for E/E' in normal individuals and patients with hypertension and LV hypertrophy. E/E' showed a significant increase with age in patients with hypertension and LV hypertrophy ($p < 0.001$ in ANOVA). Furthermore, for each age category patients with LV hypertrophy had slightly higher E/E' values compared to normal individuals.

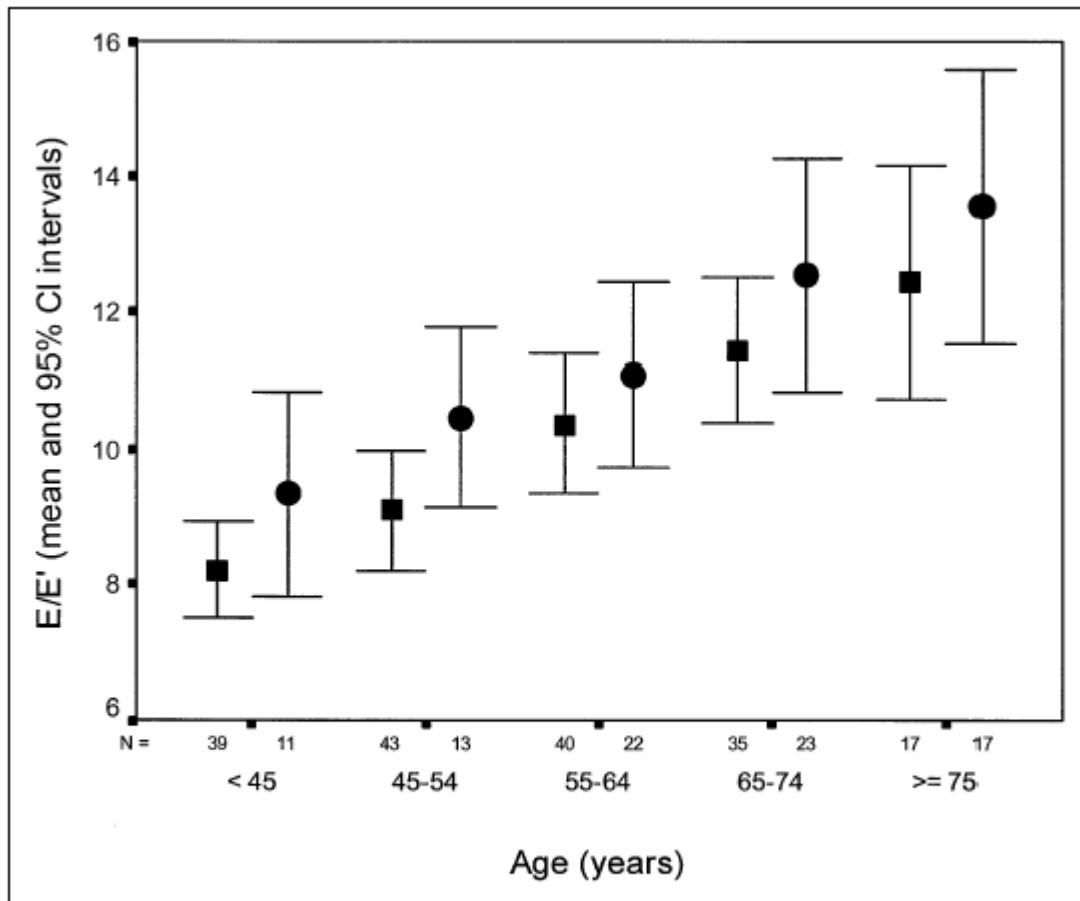


FIGURE 3. Values for E/E' in normal patients (*squares*) and patients with hypertension and LV hypertrophy (*circles*) across 5 age groups. Data are expressed as mean and 95% CI. Abbreviation as in Figure 1.

According to Nagueh et al (5), a ratio of $E/E' > 10$ is a marker of elevated LV filling pressures. The total number of normal individuals with $E/E' > 10$ in the present study was 6/39 (15%) in the group < 45 years, 11/43 (26%) in the group 45-54 years, 19/40 (48%) in the group 55-64 years, 22/35 (63%) in the group 65-74 years and 12/17 (71%) in the group > 74 years. The total number of patients with LVH and $E/E' > 10$ was 5/11 (45%) in patients < 45 years, 8/13 (62%) in patients 45-54 years, 14/22 (64%) in patients 55-64 years, 15/23 (65%) in patients 65-74 years and 14/17 (82%) in patients > 74 years.

Ommen et al (6) suggested a cutoff value for E/E' of 15 as a marker for elevated LV filling pressures. Figure 4 shows the prevalence of normal individuals and patients with LV hypertrophy with E/E' > 15 in the different age groups. In normal asymptomatic individuals < 65 years, E/E' > 15 was rarely noticed. In contrast, in normal asymptomatic individuals ≥ 65 years, a significant proportion showed E/E' values > 15. (14% in the group 65-74 years and 24% in the group older than 74 years).

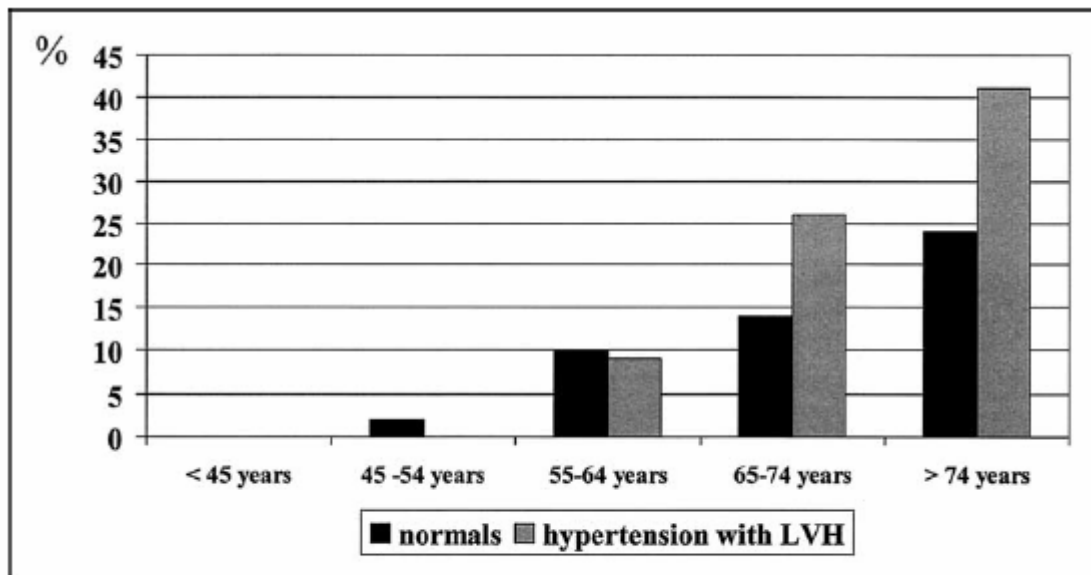


FIGURE 4. Prevalence of normal patients and patients with hypertension and LV hypertrophy (LVH) with E/E' > 15 in the different age groups.

DISCUSSION

In this study we evaluated the effects of age, gender and LV hypertrophy on E' and E/E' in normals and in patients with LV hypertrophy due to hypertension. Age appeared to be the strongest determinant of E' and E/E' suggesting that both in

normals and patients with LV hypertrophy age dependent cut-off values should be taken into consideration.

We documented across a wide age range a decrease of E' of approximately 1 cm/s per decade and an increase of E/E' of approximately 1 unit per decade both in normal individuals and in patients with LV hypertrophy due to hypertension. This age dependency has important implications for the diagnosis of diastolic dysfunction or elevated LV filling pressures, especially in the elderly. Nagueh et al (5) showed previously that the E/E' ratio correlated well to pulmonary capillary wedge pressure measured invasively in 60 patients evaluated in the intensive care unit or in the catheterization laboratory. An E/E' ratio >10 detected a mean pulmonary capillary wedge pressure > 15 mmHg with a sensitivity of 97% and a specificity of 78% while a ratio of 12 resulted in a higher specificity (88%) but a lower sensitivity (68%). Based on these and other studies a cut-off value for E/E' of 10 has been increasingly used as one of the parameters to evaluate diastolic function and LV filling pressures (2). Recently this cut-off value was also used in large epidemiological studies that evaluated the prevalence of systolic and diastolic LV dysfunction in the community (9,10). In our normal individuals however, an E/E' ratio > 10 was frequently encountered in individuals < 65 years (15% in the group < 45 years, 26% in the group 45-54 years, and 48% in the group 55-64 years). Moreover, most asymptomatic individuals ≥ 65 years showed a ratio > 10 (63% in the group 65-74 years and 71% in the group > 74 years) suggesting that this cut-off is probably too low for the evaluation of elderly subjects.

In a study of 100 consecutive patients referred for cardiac catheterization, Ommen et al (6) showed that $E/E' > 15$ identified an increased mean LV diastolic pressure (>12 mmHg, measured by high-fidelity micro manometer-tipped catheters) with a predictive accuracy of 76% which was higher than the accuracies of parameters derived from transmitral or pulmonary venous flow signals. The mean age of this population was 63 years and 61% were men. In our study of normal asymptomatic individuals an E/E' ratio > 15 was rarely found in individuals < 65 years (figure 4). However, in individuals ≥ 65 years, an E/E' ratio > 15 was more frequently encountered (14% in the group 65-74 years and 24% in the group older than 74 years). Especially in women older than 74 years the normal data suggest that possibly an even higher cut-off for E/E' should be used (figure 2). This hypothesis needs however confirmation in further comparative studies in the elderly.

Our multivariate regression analysis shows a relationship between gender and values of E/E' in the normal population. Women had indeed higher values than men across all age groups but the differences were small with wide confidence intervals. Comparable with these findings, Nikitin et al (11) reported recently in a smaller group of middle-aged normal individuals slight but significant sex-related differences for systolic and early diastolic velocities at different myocardial regions determined with colour TDI. This age and gender dependency of E/E' in normal individuals is very similar to the age and gender dependency that has been described for brain natriuretic peptides (12). Normal values for these neurohormones that are increasingly used for the diagnosis and prognosis of heart failure and estimation of LV filling pressures are also higher in women and increase with age.

CONCLUSION

In summary, our results strongly suggest that a single cut-off value for E/E' for the evaluation of diastolic function or elevated LV filling pressures should not be used in clinical practice. Instead age dependent normal values should be taken into consideration. Also, women appear to have slightly higher normal values of E/E' but differences are small. Finally, the effect of left ventricular mass is only modest after correction for age and gender.

ACKNOWLEDGEMENTS

Johan De Sutter is a Senior Clinical Investigator of the Fund for Scientific Research – Flanders (Belgium) (F.W.O. – Vlaanderen). Julie De Backer is a recipient of a BOF mandate of the University Gent, Belgium. Nico Van de Veire is a Research Assistant of the Fund for Scientific Research – Flanders (Belgium) (F.W.O. – Vlaanderen).

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Effect of ischemic mitral regurgitation on the ratio of early transmitral flow velocity to mitral annulus early diastolic velocity in patients with stable coronary artery disease.

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Am J Cardiol 2006; 97: 1449-1451

Moderated electronic poster presentation at the European Society of Cardiology
Congress, September 2005, Stockholm

ABSTRACT

The aims of the present study were 1) to evaluate the prevalence of ischemic mitral regurgitation (MR) in a large population of patients with documented coronary artery disease referred for echocardiography and 2) to assess whether IMR is an independent determinant of echocardiographically estimated left ventricular (LV) filling pressures. We studied 849 consecutive CAD patients (67 ± 10 years, 76% men) without organic valvular disease. Ischemic MR was semi quantitatively graded as absent or trace, grade I, grade II and grade III-IV by assessment of the colour-flow jet in relation to the left atrium in multiple orthogonal views. The ratio of early transmitral flow velocity (E) over mitral annulus early diastolic velocity (E'), E/E' , was determined to estimate LV filling pressures. Ischemic MR was absent in 25% of the patients and 28% had a grade II or more ischemic MR. Only 18% of the patients with preserved LV function had a significant ischemic MR but up to 66% of the patients with poor LV function had a grade II or more MR. The E/E' was independently predicted by age, gender, LV ejection fraction but also by ischemic MR severity. Even mild ischemic MR was associated with an increase of this non-invasive marker of LV filling pressures.

INTRODUCTION

The ratio of early transmitral flow velocity (E) over mitral annulus early diastolic velocity (E') is a widely used non-invasive tool to estimate left ventricular (LV) filling pressures. (1,2) The E/E' value has also been shown to be a powerful predictor of survival in patients with coronary artery disease (CAD). (3) Bruch et al validated the use of E/E' for estimation of filling pressures in patients with ischemic mitral regurgitation (MR). (4) Among CAD patients, changes in ventricular structure and function related to ischemia and remodelling can lead to MR. (5) A higher degree of ischemic MR is associated with a worse prognosis. (6,7,8) The present study evaluates the prevalence of ischemic MR in a large series of consecutive CAD patients and assesses whether ischemic MR is a determinant of E/E' in CAD patients.

METHODS

We retrospectively analyzed 849 consecutive patients with a documented history of CAD (myocardial infarction, significant coronary stenosis and/or revascularisation), referred for transthoracic echocardiography. Patients with organic mitral or aortic valve disease such as prolaps, rheumatic valve disease or endocarditis were excluded. Patients with ischemic MR had as underlying mechanism a Carpentier type IIIb dysfunction correlating to restricted leaflet motion during systole secondary to papillary muscle displacement.

Echocardiography

LV diameters were determined with 2D echocardiography (VIVID 7, GE, Horten, Norway). LV mass was calculated using the Penn formula: $1.04 ((LV \text{ end-diastolic diameter} + \text{posterior wall} + \text{interventricular septum})^3 - (LV \text{ end-diastolic diameter})^3) - 14 \text{ g}$ and was indexed for body surface area. LV systolic function was visually scored in 4 categories: LV ejection fraction >55%, 41-55%, 26-40%, and < 26%. Using pulsed wave Doppler the sample volume was placed at the mitral leaflets tips to assess the E value. E' was determined at the medial mitral annulus using pulsed wave tissue Doppler and the E/E' was calculated. Ischemic MR was semi quantitatively graded as absent or trace, grade I, grade II and grade III-IV by assessment of the colour-flow jet in relation to the left atrium in multiple orthogonal views.

Statistical analysis

Patients were divided in 4 categories according to MR severity and statistical comparisons were made with analysis of variance (ANOVA) using SPSS statistical software version 11.5 (SPSS Inc, Chicago, IL., USA).

RESULTS

The 849 included patients (76% men) had a mean age of 67 ± 10 years ranging between 24 and 92 years. Mean LV end-diastolic diameter was 48 ± 8 mm (range 24-87 mm), mean LV end-systolic diameter was 34 ± 10 mm (range 11-81 mm) and mean

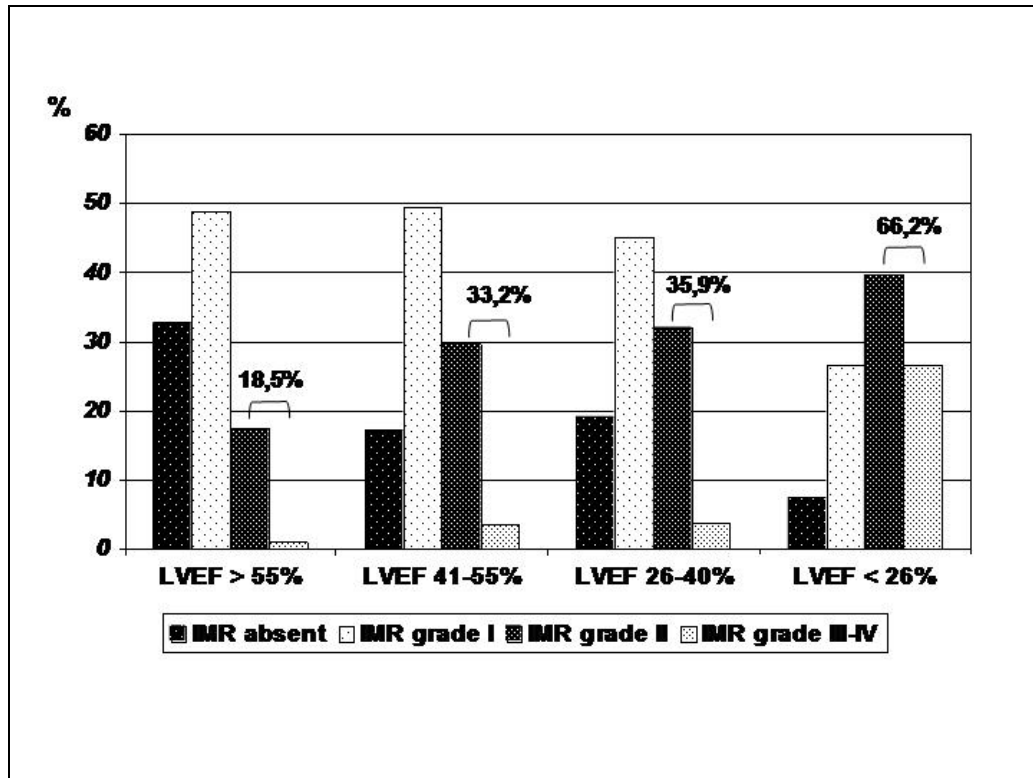
LV mass index was 124 ± 39 g/m² (range 51-302 g/m²). A preserved LV systolic function (EF > 55%) was present in 53%, 24% had LVEF between 41-55%, 15% between 26-40% and 8% had a poor LV function (EF < 26%).

Table 1 shows the distribution of ischemic MR severity. Figure 1 illustrates that in patients with a preserved LV function only 18% have a significant ischemic MR; this percentage increased as LV function became worse and up to 66% of the patients with poor LV function had a significant ischemic MR.

Table 1: Left ventricular dimensions and filling pressures according to ischemic mitral regurgitation severity

Variable	Ischemic Mitral Regurgitation				p value
	Absent (n=212) (25%)	Grade I (n=395) (47%)	Grade II (n=207) (24%)	Grade III-IV (n=35) (4%)	
Left ventricular end-diastolic diameter (mm/m ²)	24 ± 4	25 ± 4	27 ± 4	32 ± 6	< 0.001
Left ventricular end-systolic diameter (mm/m ²)	16 ± 4	17 ± 5	19 ± 5	26 ± 8	< 0.001
Early transmitral flow velocity: E (cm/s)	66 ± 24	68 ± 25	70 ± 30	75 ± 42	< 0.001
Early diastolic medial mitral annulus velocity: E' (cm/s)	5.9 ± 2.0	5.7 ± 2.2	5.0 ± 1.8	4.7 ± 1.9	< 0.001
E/E'	11.9 ± 4.8	12.8 ± 5.6	15.1 ± 7.0	16.7 ± 9.3	< 0.001

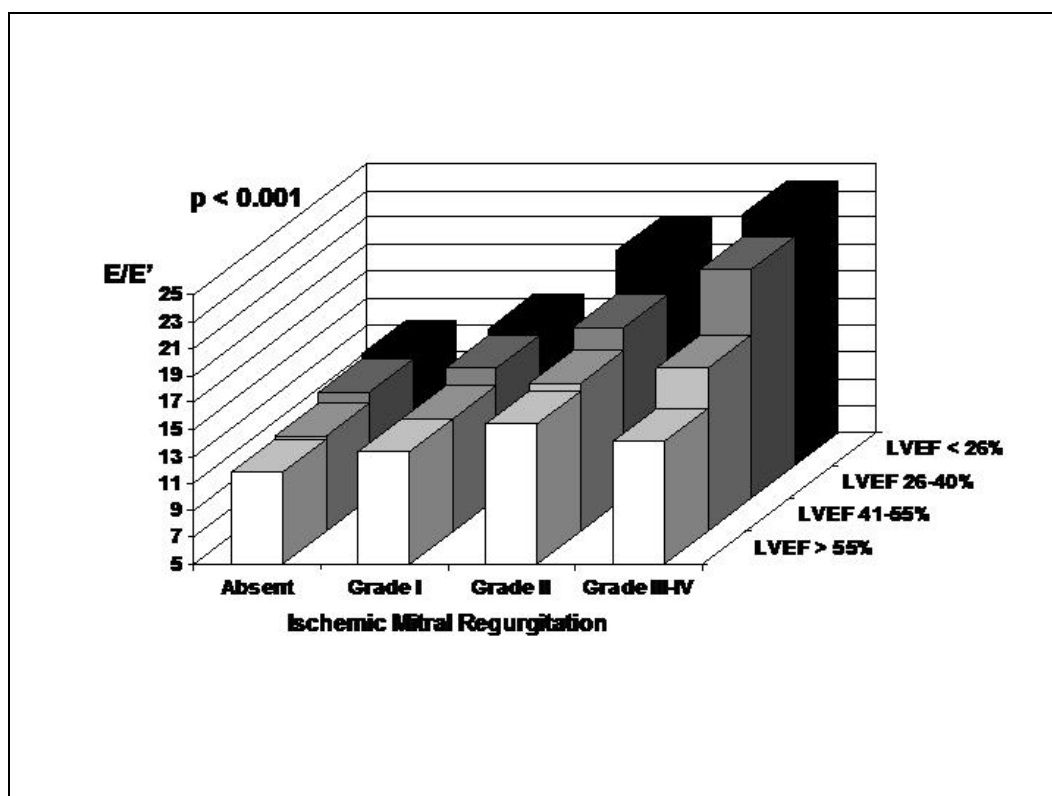
Figure 1: Distribution of ischemic mitral regurgitation (IMR) severity according to left ventricular ejection fraction (LVEF)



As ischemic MR increased, LV dimensions increased (table 1). The E value increased and the E' decreased as ischemic MR became more prominent resulting in higher E/E' values in patients with MR grade III-IV. The E/E' ratio was also determined by LV systolic function: in patients with preserved function the mean E/E' was 13.4 ± 4.8 , in patients with LVEF between 41-55% 14.0 ± 5.5 , in patients with LVEF between 26-40% 15.7 ± 5.6 and in patients with poor LVEF it was 19.5 ± 6.8 (overall p value < 0.001).

Figure 2 illustrates that E/E' is determined both by LV systolic function and ischemic MR severity. Within each ischemic MR category patients with a worse LV function had a higher E/E' value. Patients without MR and with preserved LV function had the lowest E/E' value, patients with poor LV function and grade III-IV MR had the highest E/E' ratio. Multiple linear regression analysis was used to fit a model to predict the E/E' ratio. The following parameters predicted independently E/E': mitral regurgitation severity ($\beta=0.68$, $p<0.0001$), left ventricular ejection fraction ($\beta=0.68$, $p<0.0001$), gender ($\beta=-2.2$, $p<0.0001$), LV mass index ($\beta=0.003$, $p=0.008$), LV end-diastolic diameter ($\beta=0.023$, $p=0.02$) and age ($\beta=0.059$, $p<0.0001$).

Figure 2: The early transmitral flow velocity (E) over mitral annulus early diastolic velocity (E') according to severity of ischemic mitral regurgitation (IMR) and according to left ventricular ejection fraction (LVEF)



DISCUSSION

Bursi et al showed in 773 patients who underwent echocardiography within 39 days after myocardial infarction that the overall prevalence of MR was 40%. (8) In the present study including CAD patients with and without previous myocardial infarction the overall prevalence of ischemic MR was 53%; 28% of the patients had a significant MR and this increased up to 66% in patients with poor LV function.

In the first validation studies on E/E' by Nagueh and Ommen (1,2) patients with MR were excluded or not separately evaluated. Bruch et al (4) demonstrated that the E/E' ratio also correlated significantly with LV end-diastolic pressure in patients with ischemic MR and showed that E/E' > 15 had a 80% sensitivity and 100% specificity for prediction of LV end-diastolic pressure \geq 15 mmHg. If we implement this cut-off in the present study, a large proportion of the patients with IMR grade II or more have elevated LV end-diastolic pressures but also patients with a grade I ischemic MR and poor LV systolic function have E/E' values \geq 15. The poor prognosis of patients with more severe IMR could be related to the development of heart failure and higher LV filling pressures.

It would also be interesting to investigate if patients with elevated E/E' ratio at rest develop more severe MR during exercise. Recently, Lancellotti et al have extensively shown the importance of evaluating MR echocardiographically during semi-supine exercise. (9,10) Their results indicate that patients with a large increase in the degree of MR during exercise have a worse outcome.

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PART 2

Noninvasive evaluation of potential candidates for cardiac resynchronization therapy

CHAPTER 2.1

Global and regional parameters of dyssynchrony in ischemic and non-ischemic cardiomyopathy.

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Am J Cardiol 2005; 95: 421-423

Moderated poster presentation at Euroecho, December 2004, Athens

ABSTRACT

In this study we used Colour Tissue Doppler Imaging to assess global and regional mechanical dyssynchrony in patients with ischemic (IC) and idiopathic dilated cardiomyopathy (IDC). Potential differences in the area of latest mechanical activation could have practical implications regarding lead positioning and success rate of biventricular pacemaker implantation.

INTRODUCTION

Cardiac resynchronization therapy is a recent therapeutic option for patients with symptomatic heart failure, an impaired left ventricular systolic function and a broad QRS on the surface electrocardiogram (1-3). In order to avoid non-responders several novel echocardiographic tools have been introduced. These parameters should improve patient selection by identifying individuals with mechanical dyssynchrony (4). We used Colour Tissue Doppler Imaging to assess intraventricular dyssynchrony in patients with IC and in patients with IDC.

The aim of the present study was to evaluate potential differences between patients with IC and IDC in global and regional parameters of dyssynchrony. We neutralized the confounding effect of severity of heart failure by comparing groups matched for New York Heart Association class and N-terminal prohormone Brain Natriuretic Peptide (NT-proBNP). To study the effect of QRS duration we included both small and broad QRS groups.

METHODS

Study population

From an ongoing registry for dyssynchrony we selected 4 groups of patients: Group 1: IC & QRS < 120 ms, Group 2: IDC & QRS < 120 ms, Group 3: IC & QRS ≥ 120 ms, Group 4: IDC & QRS ≥ 120 ms. Patients with IC had either evidence of previous (> 3 months) myocardial infarction or angiographic evidence of significant coronary artery disease with or without previous revascularization procedures. Groups 1 and 2, as well as groups 3 and 4 were matched for left ventricular ejection fraction and severity of heart failure. Patients in atrial fibrillation were excluded.

To assess the severity of heart failure, patients were classified by an experienced cardiologist according to the New York Heart Association. In addition blood samples were taken after overnight fasting and NT-proBNP levels were measured in 10 microL of serum with an automated electrochemiluminescence immunoassay using an Elecsys 2010 (Roche Diagnostics).

Echocardiography

The echocardiographic studies were performed with a commercially available ultrasonographic system, equipped with a 2.5 to 3.5 MHz transducer (VIVID 7, GE Vingmed Ultrasound). All subjects were examined in the left lateral recumbent position using standard parasternal short- and long-axis and apical views. Two-dimensional and M-mode echocardiograms were obtained according to the American

Society of Echocardiography guidelines. Global left ventricular function was assessed by measuring left ventricular end-diastolic and end-systolic volume and left ventricular ejection fraction using the modified biplane Simpson rule.

Colour Tissue Doppler Imaging was performed using the apical 4, 2 and 3 chamber views to assess longitudinal myocardial regional function. Gain settings, filters and pulse repetition frequency were adjusted to optimize colour saturation. Sector size and depth were optimized for the highest possible frame rate. Three consecutive beats were recorded from each view and the images were digitally stored for offline analysis (EchoPac 3.1.0, GE Vingmed Ultrasound). From the 3 apical views a 6-basal and 6-mid segmental model was obtained, namely the septal, lateral, inferior, anterior, anteroseptal and posterior segments at both basal and mid levels. In each segment the time from the beginning of the QRS complex to peak systolic motion (T_s) was measured. The individual segmental T_s values were corrected for heart rate by dividing them by the square root of the RR interval; these values represent *regional* dyssynchrony.

The following parameters of *global* dyssynchrony were calculated: The *dispersion* defined as the difference between the longest and shortest T_s of the basal septal, lateral, inferior and anterior segments and the *standard deviation of T_s intervals* measured at all 12 segments (SD_{12}) according to Yu et al (5) (6).

Statistical analysis

Categorical variables were compared with a Pearson Chi Square test and group comparisons of continuous variables were made with an Independent Samples T-test making use of statistical software (SPSS 11.5).

RESULTS

The clinical characteristics and global parameters of dyssynchrony of the 4 groups are shown in table 1. The larger number of IC patients is a reflection of daily clinical practice. As intended there were no significant differences between groups 1 and 2 or between groups 3 and 4 concerning functional classification or NT-proBNP levels. No major differences were observed regarding medical treatment (Table 1).

Variable	IC, QRS <120 ms (n = 35)	IDC, QRS <120 ms (n = 18)	IC, QRS ≥120 ms (n = 35)	IDC, QRS ≥120 ms (n = 17)
Age (yrs)	67 ± 9	62 ± 14	71 ± 9	62 ± 14 [†]
ACE inhibitors	22/35 (63%)	17/18 (94%)*	25/35 (71%)	11/17 (65%) [§]
ATII antagonists	3/35 (9%)	0/18 (0%)	8/35 (23%)	3/17 (18%)
β blockers	23/35 (66%)	8/18 (44%)	25/35 (71%)	7/17 (41%)
Digoxin	2/35 (12%)	8/18 (44%)*	7/35 (27%)	5/17 (29%)
Diuretics	16/35 (46%)	11/18 (61%)	30/35 (86%) [‡]	10/17 (59%)
Spironolactone	8/35 (23%)	6/18 (33%)	10/35 (29%)	5/17 (29%)
LVEF (%)	37 ± 12	39 ± 14	29 ± 7 [‡]	25 ± 10 [§]
NYHA class	1.9 ± 0.9	2.2 ± 0.6	2.5 ± 0.8 [‡]	2.4 ± 0.8
NT-pro-BNP (pg/ml)	561 ± 453	409 ± 374	2,987 ± 408 [‡]	2,452 ± 2,590 [§]
QRS (ms)	95 ± 13	95 ± 14	163 ± 28 [‡]	165 ± 32 [§]
Dispersion (ms)	56 ± 34	52 ± 26	76 ± 48	73 ± 43
SD 12 (ms)	30 ± 11	28 ± 10	39 ± 21	39 ± 17 [§]

*p <0.05 small QRS IDC versus small QRS IC; †p <0.05 broad QRS IDC versus broad QRS IC; ‡p <0.05 broad QRS IC versus small QRS IC; §p <0.05 broad QRS IDC versus small QRS IDC.

ACE = angiotensin-converting enzyme; ATII = angiotensin II receptor; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NT-pro-BNP = N-terminal pro-hormone brain natriuretic peptide; SD 12 = the SD of time to systolic peak motion intervals measured at 12 left ventricular segments.

The two parameters representing *global* intraventricular dyssynchrony (dispersion and SD12) were higher in the broad QRS groups compared to the small QRS groups (table 1). In the small QRS groups an SD 12 higher than 32.5 ms (upper limit of normality according to ref 7) was noted in 34 % of the IC and 39% of the IDC patients. In the broad QRS groups 49 % of the IC and 65% of the ICD patients exceeded this limit. No significant differences in *global* mechanical dyssynchrony could be observed between IDC and IC patient groups. *Regional* mechanical dyssynchrony parameters did not differ significantly between IC patients with a small QRS and IDC pts with a small QRS. The *regional* mechanical dyssynchrony within the broad QRS groups (groups 3 and 4) is graphically depicted in Figure 1.

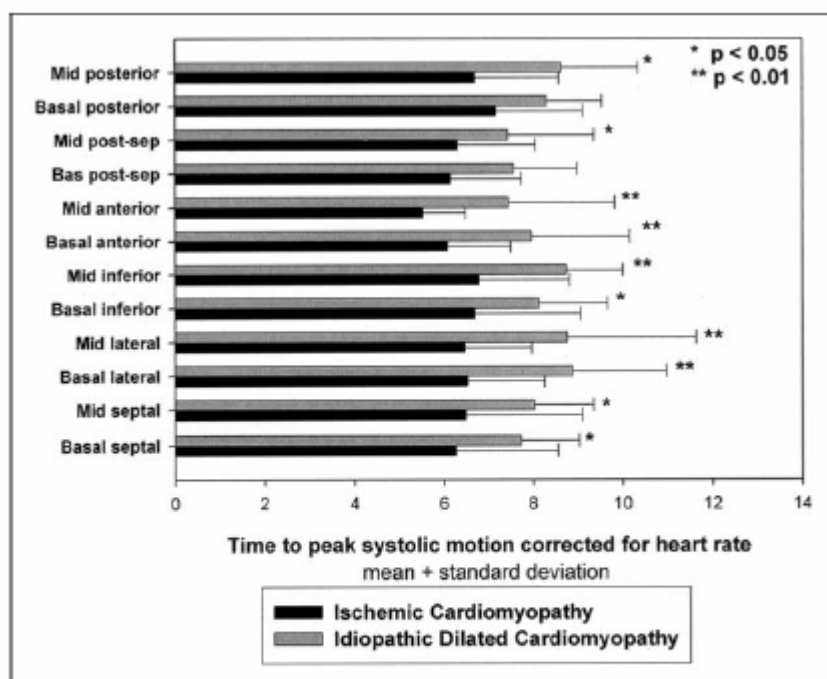


FIGURE 1. Regional dyssynchrony (as assessed by time to peak systolic motion corrected for heart rate) in 12 left ventricular segments: comparison between IDC (gray bars) and IC (black bars). post-sep = posteroseptal segment.

For nearly all individual left ventricular segments a significant or highly significant difference could be observed between the IC and IDC broad QRS patient groups. The time to peak systolic motion was consistently later among the IDC patients with broad QRS compared to IC patients with broad QRS. In figure 2 the area of latest activation is shown for the 17 patients with IDC and a broad QRS (panel A) and the 35 patients with IC and a broad QRS (panel B). The area of latest mechanical activation was predominantly located in the lateral segment for IDC patients whereas in IC patients it was more spread over all segments with the majority of latest activation situated in the inferior (26%) and lateral segment (37%).

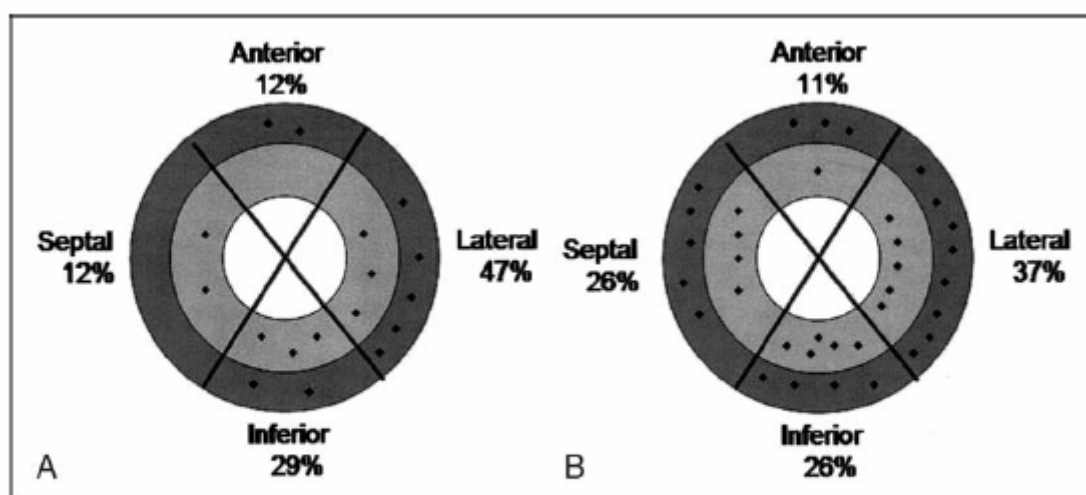


FIGURE 2. Area of latest mechanical activation (as assessed by time to peak systolic motion) in 17 patients with IDC and $QRS \geq 120$ ms (A) and in 35 patients with IC and $QRS \geq 120$ ms (B).

DISCUSSION

Our results confirm previous reports concerning global parameters of intraventricular dyssynchrony (8) : the amount of dyssynchrony tends to be more pronounced in patients with heart failure and a broad QRS (49% & 65%) then in patients with heart failure and a narrow QRS (34% & 39%) interval. Ghio et al reported prevalences of

30 % in a narrow QRS group, 57% in patients with QRS between 120-150 ms & 71% in patients with QRS \geq 150 ms. (9)

We were not able to demonstrate a difference between IC and IDC patients regarding global mechanical dyssynchrony, nor could we demonstrate a difference in regional dyssynchrony parameters between IC and IDC patients with a small QRS interval. We do, however, report for the first time a significant difference in regional mechanical dyssynchrony between IC and IDC patients with broad QRS intervals. The time to systolic peak motion was significantly longer in the IDC group and this for nearly all LV segments (Fig. 1).

Despite similar QRS width and heart failure severity patients may present with a different location of mechanical dyssynchrony, which seems to be related to the underlying etiology: the area of latest mechanical activation was mainly located in the lateral wall of the left ventricle for IDC patients. This is in accordance with previous publications based on other techniques to evaluate mechanical dyssynchrony. Sogaard et al used 3D echocardiography and tissue tracking to show in a small number of subjects that in patients with IDC the myocardium with delayed longitudinal contraction was tended to be located in the lateral and posterior walls of the left ventricle (10). In contrast they found that delayed longitudinal contraction was more frequent in the septum and in the inferior wall in patients with IC. Ansalone et al used Pulsed Wave Tissue Doppler Imaging to assess dyssynchrony in 31 patients with non-ischemic heart failure and left bundle branch block by measuring time between closure and re-opening of mitral valve (11). The most delayed site in their study was the lateral site (35%).

The localisation of the area of latest mechanical activation could have practical implications towards the success rate of biventricular pacing. Standard coronary sinus lead positioning in biventricular pacing has mainly an effect on the activation of the lateral wall and its precisely here that latest activation is predominantly located in IDC patients whereas in IC patients the area of latest activation is not necessarily the lateral wall. Sogaard proved that individual tailoring of the interventricular delay with preactivation of regions showing mechanical asynchrony produced a further significant reduction in the extent of delayed contraction (10). Mehra pointed out that the definition of a successful implant should not be narrowed to merely accepting device implantation, but must include demonstration and identification of the precise area of ventricular asynchrony, followed by positioning the coronary sinus catheter in the optimal location to tackle the mechanical dyssynchronous contractility (12). We believe that colour TDI assessment of mechanical dyssynchrony offers a non-invasive approach to resolve this problem.

CONCLUSION

In conclusion we have shown with colour TDI echocardiography that broad QRS patients with idiopathic dilated cardiomyopathy have a longer regional time to peak contraction compared to broad QRS patients with ischemic cardiomyopathy. Also their area of latest activation is more frequently located in the lateral wall. Regional dyssynchrony in small QRS patients and global calculated parameters of dyssynchrony are however not different between ischemic and non-ischemic cardiomyopathy patients.

ACKNOWLEDGMENTS

The following members of the Belgian Working Group on Echocardiography and Cardiac Doppler participated in the Belgian Multicenter Registry on Dyssynchrony:

L. Muyldermans (AZ Sint Jan Brugge), L. Gabriel (UCL Mont Godinne), T. De Backer (OLV Aalst), M. Vaerenberg (AZ Middelheim Antwerpen), P. Decoodt (CHU Brugmann Brussels), B. Paelinck (UZA Antwerpen) & E. Hoffer (CHR de la Citadelle Liege).

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CHAPTER 2.2

**Prevalence of mechanical dyssynchrony in patients with
heart failure and preserved left ventricular function.
(a report from the
Belgian Multicenter Registry on Dyssynchrony).**

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Am J Cardiol 2005; 96: 1543-1548

Oral presentation at the American College of Cardiology Scientific Sessions,
March 2005, Orlando (Florida)

ABSTRACT

Aim

The present study evaluates the prevalence of mechanical inter- and intraventricular dyssynchrony in heart failure patients with preserved left ventricular (LV) ejection fraction (EF).

Methods

We studied 138 heart failure patients (age 67 ± 11 years, 76% men); 60 patients had a preserved LVEF ($>40\%$). Using conventional Doppler echocardiography, interventricular mechanical delay (IVMD) ≥ 40 ms was defined as interventricular dyssynchrony. Using pulsed wave Tissue Doppler Imaging (TDI), time from beginning of QRS complex to onset of systolic motion was measured in 4 basal LV segments and a dispersion ≥ 60 ms, was defined as intraventricular dyssynchrony.

Results

Prevalence of inter- and intraventricular dyssynchrony was lower in patients with preserved as compared to patients with reduced LVEF (17% vs 41%, $p < 0.01$ for interventricular dyssynchrony, 18% vs 36%, $p < 0.01$ for intraventricular dyssynchrony). However, patients with preserved LVEF and QRS width ≥ 120 ms showed higher values for parameters for inter- and intraventricular dyssynchrony compared to patients with QRS width < 120 ms (IVMD 33 ± 20 ms vs 20 ± 16 ms, $p < 0.05$ and TDI dispersion 42 ± 26 ms vs 33 ± 22 ms, $p < 0.05$). In patients with QRS width ≥ 120 ms, prevalence of inter- and intraventricular dyssynchrony was comparable for

patients with preserved and reduced LVEF (42% vs 55%, p=ns for interventricular dyssynchrony and 45% vs 46%, p=ns for intraventricular dyssynchrony).

Conclusion

In conclusion, the prevalence of inter- and intraventricular dyssynchrony is low (17 and 18% respectively) in heart failure patients with preserved LVEF. However, in the presence of QRS width ≥ 120 ms, this prevalence raises to almost 50%, which is comparable to heart failure patients with reduced LVEF and QRS width ≥ 120 ms.

INTRODUCTION

Cardiac resynchronization therapy is increasingly used in heart failure patients with reduced left ventricular (LV) ejection fraction (EF) (1-4). However, as many as 30-40% of all heart failure patients have a (nearly) normal LVEF. Although mortality rates are lower, their hospitalisation rates are comparable to those of patients with reduced LVEF (5-7). No studies have assessed the potential effect of biventricular pacing in these patients. Data on mechanical dyssynchrony assessed by echocardiography including Tissue Doppler Imaging (TDI) in these patients are scarce (8). The aim of the present study was to evaluate the prevalence of inter- and intraventricular dyssynchrony in heart failure patients with preserved LVEF and compare the findings to heart failure patients with reduced LVEF. In this multicenter study we used previously validated and more widely available conventional echocardiographic (9-12) and Pulsed Wave TDI (13,14) techniques to assess mechanical dyssynchrony.

METHODS

Study population

During the 6 months study period, controls and patients were enrolled in 12 centers. Controls were in sinus rhythm without cardiovascular disease, systemic disease or diabetes mellitus, with normal physical examination, electrocardiogram and echocardiography. Individuals with hypertension (blood pressure \geq 140/90mmHg or antihypertensive treatment) were excluded. Patients had ischemic or nonischemic cardiomyopathy with a broad range of LVEF and QRS duration. They were in New

York Heart Association class II or more. Heart failure patients were divided into patients with preserved LVEF ($> 40\%$) and patients with reduced LVEF ($\leq 40\%$). Exclusion criteria were primary valvular heart disease or hypertrophic cardiomyopathy, atrial flutter or fibrillation and pacing.

Echocardiography

Studies were performed with the same ultrasonographic system (VIVID 7, GE Vingmed Ultrasound, Horten, Norway). A training session was organized to standardize image acquisition. In each center images were recorded by the same level III echocardiographer. Subjects were examined in the left lateral recumbent position using standard parasternal short- and long-axis and apical views. Two-dimensional and M-mode echocardiograms were obtained according to the American Society of Echocardiography guidelines. Global LV function was assessed by measuring LV end-diastolic and end-systolic volume and LVEF, using the modified biplane Simpson rule.

Pulsed wave Doppler recordings across aortic and pulmonary valve were obtained from the apical 5-chamber view and the parasternal short-axis view. Aortic and pulmonary preejection times were defined as time intervals between onset of the QRS complex and onset of aortic and pulmonary flow, respectively. Interventricular mechanical delay (IVMD) was defined as the difference between aortic and pulmonary preejection times (9,10). M-mode tracings were recorded from the parasternal short axis at the papillary level of the mitral valve. Septal to posterior wall motion delay (SPWMD) was calculated as the shortest interval between the maximal

posterior displacement of the septum and the maximal displacement of the left posterior wall as described by Pitzalis et al (11,12).

For the pulsed wave TDI recordings, velocities of long-axis wall motion were assessed in apical 4 and 2 chamber views during end-expiration, with a sample volume of 5 mm positioned at the basal septum, lateral, inferior and anterior segments. Three consecutive beats were recorded from each view and images were digitally stored for offline analysis (EchoPac PC version 3.1.0, GE Vingmed Ultrasound, Horten, Norway). Time from beginning of QRS to onset of systolic motion was measured in the 4 basal segments of the left ventricle and the dispersion was defined as the difference between the longest and shortest time interval in these 4 segments (13,14). Dyssynchrony analyses were performed centrally (Ghent University, Belgium) by 2 observers (JDS and NVDV). The average value from 3 consecutive beats was taken for each measurement. Inter- and intraobserver variabilities were calculated from 10 subjects.

Statistical analysis

SPSS 11.5.1 (SPSS Inc, Chicago, USA) was used for statistical analysis. Data are presented as mean \pm SD or total number (%). Also 75th and 95th percentile for the values in the normal subjects are given. Paired and unpaired t test, Fisher's exact test, and Pearson test were used when appropriate. Analysis of variance (ANOVA) with post hoc testing was performed for group comparisons. Intra and interobserver variability was determined by the coefficients of variance by comparing the SD of the

test differences as percentage of the average in both series. Statistical significance was defined at $p < 0.05$.

RESULTS

Characteristics of normal subjects and heart failure patients

A total of 192 subjects were prospectively enrolled: 54 controls and 138 heart failure patients. Controls (63% men) had an average age of 48 ± 16 years, a mean LVEF of $63 \pm 8\%$ and a mean QRS width of 89 ± 10 ms. Table 1 shows the clinical characteristics of the heart failure patients divided in 4 groups according to LVEF and QRS width.

Table 1
Clinical characteristics of patients according to left ventricular ejection fraction (LVEF) and QRS width

Variable	LVEF >40%, QRS <120 ms (n = 41)	LVEF >40%, QRS \geq 120 ms (n = 19)	LVEF \leq 40%, QRS <120 ms (n = 24)	LVEF <40%, QRS \geq 120 ms (n = 54)	Overall p Value (ANOVA)
Age (yrs)	65 ± 11	72 ± 9	64 ± 10	68 ± 11	NS
Men	76%	84%	79%	74%	NS
LVEF (%)	54 ± 9	50 ± 8	27 ± 7	26 ± 7	<0.001
LVEDV (ml)	114 ± 38	135 ± 58	177 ± 52	200 ± 86	<0.001
LVESV (ml)	55 ± 24	67 ± 34	133 ± 45	151 ± 75	<0.001
QRS (ms)	91 ± 14	157 ± 36	97 ± 12	165 ± 27	<0.001
NYHA III-IV	10%	37%	46%	46%	<0.01
NT-pro-BNP (pg/ml)	338 ± 278	934 ± 1016	757 ± 460	3148 ± 4065	<0.01
Ischemic heart disease	80%	83%	71%	67%	NS
Hypertension	49%	56%	46%	40%	NS
Diabetes mellitus	12%	17%	29%	25%	NS
Medication					
ACE/AT-2 inhibitors	66%	66%	87%	88%	NS
β Blockers	73%	72%	64%	63%	NS
Aldosterone antagonists	12%	39%	33%	29%	NS
Diuretics	32%	44%	66%	83%	<0.01
Digoxin	11%	9%	31%	29%	NS

ACE = angiotensin-converting enzyme; ANOVA = analysis of variance; AT-2 = angiotensin-2; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NT-pro-BNP = N-terminal pro-brain natriuretic peptide (available in 62 patients); NYHA = New York Heart Association.

Feasibility and reproducibility of conventional and Pulsed Wave TDI measurements

Aortic preejection time measurements were feasible in all subjects. Pulmonary preejection time could not be measured in only 2 normals (4%) and 2 patients (1%) because of poor visualization of the right ventricular outflow tract. SPWMD measurements were only possible in 39/54 normals (72%) and in 61/138 heart failure patients (44%). Pulsed wave TDI measurements were feasible in 97% of all segments in controls and in 93% of all segments in heart failure patients. Intraobserver variability was 3.5% for aortic preejection time, 4.7% for pulmonary preejection time, 18.7% for SPMWD and 3.8% for the intraventricular dispersion. Interobserver variability was 7.2% for aortic preejection time, 6.5% for pulmonary preejection time, 37.7% for SPWMD and 9.3% for the intraventricular dispersion measured by pulsed wave TDI.

Measurements of inter- and intraventricular mechanical dyssynchrony

Normal values are shown in table 2. For the conventional as well as the pulsed wave TDI parameters no significant correlations were found with age, LVEF or QRS width.

Table 2
Normal values for conventional echocardiographic and pulse-wave tissue Doppler imaging (TDI) parameters

Parameter	Mean ± SD	75th Percentile	95th Percentile
Conventional echocardiographic			
Aortic preejection time (ms)	84 ± 21	97	121
Pulmonary preejection time (ms)	87 ± 18	100	122
IVMD (ms)	15 ± 11	23	38
Septal to posterior wall motion delay (ms)	88 ± 27	107	137
Pulse wave TDI			
Dispersion 4 basal segments (ms)	25 ± 15	60	63

Results for heart failure patients according to LVEF and QRS width are shown in table 3.

Table 3
Echocardiographic parameters of dyssynchrony according to left ventricular ejection fraction (LVEF) and QRS width

Parameter	LVEF >40%, QRS <120 ms (n = 41)	LVEF >40%, QRS ≥120 ms (n = 19)	LVEF ≤40%, QRS <120 ms (n = 24)	LVEF ≤40%, QRS ≥120 ms (n = 54)	Overall p Value (ANOVA)
Aortic preejection time (ms)	109 ± 36	128 ± 36*	117 ± 25	148 ± 33 [†]	<0.01
Pulmonary preejection time (ms)	105 ± 38	113 ± 31	107 ± 21	113 ± 26	NS
IVMD (ms)	20 ± 16	33 ± 30*	18 ± 14	44 ± 27 [†]	<0.01
SPWMD (ms)	115 ± 42	144 ± 96	120 ± 60	178 ± 131	NS
Pulse-wave TDI dispersion (ms)	33 ± 22	42 ± 26*	29 ± 23	57 ± 29 [†]	<0.01

* p <0.05 compared with patients with preserved function and small QRS.
[†] p <0.05 compared with patients with impaired function and small QRS.
 Abbreviations as in Table 1.

Echocardiographic dyssynchrony parameters were not related to age. There were significant positive correlations with QRS width (r=0.48, p<0.01 for aortic preejection time, r=0.50, p<0.01 for IVMD, r=0.36, p<0.01 for SPWMD and r=0.48, p<0.01 for pulsed wave TDI dispersion). Also, significant negative correlations were noted with LVEF (r=-0.38, p<0.01 for aortic preejection time, r=-0.30, p<0.01 for IVMD, r=-0.22, p=0.09 for SPWMD and r=-0.30 (p<0.01) for pulsed wave TDI dispersion). Heart failure patients with a QRS width ≥ 120 ms had a longer aortic preejection time, IVMD and pulsed wave TDI dispersion as compared to patients with QRS width < 120 ms. This difference was present both in patients with preserved and reduced LVEF.

Similar trends were found for SPWMD although differences were not statistically significant.

Prevalence of inter and intraventricular dyssynchrony

The prevalence of interventricular mechanical dyssynchrony (defined as IVMD \geq 40 ms) was significantly lower in patients with preserved LVEF (10/60 patients, 17%) as compared to patients with reduced LVEF (32/78 patients, 41%, $p < 0.01$). Also the prevalence of intraventricular dyssynchrony (defined as a dispersion \geq 60 ms assessed by pulsed wave TDI) was significantly lower in patients with preserved LVEF (11/60 patients, 18%) as compared to patients with reduced LVEF (28/78 patients, 36%, $p < 0.01$). However, in the presence of a QRS width \geq 120ms, the prevalence of inter- and intraventricular dyssynchrony was higher and even comparable to heart failure patients with reduced LVEF and a QRS width \geq 120ms (42% vs 55%, $p = ns$ for interventricular dyssynchrony and 45% vs 46%, $p = ns$ for intraventricular dyssynchrony).

Figure 1 shows the prevalence of interventricular mechanical dyssynchrony, assessed by conventional Doppler measurements, according to LVEF and QRS width.

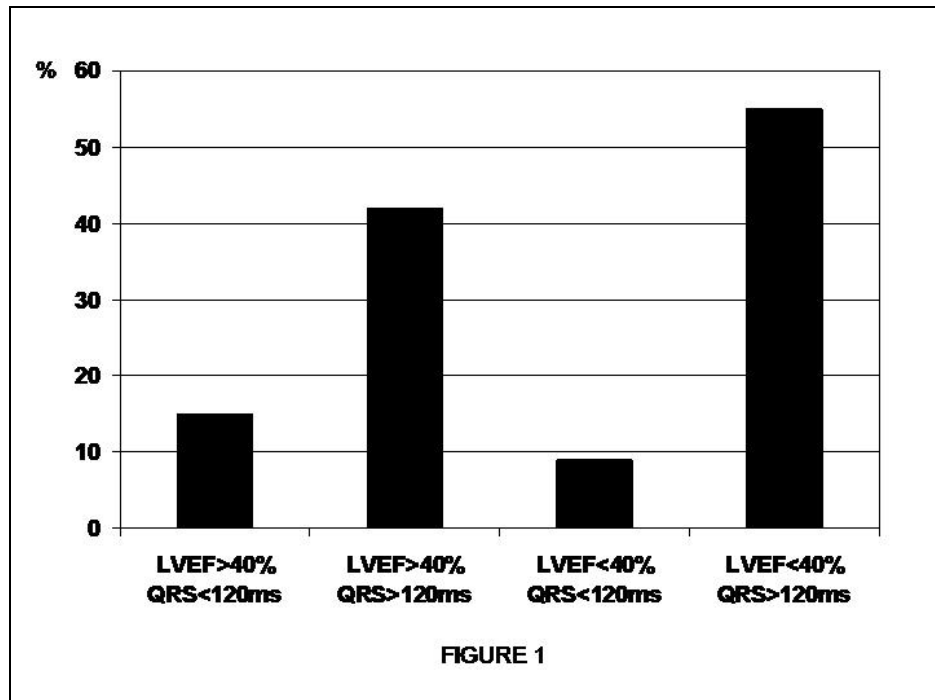
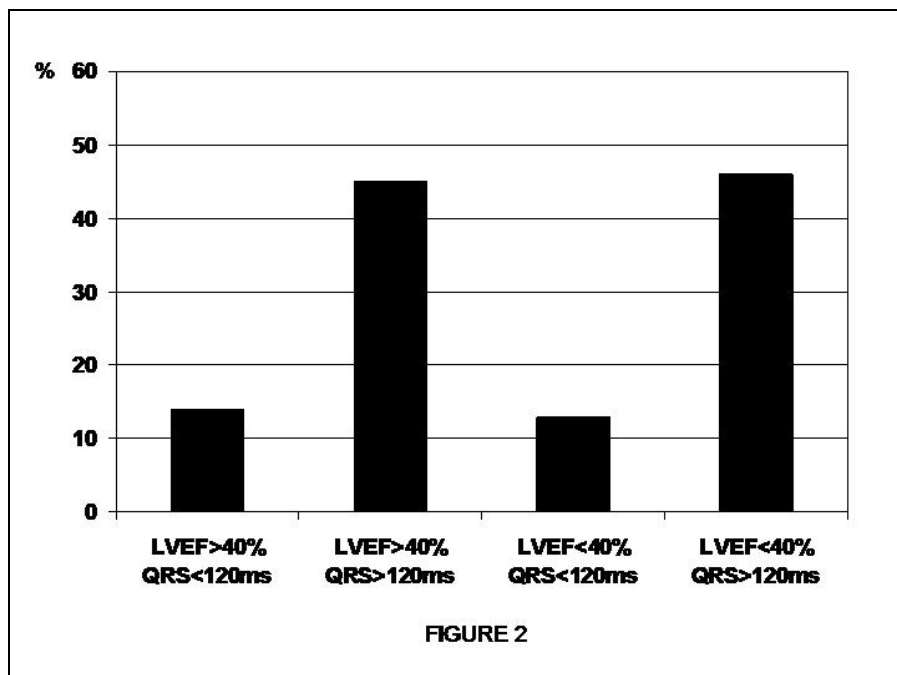


Figure 2 shows the prevalence of intraventricular dyssynchrony, assessed by Pulsed Wave TDI, according to LVEF and QRS width.



DISCUSSION

The main findings of our study are the following: 1) the overall prevalence of inter- and intraventricular dyssynchrony is low in heart failure patients with preserved LVEF (17% for interventricular dyssynchrony and 18% for intraventricular dyssynchrony) but 2) in the presence of a QRS width ≥ 120 ms, this prevalence raises to almost 50%, which is comparable to heart failure patients with reduced LVEF and QRS width ≥ 120 ms.

As many as 30-40% of all patients with heart failure symptoms have a normal or slightly reduced LVEF. Also, in our study, the prevalence of heart failure with preserved LVEF was high (43%). Although the mortality rate of these patients is lower, their hospitalization rate for heart failure is comparable to that of heart failure patients with reduced LVEF (5-7). To the best of our knowledge no larger studies are published on the prevalence of inter- and intramechanical dyssynchrony in these patients.

The prevalence of interventricular dyssynchrony was 17% in heart failure patients with preserved LVEF and this prevalence increased to 42% in patients with preserved LVEF and QRS duration ≥ 120 ms. This was similar to the prevalence of 55% in patients with reduced LVEF and increased QRS width. Other studies reported similar interventricular dyssynchrony prevalence in patients with reduced LVEF. Bader et al (13), using a cutoff of 38 ms, reported a prevalence of 12% in small QRS and 34% in broad QRS patients. Ghio et al (15), using a cutoff of 40 ms, found a prevalence of 12.5% in small QRS patients, 52% in patients with QRS between 120-

150 ms and 72% in patients with a QRS width > 150 ms. In view of these similar results in patients with reduced LVEF, we believe that our findings in patients with preserved LVEF are valid and that interventricular dyssynchrony is mainly present in heart failure patients with preserved LVEF in the presence of an increased QRS width. It remains however to be proven, even in patients with an accepted indication for cardiac resynchronization, whether it is necessary to achieve interventricular synchronization or whether it is sufficient to correct LV intraventricular dyssynchrony (16,17).

Using pulsed wave TDI, we report a prevalence of intraventricular dyssynchrony of 18% in heart failure patients with preserved LVEF and this prevalence increased to 45% in patients with preserved LVEF and QRS duration ≥ 120 ms. This was again similar to the prevalence of 46% in patients with reduced LVEF and increased QRS width. Salo et al (8) reported on the prevalence of mechanical dyssynchrony in 8 patients with LVEF $\geq 50\%$ and NYHA class II-III heart failure. They found arguments for dyssynchrony in 6 of the 8 patients (75%). In the present study we found a clearly lower prevalence of intraventricular dyssynchrony which could be related to the larger sample size and different methodology. Already in 2002, Ansalone et al (18) showed the potential of pulsed wave TDI for selecting patients for biventricular pacing. More recently, measurements of electromechanical delays using pulsed wave TDI in 4 basal segments with calculation of the dispersion has been proposed as a marker of intraventricular dyssynchrony. Penicka et al (14) showed that this parameter was the best predictive parameter of reverse remodeling in 49 heart failure patients with wide QRS treated with biventricular pacing. Our 95th percentile in normals of 63 ms using pulsed wave TDI is very close to the suggested cut-off of

60 ms for therapy prediction (14). Using a cutoff of 60 ms, our prevalence of intraventricular dyssynchrony in heart failure with reduced LVEF and increased QRS was 46% which is similar to the prevalence of 57% in the study by Penicka et al (14). Bader et al (21) reported a higher prevalence of 84% but these authors used a lower cutoff of 40 ms in a population of heart failure patients without myocardial infarction. Using colour TDI, different authors reported prevalences of intraventricular dyssynchrony in heart failure patients with reduced LVEF and increased QRS similar to our findings: 57% by Yu et al (19), 61% by Bax et al (20) and 57% in patients with a QRS width between 120-150 ms by Ghio et al (15).

Finally, Pitzalis et al (11) proposed a simple M-mode parameter, the SPWMD as a marker for intraventricular asynchrony. A prolonged SPWMD (> 130 ms) was a predictor for clinical benefit and remodeling with biventricular pacing (11,12). Our 95th upper limit of normality of 137ms is close to the suggested cutoff of 130ms, but we were unable to measure SPWMD correctly in 28% of the normals and in 56% of the heart failure patients. Inter- and intraobserver variability was poorer as compared to the other echocardiographic parameters. Although both patients with preserved and reduced LVEF and a QRS ≥ 120 ms showed higher mean values of SPWMD as compared to the other groups, differences did not reach statistical significance due to the larger standard deviations.

STUDY LIMITATIONS

Our study has some limitations. First, no evaluation of tissue tracking, strain or strain rate parameters was performed. It has been suggested that timing of myocardial

motion could underestimate the degree of asynchrony, in particular in the presence of ischemic heart disease. Noninvasive identification of specific abnormal but reversible strain and strain rate patterns could help to further improve patient selection for biventricular pacing compared to velocity imaging (22, 23). However strain and strain rate analysis are not yet widely available and technical improvements are required to make data analysis easy applicable for routine clinical use. Secondly, as in most studies on dyssynchrony and cardiac resynchronization therapy, we did not evaluate patients in atrial fibrillation. Further studies are needed in this specific group of heart failure patients. Finally, although heart failure patients with preserved LV function were selected with great care it is theoretically possible that a small percentage of these patients could in fact be heart failure patients with an impaired LVEF that improved under therapy.

ACKNOWLEDGEMENTS

The following members of the Belgian Working Group on Echocardiography and Cardiac Doppler participated in the Belgian Multicenter Registry on Dyssynchrony: Patrizio Lancellotti (CHU Sart Tilman, Liège, Belgium), Philippe Unger (Hôpital Erasme, Brussels, Belgium), Pieter Vandervoort (ZOL, Genk, Belgium), Bernard Cosyns (CHIREC, Braine l'Alleud, Belgium), Veerle Decuypere (AZ Sint Jan, Brugge, Belgium). The authors want to thank Liliane Matthys, RN for her cooperation in the acquisition of the data. J. De Sutter is a Senior Clinical Investigator and N. Van de Veire a Research Assistant of the Fund for Scientific Research – Flanders (Belgium) (F.W.O. - Vlaanderen).

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Relationship between QRS duration, left ventricular volumes and prevalence of nonviability in patients with coronary artery disease and severe left ventricular dysfunction.

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Eur J Heart Fail 2006; 8 : 275-277

ABSTRACT

Background

Patients with coronary artery disease (CAD), a QRS duration ≥ 120 ms and left ventricular ejection fraction (LVEF) $\leq 30\%$ are potential candidates for cardiac resynchronization therapy (CRT). Our aim was to investigate the relationship between QRS duration, left ventricular volumes and prevalence of nonviable tissue in this patient population.

Methods

We studied 132 patients (118 men, age 68 ± 5 years) with CAD and LVEF $\leq 30\%$ (mean LVEF $24 \pm 6\%$). LV volumes and myocardial viability were determined by gated myocardial perfusion imaging.

Results

A QRS duration ≥ 120 ms was present in 91 patients (69%). Although there were no differences in LVEF, patients with longer QRS durations had significant larger end-diastolic and end-systolic volumes ($p < 0.01$). Substantial non-viable tissue in the inferior or lateral wall was present in 29% of patients with a QRS duration ≥ 120 ms versus 7% of those with a QRS duration < 120 ms ($p < 0.01$).

Conclusions

An increased QRS duration is associated with more advanced remodeling in patients with CAD and poor LV function. Almost one third of these patients with a prolonged QRS duration have no viable tissue in the inferolateral wall, an area that is usually stimulated with CRT.

BACKGROUND

Cardiac resynchronization therapy (CRT) is considered as a potential therapeutic option in patients with heart failure, reduced left ventricular ejection fraction (LVEF) and an increased QRS duration. Although functional improvements and effects on morbidity and mortality have been reported, up to 30 % of CRT patients do not respond to this therapy and this percentage could be even higher in patients with underlying coronary artery disease (CAD) (1-3). One of the reasons could be the presence of non-viable tissue in the inferolateral wall which is usually paced when the LV lead is placed transvenously via the coronary sinus.

AIMS

Our study aims were to assess the relationship between QRS duration on the surface ECG, left ventricular volumes and the prevalence of nonviable tissue-in patients with CAD and poor LV function.

METHODS

Study population

We studied 132 consecutive patients with CAD and a resting LVEF \leq 30 %. The diagnosis of CAD was based on a history of myocardial infarction, coronary revascularisation or angiographic significant CAD (at least one vessel with \geq 75 % stenosis). All patients were studied more than 3 months after myocardial infarction or

revascularisation and patients with ventricular pacing on the resting ECG were excluded. QRS duration was measured on a 12-lead surface ECG, at a speed of 25 mm/s, from the resting ECG.

Gated SPECT

All patients underwent a resting gated myocardial perfusion SPECT study using technetium-99m tetrofosmin as described previously (4). Quantified Gated SPECT software (QGS[®], Cedars-Sinai, Los Angeles, CA, USA) was used to obtain resting LV ejection fraction and volumes. For viability scoring, the myocardium was divided in 5 regions, anterior wall, lateral wall, inferior wall, septal wall and apex. The anterior, lateral, inferior and septal wall were subdivided in 3 regions (apical, mid and basal region), the apex was subdivided in 2 regions (5). A myocardial wall was considered to contain substantial non-viable tissue if none of the segments had a mean myocardial uptake higher than 55% of the maximum uptake in the myocardium on the resting perfusion images (6).

Statistical Analysis

Statistical analyses were performed using SPSS 11.0.1 statistical software (SPSS Inc., Chicago, USA). Spearman rank correlations, Mann-Whitney U and Kruskal-Wallis testing were used to investigate relations between QRS duration and LV volumes and prevalences of nonviable myocardium according to QRS duration.

Ethics

The study was approved by the local Ethics Committee of the Ghent University Hospital.

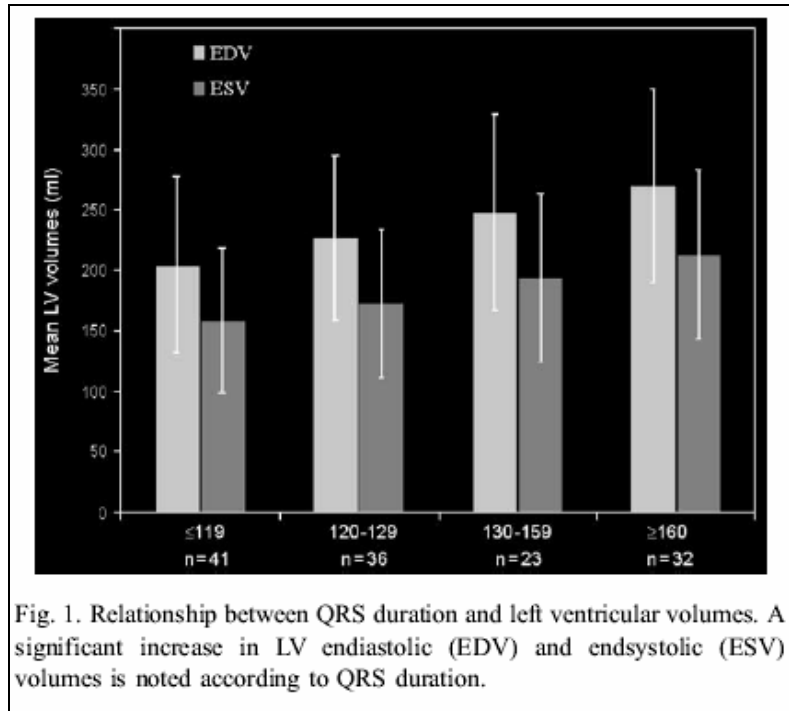
RESULTS

Mean age of the 132 patients was 68 ± 5 years and mean LVEF was 24 ± 6 %. Previous myocardial infarction was present in 86 (65%) and previous coronary revascularisation in 63 (48%) patients.

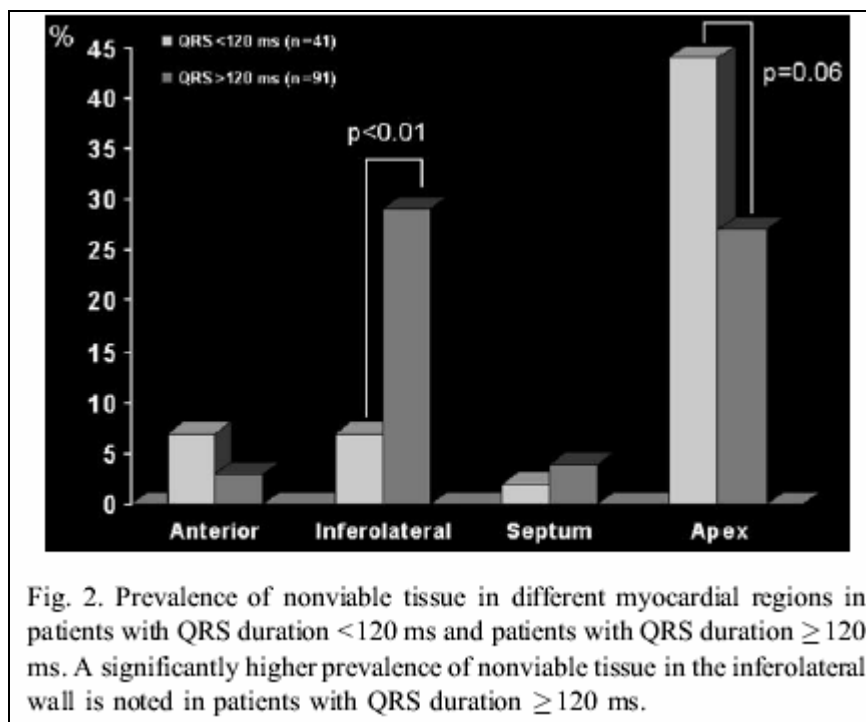
According to the SPECT findings, the anterior wall was infarcted in 21 (16 %), the septal wall in 19 (14 %) and the inferolateral in 73 (55 %) patients.

Patients were treated with ACE-inhibitors or AT-2 receptor blockers (n=98, 74%), beta-blockers (n=59, 45%) and diuretics (n=48, 36%).

Mean QRS duration was 131 ± 32 ms and a QRS duration ≥ 120 ms was present in 91 patients (69%). For the whole group QRS duration correlated significantly with LV enddiastolic volumes ($r=0.31$, $p<0.001$) and LV endsystolic volumes ($r=0.30$, $p<0.001$). As compared to patients with small QRS, patients with QRS duration > 120 ms had significantly higher LV enddiastolic volumes (248 ± 77 vs 205 ± 73 ml, $p<0.01$) and LV endsystolic volumes (193 ± 68 vs 159 ± 60 ml, $p<0.01$). Figure 1 shows the mean LV enddiastolic and endsystolic volumes according to four classes of QRS duration. No significant relation was found between LVEF and QRS duration.



The inferior or lateral wall was nonviable in 26 patients with a QRS duration ≥ 120 ms (29%). This frequency was significantly higher than in patients with QRS duration < 120 ms (29% vs 7%, $p < 0.01$). Prevalences of nonviable tissue in different regions for patients with QRS < 120 ms and QRS ≥ 120 ms are shown in figure 2.



CONCLUSION

Our results indicate that a prolonged QRS duration (≥ 120 ms) is frequent in patients with CAD and LVEF $\leq 30\%$ with a prevalence of almost 70%. Similar to previous studies in patients with idiopathic dilated cardiomyopathy (7-9), this increase in QRS duration is clearly related to an increase in LV enddiastolic and endsystolic volumes, indicating more advanced remodeling in these patients. More importantly, absence of viable tissue in the inferolateral wall in CAD patients with poor LV function is frequent, with a prevalence of 29% when QRS duration is increased as compared to only 7% when QRS duration is < 120 ms. This implicates that almost 30% of potential candidates for CRT with CAD have non-viable tissue in the inferolateral wall. Since non-viable tissue is electromechanically non-functional (10) placement of the lead in the inferolateral region could lead to ineffective pacing in these patients (11). This could therefore be one of the explanations why CRT is ineffective in a substantial number of patients with CAD. Further studies are however needed to determine whether viability assessment can help in the selection of candidates for CRT and in the determination of optimal lead localization.

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CHAPTER 2.4

Noninvasive visualisation of the cardiac venous system in coronary artery disease patients using 64-slice Computed Tomography

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J Am Coll Cardiol 2006; in press

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Oral presentation at the World Congress of Cardiology,

September 2006, Barcelona

ABSTRACT

Objectives

To evaluate the value of 64-slice computed tomography (CT) to visualise the cardiac veins and evaluate the relation between variations in venous anatomy and history of infarction.

Background

Cardiac resynchronization therapy (CRT) is an attractive treatment for selected heart failure patients. Knowledge on venous anatomy may help identifying candidates for successful left ventricular lead implantation.

Methods

The 64-slice CT of 100 individuals (age 61 ± 11 years, 68% men) was studied. Subjects were divided in 3 groups: 28 controls, 38 patients with significant coronary artery disease (CAD), 34 patients with a history of infarction. Presence of the following coronary sinus (CS) tributaries was evaluated: posterior interventricular vein (PIV), posterior vein of the left ventricle (PVLV) and left marginal vein (LMV). Vessel diameters were also measured.

Results

CS and PIV were identified in all individuals. PVLV was observed in 96% of controls, 84% of CAD and 82% of infarction patients. In patients with a history of infarction, a LMV was significantly less observed as compared to controls and CAD patients (27% versus 71% and 61% respectively, $p < 0.001$). None of the patients with lateral

infarction and only 22% of patients with anterior infarction had a LMV. Regarding quantitative data no significant differences were observed between the groups.

Conclusion

Non-invasive evaluation of cardiac veins with 64-slice CT is feasible. There is considerable variation in venous anatomy. Patients with a history of infarction were less likely to have a LMV which may hamper optimal left ventricular lead positioning in CRT implantation.

INTRODUCTION

Cardiac resynchronization therapy (CRT) has become an attractive treatment option for highly symptomatic heart failure patients with a broad QRS complex on the surface ECG and poor left ventricular (LV) systolic function. (1-3) In selected patients CRT reduces symptoms and improves exercise capacity. The CARE-HF trial also reported a significant reduction of morbidity and mortality, compared to optimized medical treatment. (4) However, in large randomized trials, up to 30% of the patients undergoing CRT do not respond favourably to this invasive treatment. (5) In order to improve the success rate, several issues including echocardiographic evaluation of mechanical dyssynchrony and the evaluation of viability in the target region for the LV pacing lead, should be addressed during the selection of potential candidates. (6) Another important pre-implantation issue is knowledge on the cardiac venous anatomy of the candidate. Even if viable tissue is identified in the region with the latest mechanical activation, endocardial CRT implantation will only be successful if the LV lead can be positioned in a vein draining this region. Ideally, venous anatomy should be assessed before implantation, non-invasively in the outpatient clinic, to determine whether a transvenous approach is feasible. The feasibility of multi-slice computed tomography (MSCT) to visualize the venous anatomy was recently demonstrated in a study with 16-detector row CT. (7) The authors described a marked variability in venous anatomy, confirming previous invasive studies. (8) The absence of coronary sinus tributaries may be related to scar formation secondary to previous myocardial infarction in the region drained by these specific veins. In the present study, the cardiac venous anatomy of 100 subjects undergoing non-invasive coronary angiography with 64-slice MSCT was retrospectively evaluated. The study

aims were 1) to evaluate the feasibility of 64-slice MSCT to depict the cardiac venous system and 2) to evaluate the relationship between variations in cardiac venous anatomy and previous myocardial infarction.

METHODS

Study population

The anatomy of the cardiac venous system was retrospectively studied in 100 consecutive subjects (68 men, age 61 ± 11 years) in whom MSCT was performed for non-invasive evaluation of the coronary arteries. The population was divided in three groups. Twenty-eight subjects had normal coronary arteries (controls). Thirty-eight patients had significant coronary artery disease (CAD) without a history of previous infarction. Thirty-four patients had CAD and a history of myocardial infarction; mean time between occurrence of the myocardial infarction and CT acquisition was 49 ± 7 months.

Multi-slice computed tomography

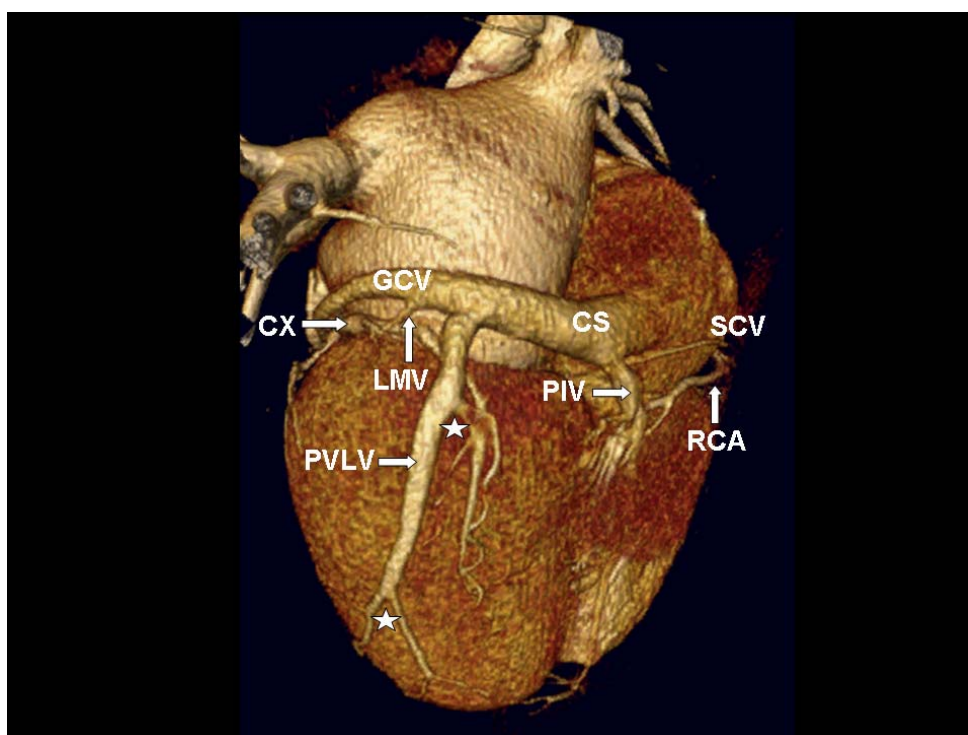
Imaging was performed with a 64-detector row Toshiba Multislice Aquilion 64 system (Toshiba Medical Systems, Otawara, Japan). Between 80 and 110 ml of contrast material (Iomeron 400, Bracco Altana Pharma GmbH, Konstanz, Germany) at an injection rate of 5 ml/minute was used. Scanning was performed using simultaneous acquisition of 64 sections with a collimated slice thickness of 0.5 mm. Rotation time ranged from 400 to 500 ms depending on heart-rate and tube voltage was 120 kV at 300 mA. A segmental reconstruction algorithm allowed inclusion of patients with a range of heart rates without the need for pre-oxygenation or beta-blocking agents.

Retrospective ECG gating was performed to eliminate cardiac motion artefacts. Data reconstruction was performed on a Vitrea post-processing workstation (Vital Images, Plymouth, Minnesota).

Anatomic observations

The tributaries of the cardiac venous system (Figure 1) were identified on volume-rendered reconstructions. Thereafter, the course of the veins was evaluated in three orthogonal planes using multiplanar reformatting. The presence of the following cardiac veins was evaluated: CS, Anterior Interventricular Vein, Posterior Interventricular Vein (PIV), Posterior Vein of the Left Ventricle (PVLV) and Left Marginal Vein (LMV). The number of side branches of these tributaries was also evaluated.

Figure 1. Volume-rendered reconstruction of the heart, posterolateral view. The first tributary of the Coronary Sinus (CS) is the Posterior Interventricular Vein (PIV), running in the posterior interventricular groove. The second tributary of the CS is the Posterior Vein of the Left Ventricle (PVLV) with several side branches (asterix). The next tributary is the Left Marginal Vein (LMV). The Great Cardiac Vein (GCV) will then continue as Anterior Cardiac Vein in the anterior interventricular groove. Also note the Circumflex Coronary Artery (CX) and Right Coronary Artery (RCA)



Quantitative data

The ostium of the CS was defined as the site where the CS makes an angle with the right atrium in the crux cordis area. Multiplanar reformatting was used to determine the size of the ostium in two directions (Figure 2). The diameters of the proximal parts of the PIV, PVLV and LMV were measured. The proximal diameter of the Great Cardiac Vein (GCV) and the distal diameter of the GCV before continuing its course in the anterior interventricular groove as Anterior Cardiac Vein were also evaluated. Finally, the distance between the origins of the various venous tributaries was measured on volume-rendered reconstructions (Figure 3).

Figure 2. Measurement of the diameter of the Coronary Sinus in the antero-posterior direction, transverse plane (Panel A) and in the supero-inferior direction, coronal plane (Panel B). RA: right atrium, LA: left atrium, RV: right ventricle.

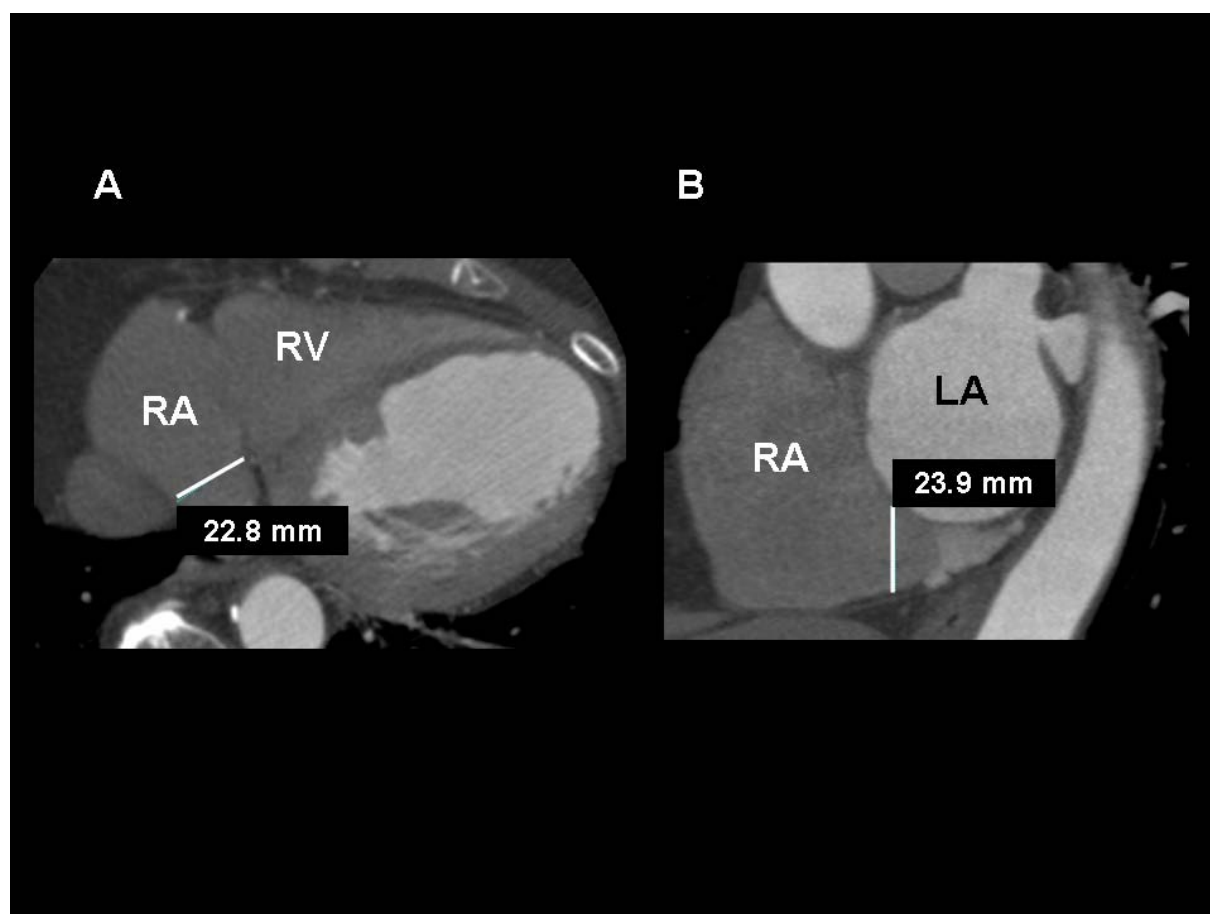
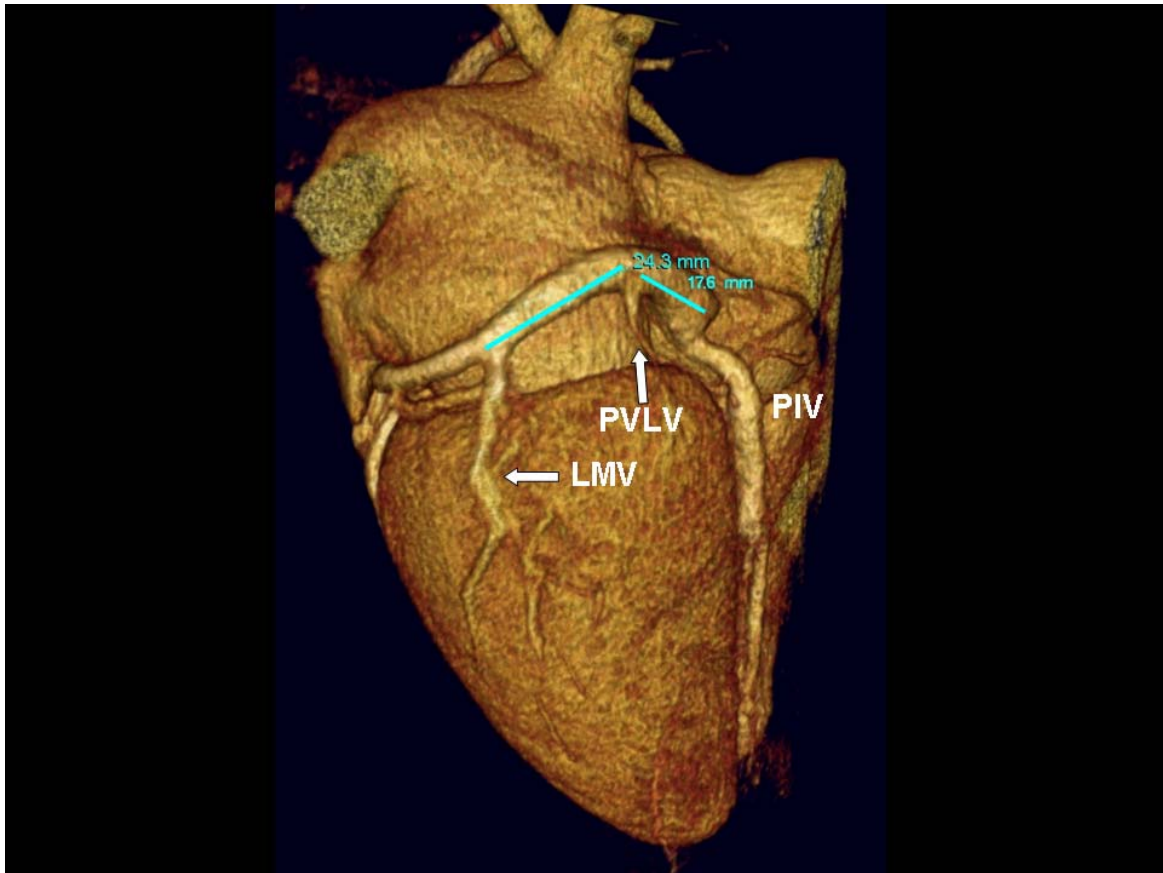


Figure 3. Example of measurement of the distance between the origins of the tributaries of the Coronary Sinus. (PIV: Posterior Interventricular Vein, PVLV: Posterior Vein of the Left Ventricle, LMV: Left Marginal Vein).



Statistical analysis

A statistical software program SPSS 12.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Continuous variables are presented as mean \pm standard deviation. Categorical variables are presented as absolute number (percentage). Analysis of variance (ANOVA) was used to study differences between the groups regarding continuous variables; Chi-square testing was used to study differences regarding categorical data. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In Table 1, baseline characteristics of the individuals are summarized. Compared to controls, patients with significant CAD or a history of infarction were older and were more frequently male. They also had a higher frequency of cardiac risk factors including hypercholesterolemia, smoking and diabetes mellitus.

Table 1. Baseline characteristics of the study population

	Controls n = 28	CAD n = 38	Infarction n = 34	p-value
Age (yrs)	56 ± 11	64 ± 10	62 ± 11	0.02
Male gender	14 (50%)	26 (68%)	28 (82%)	0.03
LV ejection fraction	64 ± 9 %	58 ± 14 %	50 ± 13 %	0.0001
Cardiac risk factors				
Hypertension	10 (40%)	17 (50%)	11(37%)	NS
Hypercholesterolemia	11 (44%)	24 (71%)	22 (73%)	0.047
Smoking	4 (16%)	10 (29%)	14 (47%)	0.048
Diabetes mellitus	9 (35%)	14 (40%)	3 (10%)	0.02
Familial history CAD	7 (28%)	7 (21%)	12 (39%)	NS

CAD: coronary artery disease; LV: left ventricular.

Left ventricular ejection fraction was significantly lower in patients with a history of infarction. Regarding the coronary artery lesions: none of the controls had significant coronary stenosis (by definition). In the CAD group, 10 patients had lesions occluding ± 50% of the coronary lumen, 25 patients had lesions occluding ≥75% of the lumen. A significant stenosis was present in the left anterior descending coronary artery in 78%, in the left circumflex coronary artery in 38% and in the right coronary artery in

30%. For patients with a history of infarction, these percentages were 88%, 46% and 42% respectively. Regarding the location of the infarction, 23 patients (68%) had a previous anterior infarction, 4 (12%) a lateral infarction and 7 (21%) an inferior infarction. Twelve of the 34 infarction (35%) patients had a non-Q wave infarction, 22 (65%) had a Q wave infarction.

Anatomic observations

No patients had to be excluded because of suboptimal study quality. The CS, Anterior Interventricular Vein and PIV were observed in nearly all patients (100%, 100% and 99% respectively). The PVLV was observed in 96% of the controls, in 84% of the CAD patients and in 82% of the patients with previous infarction ($p=NS$). LMV was significantly less often identified in patients with a previous infarction as compared to CAD patients and controls (27% vs 61% vs 71%, $p<0.001$, Figure 4). An example of a patient with a previous infarction and absence of the LMV is presented in Figure 5. None of the patients with a history of a lateral infarction had a LMV, only 22% of the patients with a history of an anterior infarction had a LMV whereas 43% of the patients with a previous inferior infarction had a LMV.

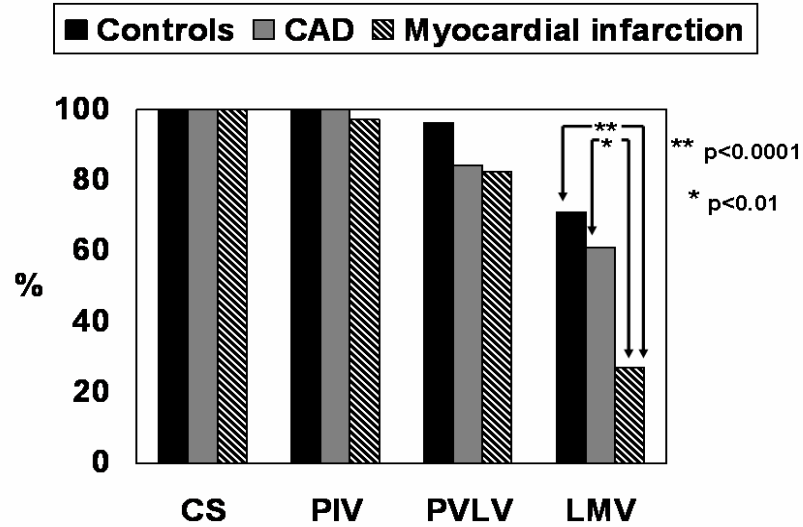


Figure 4. Presence of the Coronary Sinus (CS) and its main tributaries: Posterior Interventricular Vein (PIV), Posterior Vein of the Left Ventricle (PVLV) and Left Marginal Vein (LMV) in the three subsets (controls, patients with coronary artery disease (CAD) and patients with CAD and history of myocardial infarction).

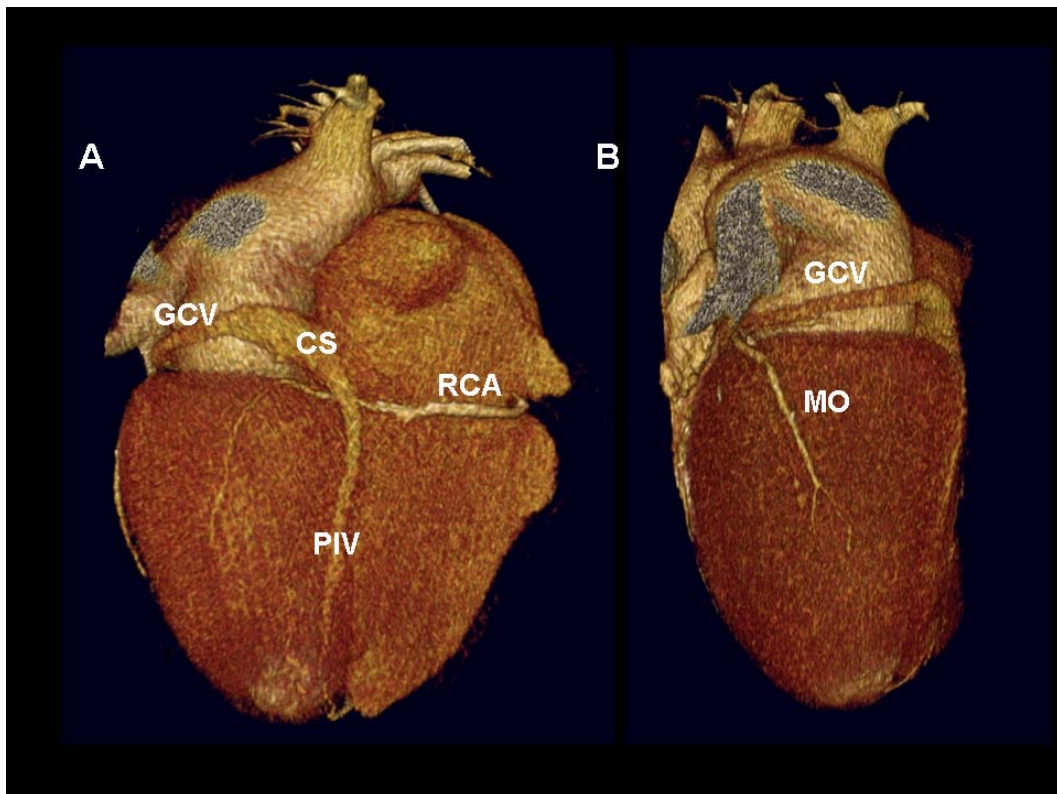
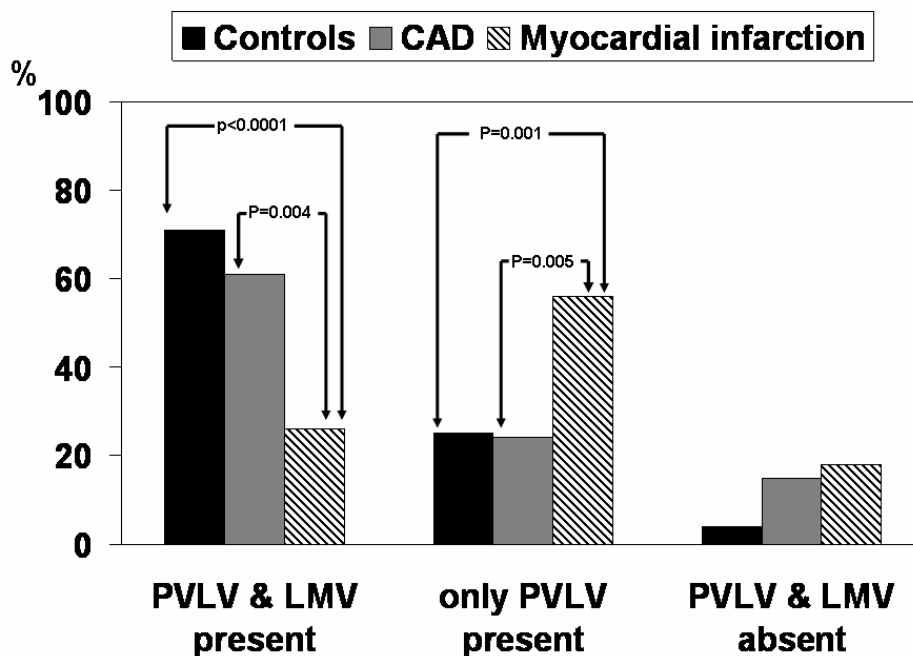


Figure 5. Example of absence of the Posterior and Left Marginal Vein in a patient with a history of an anterolateral infarction. Panel A: posterior view, Panel B: left lateral view. The only tributary of the Coronary Sinus (CS) and Great Cardiac Vein (GCV) is the Posterior Interventricular Vein (PIV). Also note the Obtuse Marginal (MO) branch of the Circumflex Coronary Artery and the Right Coronary Artery (RCA).

In the 12 non-Q wave infarction patients the PVLV was present in 11 patients (92%) and the LMV was present in 5 patients (42%). In the 24 Q-wave infarction patients the PVLV was only present in 17 patients (77%) and the LMV in 4 (18%) patients. In patients with a previous infarction, the presence of both a PVLV and LMV was significantly less often observed as compared to CAD patients and normals (26% vs 61% vs 71%, $p < 0.01$, Figure 6). Patients with a PIV exhibited one side branch in 7%, two side branches in 28% and three side branches in 2% of patients; 63% of these patients had no side branches. In the patients in whom a PVLV was identified, one side branch was observed in 2%, 2 side branches in 16% and 3 side branches in 1% of patients; 81% had no side branches. In patients with a LMV, one side branch was present in 4% and two side branches in 23% of patients, 73% of these patients had no side branches. No significant differences were observed between controls, patients with CAD with or without previous infarction regarding the number of side branches.

Figure 6. Prevalence of both the Posterior Vein of the Left Ventricle (PVLV) and the Left Marginal Vein (LMV), only the PVLV and neither PVLV and LMV according to subject category: controls, coronary artery disease (CAD) and myocardial infarction patients.



Quantitative measurements from MSCT

The quantitative measurements are presented in Table 2. Inter- and intra-observer agreement were assessed in 10 patients and were 94% and 97%. For all patients, the diameter of the CS in the supero-inferior direction was significantly larger as compared to the antero-posterior direction: 12.2 ± 3.3 mm versus 11.3 ± 3 mm ($p = 0.002$). The more distant tributaries of the CS had smaller diameters. Within the three groups (controls, CAD patients or patients with previous infarction) no significant differences were noted. The distances between the origins of the different vessels were also comparable between the three groups.

Table 2. Quantitative measurements in venous anatomy from MSCT

	Controls n = 28	CAD n = 38	Infarction n = 34	p-value
Diameters				
CS antero-posterior (mm)	11.5 ± 2.4	11.2 ± 3.7	11.2 ± 2.9	NS
CS supero-inferior (mm)	12.6 ± 3.2	11.7 ± 3.3	12.5 ± 3.3	NS
GCV proximal (mm)	7.2 ± 1.4	7.0 ± 1.8	7.4 ± 1.4	NS
GCV distal (mm)	4.9 ± 1.1	5.0 ± 1.0	5.1 ± 1.3	NS
PIV (mm)	5.0 ± 0.7	5.2 ± 1.3	5.2 ± 1.3	NS
PVLV (mm)	3.8 ± 0.7	3.9 ± 1.0	4.1 ± 1.1	NS
LMV (mm)	3.1 ± 0.8	3.6 ± 1.5	5.3 ± 5.8	NS
Distance between origin of				
PIV and PVLV (mm)	32 ± 17	27 ± 14	36 ± 22	NS
PVLV and LMV (mm)	41 ± 13	39 ± 15	38 ± 17	NS
PVLV and AIV (mm)	51 ± 16	55 ± 17	57 ± 10	NS
LMV and AIV (mm)	45 ± 9	44 ± 14	46 ± 13	NS

AIV: Anterior Interventricular Vein; CS: Coronary Sinus; GCV: Great Cardiac Vein; LMV: Left Marginal Vein; PIV: Posterior Interventricular Vein; PVLV: Posterior Vein.

DISCUSSION

The main findings in the current study are two-fold. First, non-invasive evaluation of the cardiac venous system in CAD patients is feasible using 64-slice MSCT. Second, variation of the cardiac venous anatomy in CAD patients appears related to a history of previous myocardial infarction; patients with previous infarction have significantly less left marginal veins. These observations may have important implications for selection of potential CRT candidates with a history of myocardial infarction.

Non-invasive evaluation of the cardiac venous system

Until recently, the cardiac venous system could only be evaluated invasively using retrograde venography, either by direct manual contrast injection or after occlusion of the coronary sinus. (8,9) In 2000, few studies reported on the use of non-invasive imaging with electron beam CT to depict the cardiac venous system. (10,11) Recently, Mao et al analyzed the electron beam CT of 231 patients and demonstrated that this technique provides 3-D visualization of most components of the coronary venous system. (12) In 2003, Tada et al reported the feasibility of MSCT to obtain high quality three-dimensional images of the cardiac venous system in one patient. (13) Recently, preliminary studies were published on the value of 16-slice MSCT to evaluate the cardiac veins. (7,14,15) Since then, 16-slice MSCT is gradually being replaced by 64-slice MSCT, offering a higher spatial resolution with a decreased acquisition time. Abbara et al suggested that due to the shorter scanning time, venous opacification might be insufficient using scanning protocols tailored for imaging the coronary artery system. (14) However, the feasibility of depicting the cardiac venous system with 64-slice MSCT was clearly demonstrated in the present study. Despite a shorter scanning time, the CS and its tributaries could be evaluated in all individuals. Prominent side branches - suitable for insertion of pacemaker leads - were adequately visualized but the distal parts of side branches with a smaller diameter could not be detected in all patients.

Variations in cardiac venous anatomy

In the current report the accepted terminology for the CS and its tributaries of the Nomina Anatomica (English version) as described by von Lüdinghausen was used to permit comparison with previous studies. (16) Of note, in various studies the PIV is often described as the Middle Cardiac Vein. Both in anatomical series and imaging

series, either invasive venography or non-invasive evaluation with CT, a substantial variation in anatomy was reported.

First, the CS was analyzed. The CS is the most constant component of the cardiac venous system and was detected in all patients. The diameter of the CS was larger in the supero-inferior direction as compared to the antero-posterior direction, indicating an oval shape of the ostium, confirming the 16 slice MSCT observations of Jongbloed et al. (7) and MRI observations by Wittkamp et al. (17).

Secondly, the tributaries of the CS were evaluated. The PIV was observed in (nearly) all patients. The highest variability was observed in the number of tributaries between the PIV and the Anterior Interventricular Vein. In anatomical series the PVLV existed as a single large vessel in 63% of the cases (diameter ranging from 1.0 – 5.5 mm) and the prevalence of the LMV was between 73% and 88% of cases (diameter varying from 1.0 – 3.0 mm). (15) Meisel et al studied 129 patients referred for cardioverter-defibrillator implantation with invasive venography and noted a PVLV in 55% and a LMV in 83%. (8) In studies using noninvasive modality (Electron Beam CT or 16 slice MSCT), the prevalence of the PVLV varied between 13% and 80 % and the prevalence of the LMV between 38% and 93%. (11-14) The number of patients with CAD was not specified in every study and data on the prevalence and site of infarction were frequently lacking. Mao and co-workers, analyzed 231 patients and found the CS in 100%, the PIV in 100%, the Posterior Vein in 78% and the Marginal Vein in 81%. (12) Abbara et al (14) included 54 patients with suspected CAD, referred for 16-slice MSCT. In 4 patients (7.4%) no LMV could be identified and in 11 (20.4%) patients no Posterior Vein could be found; however none of the

patients had a definite diagnosis of acute myocardial infarction. (14) Jongbloed et al studied 38 patients including 18 CAD patients. (7) The CS and PIV were observed in all patients, the PVLV was found in 95% and the LMV in 60% of patients.

A novelty of the current study is the demonstration of an association between these anatomic variations and the history of a previous myocardial infarction. None of the patients with a previous lateral infarction had a LMV and patients with anterolateral myocardial infarctions and especially Q-wave infarctions were lacking the LMV. Post-mortem studies on cardiac veins in ischemic heart disease are scarce. Hansen studied several series of patients who died from ischemic heart disease and detected thrombosis of the epicardial veins in large transmural infarctions. (18) In all cases the thrombosed veins were those draining the infarcted myocardium. (19) Indirect evidence supporting the association between previous infarction and absent cardiac veins is provided by Komamura et al who used thermodilution measurements of great cardiac vein flow after reperfusion and demonstrated that salvaged myocardium after successful thrombolysis was not observed in patients demonstrating a progressive decrease in great cardiac vein flow. (20)

Clinical implications

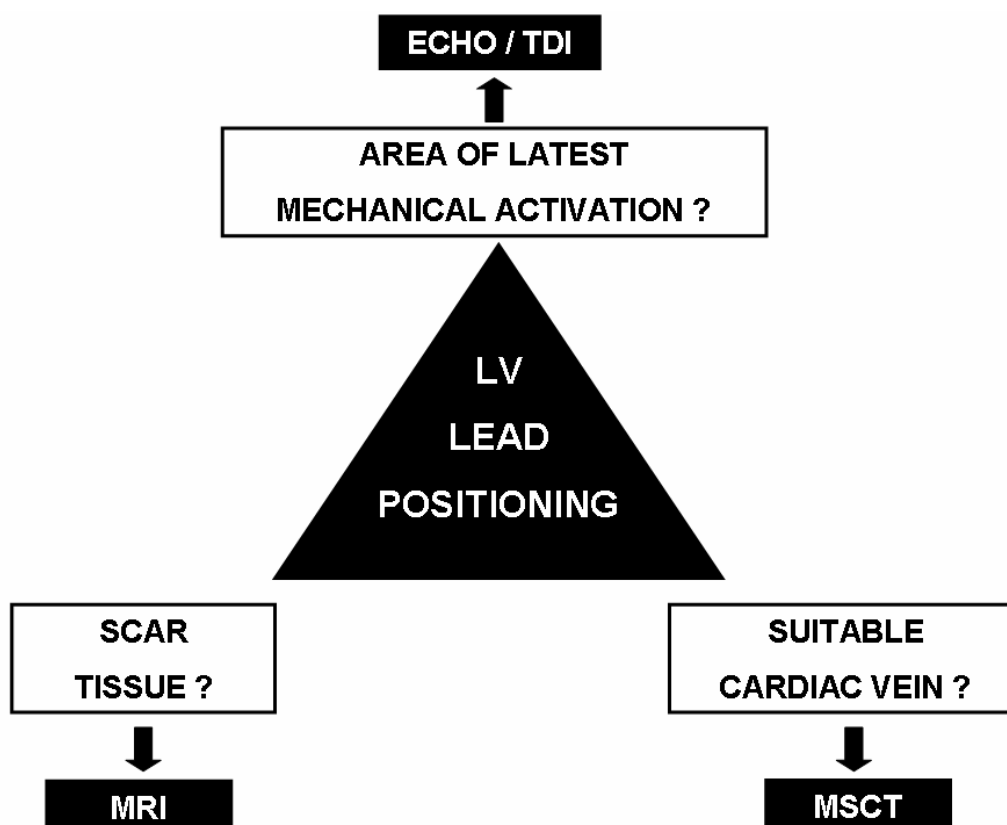
The observation that patients with previous infarction are frequently lacking the LMV has important implications for the selection of potential candidates for CRT. Positioning the LV lead is the most challenging part of CRT implantation. Before referring the patient with previous infarction for CRT implantation, a triad of questions (Figure 7) has to be answered. First: where is the area of latest activation located? As shown by Ansalone et al, the best clinical response occurs in patients who had

their LV lead placed in or near the site of latest activation. (21) Echocardiography with tissue Doppler imaging is an adequate non-invasive imaging modality to answer this question. (22,23) Second: does the area of latest mechanical activation not contain transmural scar tissue? Recently, Bleeker et al observed that patients with transmural posterolateral scar tissue on contrast-enhanced MRI failed to respond to CRT. (24) This observation underscored that assessment of LV dyssynchrony in patients with ischemic cardiomyopathy should be combined with assessment of scar tissue, to verify whether the region that will be targeted for LV pacing does not contain transmural scar tissue. After having identified the region of latest activation without scar tissue a final and third question has to be answered: are their cardiac veins, draining this target region, suitable for LV lead placement? MSCT can provide an answer to this question that appears important in patients with a history of myocardial infarction. If suitable cardiac veins are absent, a surgical approach is preferred over transvenous LV lead positioning. MSCT is a reliable technique to depict the cardiac venous system and the 3D reconstruction will also allow segmental classification to map the cardiac veins and tributaries in relation to the left ventricular wall in a manner comparable to that of echocardiography. (25) MSCT is able to detect anatomic and quantitative differences that may occur in CS and venous anatomy of heart failure patients who are candidates for CRT. MSCT will not only confirm the presence of a specific CS tributary but will also provide information on the course of the vessel, side-branches, the diameter, the distance from the CS and the relation with adjacent structures. Depending on the experience of the implanting cardiologist, no invasive venography at all or only selected venography of the target cardiac vein may be sufficient to implant the lead successfully, based on the MSCT data. In addition, information on cardiac venous anatomy acquired with MSCT could

possibly also be used during CRT implantation for 3-D navigation into the heart cavities and veins. (25)

Figure 7.

To improve the response rate to CRT, the left ventricular lead has to be positioned in the area of latest mechanical as can be identified with tissue Doppler imaging (TDI). The myocardium in this area should not contain transmural scar tissue, which can be evaluated with contrast-enhanced MRI. A transvenous approach will only be possible if a suitable vein draining this region is present, which can be detected by MSCT.



LIMITATIONS

The 64-slice MSCT scans were tailored for optimal visualisation of the coronary arteries. This could have caused suboptimal enhancement of the coronary veins, particularly of second and third degree side branches with a small diameter. Since atrial fibrillation is considered a contraindication for MSCT of the coronary arteries only patients in sinus rhythm were included. Prospective confirmation of the current findings, comparing venography and MSCT, is needed in patients referred for CRT.

CONCLUSION

Non-invasive evaluation of the cardiac venous anatomy with 64-slice MSCT is feasible. There is considerable variation in cardiac venous anatomy. Patients with a history of myocardial infarction were less likely to have a LMV possibly limiting optimal LV lead positioning for CRT.

ACKNOWLEDGEMENTS

Nico Van de Veire is a Research Assistant and Johan De Sutter a Senior Clinical Investigator of the Fund for Scientific Research – Flanders (Belgium) (F.W.O.-Vlaanderen). Gabe Bleeker is supported by the Dutch Heart Foundation grant 2002B109.

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ADDENDUM

Heart Failure patients with CAD and impaired LV function Flow Chart for the selection of potential CRT candidates

1. Optimize medical treatment, consider cardiac rehabilitation and reevaluate

2. Evaluate if the patient is eligible for CRT according to the classic criteria

- NYHA class III/IV ?
- QRS width > 120 ms?
- LV ejection fraction < 35 %?

3. Perform transthoracic echocardiography, including Tissue Doppler Imaging

- evaluate ventricular dimensions and function
- evaluate cardiac valves with emphasis on mitral regurgitation
- consider semi-supine bicycle echocardiography in case of mild mitral regurgitation
- evaluate dyssynchrony, identify area of latest activation

4. Evaluate ischemia and viability with nuclear techniques or MRI

a) If reversible ischemia is present consider revascularization. If CABG is scheduled, consider mitral valve plasty and epicardial LV lead positioning at the site of latest activation. Reevaluate the need for CRT post revascularization.

b) If reversible ischemia is absent and the amount of scar tissue is limited perform a MSCT to visualize the cardiac venous system. If a suitable cardiac vein is identified refer the patient for transvenous CRT implantation. If not consider epicardial LV lead positioning.

5. Check AICD indications

**Noninvasive markers of prognosis
in heart failure patients**

Diabetes and impaired fasting glucose as predictors of morbidity and mortality in male coronary artery disease patients with reduced left ventricular function

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Acta Cardiol 2006; 61: 137-143

Poster presentation at the Belgian Society of Cardiology Congress,
February 2005, Brussels

ABSTRACT

Objectives

To evaluate the prognostic value of impaired fasting glucose and diabetes mellitus (DM) in male patients (pts) with coronary artery disease (CAD) and a poor left ventricular function.

Methods and results

From a prospective database on patients referred for gated myocardial perfusion imaging between 1998 & 2002 all male pts with a history of CAD and poor left ventricular function were selected. Poor function was defined as left ventricular ejection fraction (LVEF) $\leq 40\%$. Subjects were categorized as nondiabetics with fasting blood glucose levels < 110 mg/dL, nondiabetics with impaired fasting glucose (fasting blood glucose between 110 and 125 mg/dL) and diabetics. Median follow-up was 2.7 years. End points were all cause mortality, cardiac death and hospitalization for heart failure. One hundred and sixty patients were selected (age 65 ± 9 years & LVEF $29 \pm 8\%$). In univariate analysis atrial fibrillation, NYHA class, glycemia and DM discriminated between survivors and non-survivors. In Cox multivariate regression analysis for all cause mortality only NYHA class and DM remained significant. Kaplan Meier analysis showed that diabetics had the worst survival and non-diabetics with glucose < 110 mg/dl had the best survival. Nondiabetics with impaired fasting glucose had intermediate survival. Analysis for cardiac death/hospitalization for heart failure showed similar results.

Conclusion

In male patients with CAD and impaired LV function DM and fasting glucose are strongly predictive of poor outcome. Diabetics have the worst prognosis but nondiabetics with impaired fasting glucose also are at higher risk compared to nondiabetics with low fasting blood glucose.

INTRODUCTION

Diabetes mellitus (DM) occupies a prominent notorious role among the risk factors for heart disease. Many diabetics develop coronary artery disease (CAD) and DM is also linked to heart failure. Using data from the SOLVD trials and registry Schindler and coworkers showed that DM is an independent predictor of morbidity and mortality both in patients with symptomatic heart failure and in patients with asymptomatic left ventricular dysfunction. (1) Dries and coworkers demonstrated in the same SOLVD population that there is a differential impact of DM on mortality and heart failure progression according to the etiology of heart failure suggesting an interaction between diabetes and ischemic heart disease. (2) This was confirmed more recently by de Groote et al; their results suggest that DM is particularly deleterious in heart failure patients with an impaired function and ischemic cardiomyopathy. (3)

The current American Diabetes Association criteria define diabetes mellitus from fasting blood glucose levels ≥ 126 mg/dL. Levels between 110 and 125 mg/dL were designated impaired fasting glucose. (4) Fisman et al showed in a population of nondiabetic patients with documented coronary artery disease that there was a substantially increased mortality rate among patients with impaired fasting glucose levels. (5) In the present study we evaluated the prognostic value of DM and fasting blood glucose levels among nondiabetics in a well defined population of male elderly adult patients with coronary artery disease and poor left ventricular systolic function. The study population was followed for a median period of 2.7 years and the following endpoints were taken into account: total mortality, cardiac death and hospitalization for heart failure.

METHODS

Study design

All male patients with CAD were selected from a prospective database comprising 2150 patients referred for a 2 day stress-rest gated myocardial single photon emission computed tomographic (SPECT) imaging study in the period ranging from October 1998 till December 2001. Diagnosis of CAD was based on a history of myocardial infarction, percutaneous coronary interventions (PCI), coronary artery bypass grafting (CABG) or angiographically significant CAD (at least one coronary artery with ≥ 75 % stenosis). In addition we further selected males with scintigraphic evidence of poor left ventricular systolic function: left ventricular ejection fraction (LVEF) ≤ 40 % as determined by 3D gated SPECT. Day to day variability of this technique in our hospital was < 5 % (6). Patients had to be stable [New York Heart Association (NYHA) class I-III] for the last three months.

Study protocol

Patients were informed to abstain from caffeine and nicotin containing products at least 24 h before testing and to visit the laboratory for exercise physiology after overnight fasting.

Blood sample

A venous blood sample was collected. Serum glucose was assayed by a standard hexokinase enzymatic method. For serum creatinine, a rate blanked kinetic Jaffé

method was used. Total serum cholesterol was assayed by the enzymatic colorimetric CHOD-PAP method of Allain et al. Serum High Density Lipoprotein (HDL) - cholesterol was determined by the homogenous enzymatic colorimetric method. For serum triglycerides the esterase PAP kinetic colorimetric reaction without glycerol correction was used. Low Density Lipoprotein (LDL) - cholesterol was calculated using the classical Friedewald formula. All serum parameters were determined at 37°C on a Modular system (Roche). All tests were performed according to an ISO 17025 Beltest accreditation.

Two days stress-rest Tetrofosmin gated SPECT study

Before starting the stress test length and weight of the patients were determined and body mass index (BMI) was calculated. After resting for 5 minutes arterial blood pressure was measured at the right brachial artery with a mercury sphygmomanometer. Stress and rest studies were performed in a 2-days protocol as described previously (6). Bicycle stress testing was used in patients able to perform maximal physical stress (n=97, 61 %). When a patient was not able to perform maximal bicycle stress, an additional intravenous infusion of dipyridamole was given (n=45, 28 %). In patients unable to perform physical stress, only intravenous dipyridamole stress testing was used (n=18, 11 %). Technetium-99m tetrofosmin was injected at peak stress. Imaging was started 15-30 minutes after injection at peak stress and 30-60 minutes after injection in the resting state. Gated images were processed to obtain LVEF.

Patient categories

Patients were classified as diabetic if they were being treated with oral hypoglycaemic drugs or insulin and/or if they had a previous history of DM, documented on their medical chart and/or if they had elevated (≥ 126 mg/dL) fasting blood glucose. The others were considered nondiabetic and were divided into two groups: nondiabetics with fasting glucose < 110 mg/dL and nondiabetics with fasting glucose between 110 and 125 mg/dL (impaired fasting glucose). Among the nondiabetics we identified individuals with the metabolic syndrome if they met with three out of five modified National Cholesterol Education Panel's Adult Treatment Panel III criteria: 1) blood pressure ≥ 130 mmHg systolic and/or ≥ 85 mmHg diastolic, 2) fasting glucose ≥ 110 mg/dL, 3) triglycerides ≥ 150 mg/dL, 4) HDL-cholesterol < 40 mg/dL 5) BMI ≥ 27 kg/m². (7) BMI was used instead of a waist circumference >102 cm (for men) since these data were not available in our database. The use of BMI in stead of waist circumference has recently been adopted by Ridker et al (8) in an analysis of the Women's Health Study and by Sattar et al in the West of Scotland Coronary Prevention Study (9).

Follow-up

Demographic data at study entrance were collected by history taking and physical examination on the day of the stress testing. Follow-up data were collected in 2003. One of the investigators (ODW), blinded to the exposure status, contacted patients' general practitioners and reviewed hospital records. A standard questionnaire was used for follow-up interviews. The following events were taken into account: all cause

mortality, cardiac death and hospitalisation for heart failure. Cardiac death was defined as death caused by acute myocardial infarction, refractory congestive heart failure, clinically important cardiac arrhythmias and sudden death without another explanation. Follow-up was limited to 36 months. The study was approved by the local Ethics Committee of the Ghent University Hospital.

Statistical analysis

All statistical analyses were performed using SPSS 11.5 statistical software (SPSS Inc., Chicago, USA). Data are shown as mean \pm standard deviation (SD) or number (%). Unpaired Student t test was used to compare continuous variables and the Fisher Exact test was used to compare categorical variables. Cumulative survival rates as function over time were obtained by the Kaplan-Meier method. Differences in survival were analysed by log-rank testing. Predictors of mortality were tested by univariate analysis. Significant parameters were entered into a stepwise multivariate Cox proportional hazards regression model. Significance level was set at < 0.05 .

RESULTS

Study population

From the 2150 subjects 160 male patients with a history of CAD and a LVEF $\leq 40\%$ could be selected. Mean age was 65 ± 9 years with a mean LVEF of $29 \pm 8\%$. At the time of myocardial SPECT imaging 73 % of these patients had a history of prior myocardial infarction, 23 % a history of PCI and 33% previously underwent CABG.

Clinical characteristics according to the metabolic status of the patients

In table 1 the patients are presented according to one of the following groups: nondiabetics with fasting glucose < 110 mg/dL, nondiabetics with fasting glucose between 110 and 125 mg/dL (impaired fasting glucose) and diabetics. Age and LVEF did not differ between the groups. As expected highly significant differences were observed for fasting blood glucose levels between the 3 groups. Patients with impaired fasting glucose and DM had a higher BMI and were more symptomatic (according to NYHA class) than nondiabetics with glucose levels below 110 mg/dL. Revascularisation rates, either by PCI or CABG were comparable between groups. No significant differences were observed regarding blood pressure levels, lipid values, renal function and smoking habits. Drug treatment was comparable between the three groups. Among the patients without diabetes and low fasting glucose levels 18 individuals (17%) had metabolic syndrome; among those with impaired fasting glucose 8 patients (44%) had metabolic syndrome ($p < 0.001$).

Prognostic significance of diabetes mellitus and impaired fasting glucose in patients with coronary artery disease and poor left ventricular function

We prospectively followed all 160 subjects during a median period of 32.4 months (range 0.7 – 36 months). During follow-up 25 patients died of which 15 deaths were considered cardiac and 8 patients were hospitalized for heart failure. Total mortality rate at the end of the study was 10/107 (9%, 4 cardiac deaths) in the normoglycemic patients, 4/18 (22%, 3 cardiac deaths) in the patients with impaired fasting glucose

Table 1 Clinical characteristics

	Non-diabetics Fasting glucose < 110 mg/dL	Impaired fasting glucose 110 – 125 mg/dL	Diabetics	p value (ANOVA)
N	107 (67%)	18 (11%)	35 (22%)	
Age (years)	65 ± 10	66 ± 7	66 ± 7	NS
BMI (kg/m ²)	26 ± 4	28 ± 5	28 ± 5	p< 0.05
LVEF (%)	30 ± 7	27 ± 9	29 ± 7	NS
NYHA class	1.2 ± 0.5	1.7 ± 1	1.5 ± 0.8	p< 0.001
Smoking	25 (25%)	5 (28%)	8 (28%)	NS
Atrial fib	4 (4%)	2 (11%)	5 (14%)	NS
Heart rate (beats/min)	65 ± 14	72 ± 15	70 ± 14	NS
SBP (mmHg)	133 ± 20	132 ± 19	130 ± 12	NS
DBP (mmHg)	80 ± 10	81 ± 7	79 ± 12	NS
PCI	26 (24%)	4 (22%)	5 (14%)	NS
CABG	39 (36%)	7 (39%)	15 (43%)	NS
Glucose (mg/dL)	86 ± 12	117 ± 5	148 ± 69	p< 0.0001
Creatinine (mg/dL)	1.2 ± 0.8	1.2 ± 0.3	1.4 ± 0.9	NS
Total-chol (mg/dL)	201 ± 36	210 ± 52	196 ± 44	NS
HDL-chol (mg/dL)	45 ± 14	43 ± 12	42 ± 12	NS
LDL-chol (mg/dL)	132 ± 31	137 ± 43	124 ± 42	NS
Triglycerides (mg/dL)	124 ± 59	139 ± 62	150 ± 70	NS
Antiplatelet agents	78 (73%)	11 (61%)	24 (69%)	NS
B blockers	60 (58%)	8 (53%)	15 (43%)	NS
ACE/AT2 blockers	74 (71%)	12 (80%)	29 (83%)	NS
Digoxin	10 (10%)	4 (27%)	8 (23%)	p=0.05
Diuretics	24 (23%)	5 (33%)	14 (40%)	NS
Calciumantagonist	10 (10%)	3 (20%)	5 (14%)	NS
Statins	26 (25%)	3 (20%)	8 (23%)	NS
Fibrates	7 (7%)	0 (0%)	2 (6%)	NS

Abbreviations: BMI: body mass index, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, fib: fibrillation, SBP: systolic blood pressure, DBP: diastolic blood pressure, MI: myocardial infarction, PCI: percutaneous coronary angioplasty, CABG: coronary artery bypass grafting, chol: cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, Antiplatelet agents (aspirin and/or ticlopidine and/or clopidogrel) B: beta, ACE: angiotensin converting enzyme, AT2: angiotensin 2 receptor, NS: non significant

and 11/35 (31%, 8 cardiac deaths) in the diabetics (overall $p = 0.005$ for all cause mortality and $p = 0.002$ for cardiac death). Hospitalization rates for heart failure in the three glucose groups were 4, 8 and 9 % respectively.

Univariate analysis for all cause mortality

Table 2 compares characteristics between survivors and non-survivors. Univariate associated with death were presence of atrial fibrillation, higher NYHA classification, fasting blood glucose levels and DM.

Multivariate predictors of all cause mortality

In a multivariate Cox proportional hazard model (chi square 18, $p < 0.0001$) NYHA class (Wald Statistic 6.4, $p = 0.01$) and DM (Wald Statistic 5.3, $p = 0.02$) were independent clinical predictors of all cause mortality.

Kaplan- Meier survival curves

Figure 1 shows survival curves for the studied population. Patients with DM have a worse survival compared to nondiabetics. Nondiabetics with impaired fasting glucose have an intermediar survival curve. In Figure 2 the combined end point of cardiac death and hospitalization for heart failure is depicted. Again diabetics had more events, nondiabetics with low fasting glucose had the lowest number of events and nondiabetics with impaired fasting glucose had an intermediar event rate.

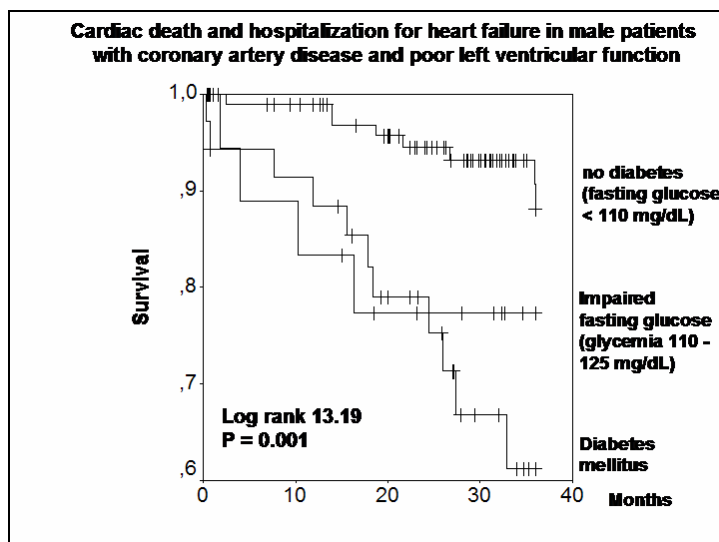
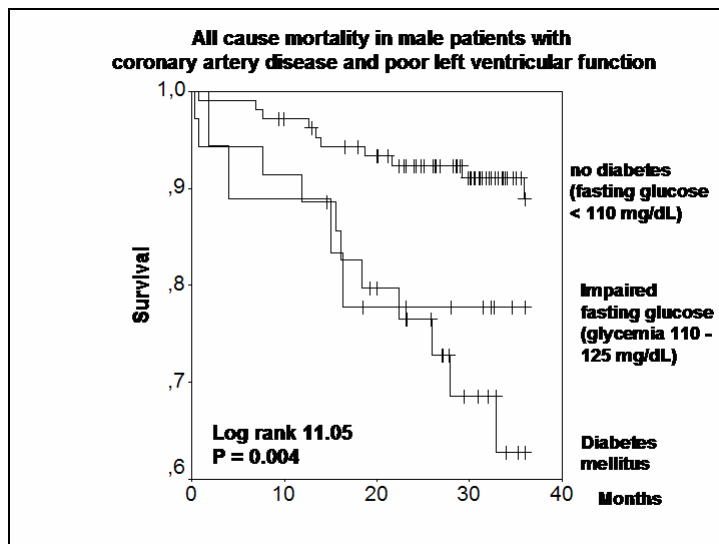
Table 2
Univariate analysis for all cause mortality.

	Survivors	Deaths	p-value
N	135	25	NA
Age (years)	65 ± 9	67 ± 9	0.164
BMI (kg/m ²)	26.4 ± 4.2	26.3 ± 5.6	0.949
LVEF (%)	30 ± 8	27 ± 6	0.138
NYHA class	1.2±0.5	1.6±1	p<0.01
Smoking	31 (23%)	7 (28%)	0.805
Diabetes	24 (18%)	11 (44%)	p<0.01
Atrial fib	10 (7%)	6 (24%)	p<0.05
SBP (mmHg)	132 ± 19	132 ± 17	0.984
DBP (mmHg)	80 ± 11	79 ± 9	0.616
PCI	32 (24%)	3 (12%)	0.297
CABG	50 (37%)	11 (44%)	0.511
Glucose (mg/dl)	100 ± 39	119 ± 54	p<0.05
Creatinine (mg/dl)	1.25 ± 0.72	1.33 ± 0.52	0.183
Total chol (mg/dl)	201 ± 40	204 ± 38	0.678
HDL-chol (mg/dl)	43 ± 13	47 ± 12	0.139
LDL-chol (mg/dl)	131 ± 35	131 ± 33	0.965
Triglycerides (mg/dl)	132 ± 63	130 ± 58	0.887
Antiplatelet agents	99 (73%)	14 (56%)	0.08
Beta blockers	73 (54%)	10 (40%)	0.191
ACE/ATII antagonists	95 (70%)	20 (80%)	0.288
Digoxin	16 (12%)	6 (24%)	0.103
Diuretics	34 (25%)	9 (36%)	0.255
Calcium antagonist	14 (10%)	4 (16%)	0.409
Statins	33 (24%)	4 (16%)	0.358
Fibrates	9 (7%)	0 (0%)	0.184

Abbreviations: BMI: body mass index, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, fib: fibrillation, SBP: systolic blood pressure, DBP: diastolic blood pressure, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, chol: cholesterol, HDL: high density lipoprotein, LDL: low density lipoprotein, B: beta, ACE: angiotensin converting enzyme, AT2: angiotensin 2 receptor

Figure 1 and 2

Kaplan-Meier curves for **all cause mortality (Fig 1)** and the **combined end point of cardiac death** (death caused by acute myocardial infarction, refractory congestive heart failure, clinically important cardiac arrhythmias and sudden death without another explanation) **and hospitalization for heart failure (Fig 2)** in male patients with coronary artery disease and poor left ventricular function according to 3 categories: nondiabetics with fasting blood glucose < 110 mg/dL, nondiabetics with impaired fasting glucose (fasting blood glucose between 110 and 125 mg/dL) and diabetic patients.



DISCUSSION

In a well defined population of male CAD patients with impaired left ventricular systolic function DM and fasting blood glucose are predictors of poor outcome. Patients with DM had the worst prognosis but nondiabetics with impaired fasting glucose also had significantly more events than nondiabetics with low fasting blood glucose.

It is well known that patients with CAD and an impaired left ventricular systolic function have in general a poor prognosis. (10) This was not different in the present study. After a median follow-up of 2.7 years 25 out of the 160 male elderly CAD patients died. A mortality rate of 16% despite the fact that most of these men were asymptomatic: 121 were in NYHA class I.

Schindler et al demonstrated that patients in the SOLVD Treatment Trial (including patients with LVEF \leq 35% and clinical evidence of heart failure) had higher morbidity and mortality rates if they had DM. (1) Also patients with a LVEF \leq 35% in the SOLVD Prevention Trial but without a history of overt heart failure did worse if DM was present. (1) Although their observations is based on a large dataset, important information is lacking namely fasting blood glucose levels. The diagnosis of DM in the SOLVD was based on self-report by the patient or documentation in the patient's medical records. In the present study treatment with oral antidiabetics or insulin and/or fasting glucose \geq 126 mg/dL (as recommended by the American Diabetes Association) were also taken into account to diagnose more correctly DM.

Dries et al retrospectively analyzed the patients in the SOLVD Prevention and Treatment Trials and showed that DM was strongly associated with an increased risk for all cause mortality in patients with ischemic cardiomyopathy, but not in patients with nonischemic cardiomyopathy suggesting that DM and ischemic heart disease interact to accelerate the progression of myocardial dysfunction. (2) They also demonstrated that previous surgical revascularization identified patients within the cohort with CAD and DM with improved prognosis. Based on these finding they concluded that the potential for revascularization may be particularly important in patients with ischemic cardiomyopathy and DM. Revascularisation procedures have shown to improve prognosis in patients with CAD and a depressed LV function. (11) Although the present study is to small to draw conclusions concerning the effect of revascularization on mortality in patients with impaired fasting glucose one could speculate about the role of early revascularization in these patients since their risk is increased just as in patients with DM.

More recently de Groote et al confirmed the findings from the SOLVD trial by studying 1246 patients with impaired left ventricular function. (3) They showed that the prognostic impact of diabetes mellitus is markedly influenced by the underlying aetiology and is particular deleterious in those with ischaemic cardiomyopathy. De Groote et al had a better characterisation of diabetic status because they included fasting blood glucose values ≥ 126 mg/dL. The recent definition of DM using the threshold of 126 mg/dL was not based on either the risk for cardiovascular disease or for all-cause mortality. (4) So there is no reason to believe that the glucose-cardiovascular relationship should not extend below the diabetes thresholds. Impaired fasting glucose, defined as a fasting blood glucose between 110 and 125

mg/dL by the American Diabetes Association is regarded by some as a prediabetic state. Fisman et al studied almost 12 000 patients with documented coronary artery disease screened for participation but not included in the Bezafibrate Infarction Prevention (BIP) study. Patients were divided into 3 groups on the basis of their fasting blood glucose concentrations at screening: (1) nondiabetic patients (glucose up to 109 mg/dL), (2) patients with impaired fasting glucose and (3) undiagnosed diabetic patients (glucose \geq 126 mg/dL). Mean follow-up was 6.2 to 9.0 years. All cause mortality was 14.3 % in nondiabetics, 20.1 % in patients with impaired fasting glucose and 24.3 % in undiagnosed subjects ($P < 0.001$). Impaired fasting glucose was identified as an independent predictor of increased all-cause and ischemic heart disease mortality with hazard ratios of 1.39 and 1.29 respectively. Fisman's study differs with the present study by the fact that patients with known DM (including pharmacologically treated patients) were excluded. Moreover no information was available in Fisman's study regarding the left ventricular systolic function.

The present study specifically investigates the prognostic role of DM but also of impaired fasting glucose levels in CAD patients with poor left ventricular function. As expected diabetics had most events but the event rate was also higher in nondiabetics with fasting glucose levels between 110 and 125 mg/dL. The worse prognosis in nondiabetics with impaired fasting glucose compared to nondiabetics with normal fasting glucose might be explained by a higher prevalence of the metabolic syndrome (44% versus 17%) among these patients; a logic consequence of the definition of metabolic syndrome since one of the conditions is fasting blood glucose \geq 110 mg/dl. The metabolic syndrome was reintroduced in 1988 by Reaven as a link between insulin resistance, hypertension, dislipidemia and DM (12). In the

past, many authors highlighted the prognostic importance of MS in the setting of primary prevention. However the number of papers addressing the prognostic significance of MS in secondary setting are scarce. Anderson et al studied a large population of over 3000 subjects (65 % of them had advanced CAD as proven by coronary angiography) and observed a very high prevalence of 64 % with metabolic syndrome (13). They also investigated the predictive value of metabolic syndrome for incident death or non-fatal myocardial infarction and found that metabolic syndrome had no prognostic implications. However, when fasting glucose was assessed individually, a worse outcome was observed for patients with glucose levels ≥ 110 mg/dL. The patients they studied had preserved left ventricular systolic function (averaging 61%) whereas we studied patients with a poor LV systolic function.

A single measurement of fasting blood glucose among men with CAD and poor systolic function provides important prognostic information. This finding suggests that CAD patients with impaired function should undergo screening for impaired fasting glucose. Whether a strategy of screening followed by aggressive treatment of both DM and impaired fasting glucose will result in better outcome deserves further investigation.

STUDY LIMITATIONS

Our study population was exclusive male and extrapolation of the findings to female patients should be performed with caution. Subjects were recruited from all patients referred to a large teaching hospital for myocardial perfusion imaging and exercise

testing. This could imply a certain degree of selection bias. Information on the duration of diabetes or on diabetic control (such as HbA1c) was not available. Blood glucose levels were determined only once; the American Diabetes Association requires elevated fasting glucose levels on at least two separate occasions to identify diabetics and patients with impaired fasting glucose. Even with this limitation a single, simple and inexpensive fasting blood glucose measurement provides important prognostic information in the studied population.

CONCLUSION

In male patients with CAD and impaired LV function DM and fasting glucose are strongly predictive of poor outcome. Patients with DM have the worst prognosis but nondiabetics with impaired fasting glucose also have a higher event rate compared to nondiabetics with low fasting glucose levels.

ACKNOWLEDGEMENTS

This work was made possible by a Special Research Grant (Bijzonder Onderzoeksfonds) of the Ghent University and the Flemish Government (BOZF 01100400). Nico Van de Veire is a Research Assistant and Johan De Sutter a Senior Clinical Investigator of the Fund for Scientific Research – Flanders (Belgium) (FWO-Vlaanderen)

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CHAPTER 3.2

Maximum oxygen uptake at peak exercise in elderly patients with coronary artery disease and preserved LV function: The role of inflammation on top of tissue Doppler-derived systolic & diastolic function

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Am Heart J 2006; 152: 297.e1-297.e7

ABSTRACT

Background

Several studies have shown that longitudinal systolic function and left ventricular (LV) filling pressures, as assessed with tissue Doppler imaging (TDI), predict exercise capacity.

Aim

To evaluate whether natriuretic peptides and inflammatory parameters can independently predict peak oxygen consumption ($VO_2\text{max}$) on top of TDI derived markers.

Methods

We evaluated 142 patients (age 70 ± 6 years, 77% men) with known or suspected coronary artery disease (CAD) and a preserved left ventricular ejection fraction ($\geq 50\%$). All patients underwent bicycle-spiroergometry and NT-proBNP levels were determined. Cytokines (Interleukin-6, soluble TNF-receptors 1 & 2) and hsCRP were measured as inflammatory markers. TDI was applied to evaluate LV longitudinal myocardial velocities (Sm) and early mitral annulus velocities (E'). Ratio of early transmitral flow (E) to E' was assessed as marker of LV filling. ANOVA, comparing

VO₂max quartiles, was used to determine univariate predictors and linear regression to determine multivariate VO₂max predictors.

Results

Average VO₂max was 18.5±5.7 ml/kg/min (range 6-36.6). Compared to the highest quartile, patients with low VO₂max were more frequently female (p<0.0001). NT-proBNP and cytokine levels were significantly higher in the lower VO₂max categories. Longitudinal myocardial velocities increased and E/E' decreased along with increasing VO₂max. In multivariate linear regression analysis VO₂max was independently predicted by gender, glucose, Sm, E/E' and cytokine levels.

Conclusion

VO₂max in patients with known or suspected CAD and preserved systolic function was independently predicted by inflammatory makers on top of tissue Doppler derived systolic and diastolic function.

INTRODUCTION

Maximum oxygen uptake at peak exercise ($VO_2\text{max}$) is widely used to assess exercise capacity and provides prognostic information. (1,2) The exact mechanisms of exercise intolerance however are not fully understood. Attempts to correlate exercise capacity with traditional systolic function markers such as left ventricular (LV) ejection fraction (EF) could only demonstrate weak correlations. Simple diastolic function parameters (transmitral flow pattern) are more strongly correlating with exercise capacity than LVEF. (3-6)

Application of tissue Doppler imaging (TDI) has introduced novel non-invasive markers for both systolic and diastolic function including filling pressures. (7) Several of these parameters predict exercise capacity. A tool to estimate LV filling pressure is the ratio of early transmitral flow E to early diastolic velocity of the mitral annulus E'. (8,9) E/E' is inversely correlated to exercise capacity. (10,11) Longitudinal myocardial velocities, a more sensitive method to determine LV systolic function, also predict exercise capacity. (12, 13)

Although both systolic and diastolic function are intrinsically related to $VO_2\text{max}$, studies focusing only on echocardiographic parameters do not take into consideration other processes influencing exercise capacity such as natriuretic peptides and inflammation. The aim of the present study was to evaluate whether information on N-terminal pro-B type Natriuretic Peptide (NT-proBNP) and inflammatory markers (including CRP and cytokines) can independently predict exercise capacity on top of information on longitudinal systolic function and LV filling in patients with known or suspected CAD and preserved LV systolic function.

METHODS

Patient population

We evaluated 196 consecutive patients, age \geq 60 years, with known or suspected CAD, referred for bicycle spiroergometry combined with 2 day stress-rest gated Single Photon Emission Computed Tomography (SPECT). Patients with severe valvular disease or with a history of heart failure were excluded. Patients were evaluated remote ($>$ 6 months) from myocardial infarction, percutaneous coronary angioplasty (PCI) and coronary artery bypass grafting (CABG). Subjects had to be free from infections, systemic diseases, malignancies, treatment with corticosteroids, anti-inflammatory agents or any other situation influencing the inflammatory system. Since it is well known that both inflammatory cytokines and neurohumoral levels are increased in patients with poor LV systolic function, 54 patients with an ejection fraction $<$ 50% on gated SPECT were excluded. The final population comprised 142 patients.

Study protocol

Day 1: Exercise testing

Patients visited the exercise physiology laboratory after overnight fasting. Body mass index (BMI) was calculated as weight/height². After resting 5 minutes, arterial blood pressure was measured, in sitting position, at the right brachial artery with a mercury sphygmomanometer and a 12 lead electrocardiogram was recorded. Each subject underwent maximal bicycle exercise testing. Standardized protocols, depending on

patient condition, were used: starting at 50 watts increasing 25 watts every 2 minutes (46%), or starting at 50 watts increasing 10 watts every minute (28%) or starting at 25 watts increasing 10 watts every minute (23%). Most of the patients were familiar with the procedure and were encouraged to exercise to exhaustion. Patients wore a tightly fitting facemask connected to an Oxycon Pro spirometer (Jaeger - Viasys Healthcare, Hoechberg, Germany). Oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE) were measured on a breath-by-breath basis. A 12-lead ECG was continuously recorded and the heart rate was followed. Blood pressure was measured at each stage and at peak exercise. Subjects were exercised to their self-determined maximal capacity or until the physician stopped the test because of chest pain or dizziness, potentially dangerous arrhythmias or ST-segment deviations, or marked systolic hypotension or hypertension. A respiratory exchange ratio (RER; VCO_2/VO_2) > 1 was taken to indicate maximal effort. Peak VO_2 was defined as the highest VO_2 obtained at the end of the test, and was expressed in $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$. A 99m-technetium labelled perfusion agent (MIBI or tetrofosmin) was injected at peak stress. Perfusion imaging was started 15-30 minutes later using a triple-headed camera (Picker Prism 3000, Marconi, Philips, Cleveland, Ohio, USA).

Day 2: blood sampling and transthoracic echocardiography

After overnight fasting patients came to the laboratory for venous blood sampling. Routine measurements (blood cell count, creatinine and glucose) were performed according to an ISO 17025 Beltest accreditation. Glomerular filtration rate (GFR) was calculated using a validated equation. (14) Serum was frozen at -80°C for further analysis. Patients were injected with a perfusion agent and resting myocardial

perfusion imaging was started 30-60 minutes later. Gated images were processed using Quantified Gated SPECT software to obtain resting LVEF.

The same day patients underwent echocardiography with a VIVID 7 scanner (GE Vingmed Ultrasound, Horten, Norway). Sample volume of the pulsed wave Doppler was placed between the tips of the mitral leaflets in apical 4-chamber view. Early (E) and late (A) transmitral flow velocities, ratio of early to peak late velocities (E/A) and deceleration time (DT) of E velocity were obtained. Pulsed wave tissue Doppler was performed by activating this function in the same platform. Sample volume was located at the septal side of the mitral annulus. Early (E') mitral annulus velocities and ratio of E/E' were obtained. Colour tissue Doppler data were acquired in the apical 4 and 2 chamber views; sector width was adjusted to obtain frame rates > 100 frames per second. Three loops were digitally stored for off-line velocity analysis (Echopac for PC, GE Vingmed Ultrasound). Peak long-axis systolic (Sm), early diastolic (Em) and late diastolic velocities (Am) within the septal, lateral, inferior and anterior walls were obtained at the basal segment and averaged.

Laboratory analysis

Serum concentration of NT-proBNP was measured on an Elecsys 2010 apparatus (Roche Diagnostics, Mannheim, Germany) with an automated electrochemiluminescence sandwich immunoassay. Serum CRP concentrations were measured by a high-sensitivity, particle-enhanced immunoturbidimetric method on an Integra 400 analyser (Roche Diagnostics). Total imprecision in our laboratory was < 3 %. Soluble tumour necrosis factor receptors I and II: sTNFr 1 and sTNFr 2 were measured with ELISA kits from BioSource (CA, USA) with sensitivities of 0.05 and 0.1 ng/mL, respectively. Interleukin 6 (IL-6) was measured with a high sensitivity

ELISA kit from R&D (R&D Systems Europe, Abingdon, Oxon, UK) in which the total amount of IL-6 is measured, thus bound and free fraction. Sensitivity is 0.1 pg/mL.

Scoring of Perfusion Imaging

Myocardial perfusion was scored semiquantitatively in a 17-segment model as described previously. (15) The summed stress score (SSS) and summed rest score (SRS) can be considered global perfusion scores of the LV myocardium during stress and resting conditions. The summed difference score (SSS-SRS) reflects the amount of myocardial ischemia with higher scores indicating worse perfusion.

Statistical analysis

Data were analyzed with a statistical software program (SPSS 11.5.1, SPSS Inc, Chicago, Illinois (USA)). Continuous variables are presented as mean \pm standard deviation. Categorical variables are presented as absolute number and percentage. Patients were divided in 4 groups according to VO₂max quartiles. Analysis of Variance (ANOVA) and chi square analysis were used when appropriate. The significance level p was set at 0.05. NT-proBNP, hsCRP, IL-6, sTNFr 1 & 2 were not normally distributed and underwent logarithmic transformation. Linear regression analysis was applied for multivariate analysis.

Ethics

The protocol was approved by the ethical committee of the University Hospital Ghent and each patient signed an informed consent form before participating.

RESULTS

Basic characteristics and univariate determinants of VO₂max

In Table 1 basic characteristics are reported. Patients with lower exercise capacity had higher BMI, were more likely female, had higher NYHA class and had more frequently hypertension and diabetes mellitus. Exercise hemodynamic variables are listed in Table 2. Patients with the lowest exercise capacity reached lower heart-rates at peak exercise. Resting ejection fraction did not differ significantly between the VO₂max quartiles. Analysis of myocardial perfusion showed no significant differences between the 4 groups regarding amount of myocardial ischemia. Diastolic function parameters, estimated LV filling and longitudinal myocardial velocities are presented in Table 3. Patients in the lowest VO₂max category had higher E velocities and lower E' velocities resulting in higher E/E' values. Patients with lower systolic and diastolic longitudinal myocardial velocities reached lower VO₂max. Biochemical univariate predictors of VO₂max are presented in Table 4. Lower VO₂max was associated with higher NT-proBNP levels. Leukocytes and inflammatory markers such as IL-6, sTNFr 1 and 2 were significantly increased in patients with the lowest VO₂max.

Table 1: Baseline characteristics

	Quartiles of VO ₂ max				p (ANOVA)
	1st quartile 6-14.5 ml/kg/min n = 35	2nd quartile 14.6-17.9 ml/kg/min n = 36	3th quartile 18.0-21.9 ml/kg/min n = 35	4th quartile 22.0-36.6 ml/kg/min n = 36	
Age (years)	71 ± 6	72 ± 7	70 ± 5	68 ± 5	NS
Male gender	19/35 (54%)	25/36 (69%)	30/35 (96%)	35/36 (97%)	< 0.0001
BMI (kg/m ²)	30 ± 5	27 ± 5	27 ± 3	26 ± 3	< 0.0001
NYHA	1.3 ± 0.6	1.1 ± 0.8	1.1 ± 0.5	0.8 ± 0.6	0.001
History of CAD	31/35 (89%)	26/36 (72%)	31/35 (89%)	27/36 (75%)	NS
Myocardial infarction	10/35 (29%)	15/36 (42%)	12/35 (34%)	12/36 (33%)	NS
PCI	14/35 (40%)	10/36 (28%)	16/36 (44%)	10/36 (28%)	NS
CABG	18/35 (51%)	13/36 (36%)	14/35 (40%)	14/36 (39%)	NS
Smoking	2/35 (6%)	4/36 (11%)	5/35 (14%)	2/36 (6%)	NS
Hypertension	25/35 (71%)	26/36 (72%)	26/35 (74%)	15/36 (42%)	0.010
Diabetes mellitus	17/35 (49%)	11/35 (31%)	4/35 (11%)	2/36 (6%)	< 0.0001
Hypercholesterolemia	30/35 (86%)	28/36 (78%)	34/35 (97%)	29/36 (81%)	NS
Familial cardiac history	16/35 (46%)	11/36 (31%)	11/35 (31%)	18/36 (50%)	NS
CARDIAC DRUGS					
Aspirin	23/35 (66%)	25/36 (69%)	27/35 (77%)	26/36 (72%)	NS
Beta-blockers	29/35 (83%)	17/36 (47%)	25/35 (71%)	21/36 (58%)	0.011
Digoxine	1/35 (3%)	0/36 (0%)	1/35 (3%)	1/36 (3%)	NS
ACE-I	17/35 (49%)	12/36 (33%)	10/35 (29%)	7/36 (19%)	NS
AT-II blockers	6/35 (17%)	8/36 (22%)	5/35 (22%)	4/36 (11%)	NS
Calcium antagonists	10/35 (29%)	10/36 (28%)	15/35 (43%)	3/36 (8%)	0.012
Diuretics	13/35 (37%)	3/36 (8%)	6/35 (17%)	2/36 (6%)	0.002
Spironolactone	2/35 (6%)	1/36 (3%)	0/35 (0%)	0/36 (0%)	NS
Nitrates	12/35 (34%)	10/36 (28%)	10/35 (29%)	7/36 (19%)	NS
Statins	20/35 (57%)	21/36 (58%)	19/35 (54%)	22/36 (61%)	NS
Fibrates	4/35 (11%)	1/36 (3%)	4/35 (11%)	1/36 (3%)	NS

Abbreviations: LV: left ventricular, BMI: body mass index, LVEF: left ventricular ejection fraction
 NYHA: New York Heart Association, CAD: coronary artery disease PCI: percutaneous coronary angioplasty, CABG: coronary artery bypass grafting, CHF: congestive heart failure, ACE-I: angiotensin converting enzyme inhibitors, AT-II blockers: angiotensin II receptor blockers

Table 2: Exercise testing results and myocardial perfusion imaging

	Quartiles of VO ₂ max				p (ANOVA)
	1st quartile	2nd quartile	3th quartile	4th quartile	
Heart-rate at rest (bpm)	65 ± 14	63 ± 12	60 ± 10	62 ± 10	NS
SBP at rest (mmHg)	151 ± 27	153 ± 24	157 ± 22	144 ± 24	NS
DBP at rest (mmHg)	82 ± 15	79 ± 12	79 ± 10	76 ± 12	NS
Heart-rate at peak (bpm)	106 ± 19	117 ± 23	118 ± 20	135 ± 20	< 0.0001
SBP at peak (mmHg)	194 ± 31	190 ± 31	189 ± 23	197 ± 24	NS
DBP at peak (mmHg)	97 ± 16	90 ± 14	92 ± 9	90 ± 14	NS
Watt at peak exercise	85 ± 27	97 ± 25	121 ± 23	156 ± 37	< 0.0001
RER	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	NS
VO ₂ max (ml/kg/min)	11.8 ± 2.2	16.2 ± 0.9	19.7 ± 1.2	26.2 ± 3.7	
EF rest (%)	65 ± 9	65 ± 10	64 ± 9	61 ± 6	NS
Summed Stress Score	4.4 ± 6.4	3.5 ± 4.8	3.7 ± 4.8	3.6 ± 4.9	NS
Summed Rest Score	2.6 ± 3.7	2.6 ± 3.8	2.9 ± 5.2	2.3 ± 4.2	NS
Summed Difference Score	1.3 ± 3.9	0.9 ± 3.8	0.8 ± 2.8	1.3 ± 2.2	NS

Abbreviations: bpm: beats per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, RER: respiratory exchange ratio, VO₂max: maximal oxygen uptake at peak exercise, EF: ejection fraction

Multivariate determinants of VO₂max.

From the list of significant univariate predictors, the following (patho)physiological variables were selected to enter in a multivariate linear regression model predicting VO₂max: gender, fasting glucose, Log(NT-proBNP), E/E' (representing diastolic function), Sm (representing systolic function) and IL-6 (representing inflammation).

Model fit: R² 0.34 (p<0.0001). The following variables independently predicted VO₂max: gender (β=4.5 p<0.0001), fasting glucose (β=-3.2, p=0.04), E/E' (β=-0.2, p=0.04), Sm (β=1.0, p=0.03) and Log(IL-6) (β=-3.8, p=0.004). If IL-6 was replaced by sTNFr 1 or 2 than these were also independent predictors of VO₂max. Adding to the

model additional basic characteristics that differed between the exercise capacity groups such as diabetes mellitus, hypertension and BMI resulted in a highly significant model: R^2 0.46 ($p < 0.0001$). The following variables independently predicted $VO_2\text{max}$: gender ($\beta = 3.7$ $p < 0.0001$), BMI ($\beta = -0.5$ $p < 0.0001$), E/E' ($\beta = -0.21$ $p = 0.03$), Sm ($\beta = 1.3$ $p = 0.003$), Log(IL-6) ($\beta = -3.2$ $p = 0.01$).

Table 3: Diastolic function, left ventricular filling pressures and longitudinal myocardial velocities

	Quartiles of $VO_2\text{ max}$				p (ANOVA)
	1st quartile	2nd quartile	3th quartile	4th quartile	
E	80.6 ± 22.4	71.3 ± 15.3	74.1 ± 16.6	68.7 ± 17.3	0.04
A	78.3 ± 20.1	82.5 ± 21.8	72.9 ± 13.8	69.9 ± 18.0	0.03
DT	217 ± 55	202 ± 40	203 ± 43	211 ± 57	NS
E/A	1.1 ± 0.5	0.9 ± 0.4	1.0 ± 0.3	1.0 ± 0.3	NS
E'	6.4 ± 1.7	6.5 ± 1.9	7.1 ± 2.0	7.4 ± 1.9	NS
A'	8.1 ± 2.4	9.2 ± 2.8	9.2 ± 2.4	9.0 ± 1.9	NS
E/E'	13.4 ± 4.9	11.8 ± 3.9	11.1 ± 3.4	10.0 ± 3.8	0.005
Sm (cm/s)	4.7 ± 1.0	5.0 ± 0.9	5.2 ± 1.1	5.5 ± 0.8	0.004
Em (cm/s)	5.2 ± 1.6	4.9 ± 1.5	5.6 ± 1.2	6.4 ± 1.5	< 0.0001
Am (cm/s)	5.6 ± 1.8	6.6 ± 1.7	6.3 ± 1.2	6.7 ± 1.5	0.019

Abbreviations: E & A: early and late transmitral flow velocity, DT: deceleration time, E' & A': early and late diastolic (medial) mitral annulus velocity; Sm: average systolic, Em: average early diastolic, Am: average late diastolic myocardial velocity of the basal septal, lateral, inferior and anterior wall

Table 4: Laboratory results

	Quartiles of VO ₂ max				p (ANOVA)
	1st quartile	2nd quartile	3th quartile	4th quartile	
Hematocrit (%)	42.6 ± 3.9	42.3 ± 2.9	43.4 ± 2.9	43.7 ± 2.6	NS
Leukocytes (10 E ³ /μl)	6.9 ± 2.1	6.0 ± 1.2	6.3 ± 1.3	5.8 ± 1.6	0.014
Creatinine (mg/dL)	0.98 ± 0.24	0.97 ± 0.20	1.04 ± 0.19	1.04 ± 0.20	NS
GFR (ml/min/1.73m ²)	74 ± 16	77 ± 16	75 ± 13	78 ± 18	NS
Glucose (g/dL)	1.17 ± 0.33	1.11 ± 0.36	1.03 ± 0.16	0.95 ± 0.13	0.005
Log (hsCRP)	0.32 ± 0.45	0.36 ± 0.40	0.29 ± 0.34	0.25 ± 0.55	NS
Log (NT-proBNP)	2.44 ± 0.44	2.23 ± 0.37	2.22 ± 0.33	2.10 ± 0.37	0.004
Log (IL-6)	0.43 ± 0.31	0.34 ± 0.30	0.29 ± 0.32	0.23 ± 0.32	0.044
Log (sTNFr 1)	0.51 ± 0.16	0.46 ± 0.12	0.41 ± 0.87	0.40 ± 0.12	0.001
Log (sTNFr 2)	0.99 ± 0.16	0.93 ± 0.14	0.88 ± 0.10	0.88 ± 0.14	0.003

Abbreviations: GFR: glomerular filtration rate, hsCRP: high sensitive C reactive protein , NT-proBNP: N-terminal pro-B-type Natriuretic Peptide, IL-6: Interleukin-6, sTNFr: soluble Tumour Necrosis Factor receptor.

DISCUSSION

Exercise capacity is generated through complex interaction between the cardiovascular, respiratory and muscular system. Physiologic conditions (e.g. aging) and pathologic conditions affecting one or more of these systems can lead to impaired exercise capacity. The present study demonstrates among elderly patients with known or suspected CAD and preserved LV function, that VO₂max is not only predicted by tissue Doppler parameters assessing filling pressures and longitudinal systolic function but also by inflammatory markers.

Diastolic function, LV filling pressures and longitudinal global systolic function as predictors of VO₂max

Although many patients with reduced LV systolic function have impaired exercise capacity only weak correlations have been found between traditional markers of global (radial) LV systolic function and exercise parameters. Many reports however, including healthy individuals (3), CAD patients (6) and heart failure patients (4,5), have been published emphasizing the role of diastolic function as an important determinant of exercise intolerance.

Some authors also studied the relation between exercise capacity and estimated LV filling pressure using TDI. Skaluba et al analyzed 121 patients with suspected CAD and normal EF, referred for exercise stress testing. (10) They found E/E' to be the strongest independent predictor of reduced exercise tolerance. A limitation was the indirect evaluation of exercise capacity with metabolic equivalents rather than with spirometry. Studies suggesting a better correlation of diastolic than systolic function with exercise capacity may reflect the insensitivity and load-dependence of EF. Smart et al sought the correlation of more sensitive methods of quantifying systolic and diastolic function and filling pressures. (11) They analyzed 95 patients with congestive heart failure (80% CAD, EF 31±10%) and found that peak VO₂ did not only correlate with diastolic function and E/E' but also with systolic velocities. Witte and co-workers used TDI to study longitudinal ventricular function in 153 patients with chronic heart failure (LVEF<45%) and 87 age and sex matched controls and also found close correlations between systolic myocardial motion and VO₂max. (12) Skaluba et al investigated the relative contributions of LV systolic and diastolic function to maximal exercise capacity in 110 subjects referred for exercise testing. (13) Mitral annular velocities in systole and diastole each correlated

moderately with exercise tolerance. Patients with preserved LV function and reduced exercise capacity had lower systolic and diastolic mitral annular velocities. This suggests, but does not prove, that the longitudinal components of LV contraction and relaxation may be a physiologically important determinant of exercise capacity. Traditional measures of systolic function focus mainly on radial shortening and are insensitive to changes in longitudinal contractile function.

The present study is in agreement with these previous studies and emphasizes the role of both diastolic and systolic function in the prediction of exercise capacity. Even in patients with a preserved LV function TDI detected small differences in longitudinal systolic velocities affecting exercise capacity. The previous studies were limited to evaluating only echocardiographic predictors of exercise capacity; the present study adds information on NT-proBNP and the inflammatory system.

VO₂max and NT-proBNP

Several authors have studied heart failure patients with impaired systolic function and report that brain natriuretic peptide levels are related to peak VO₂. (16, 17, 18, 19). Conraads et al demonstrated that combined endurance/resistance exercise training in patients with stable heart failure and LV dysfunction improved peak VO₂ and reduced NT-proBNP concentrations. (20) Although baseline NT-proBNP levels correlated significantly with VO₂max the observed decrease of NT-proBNP after 4 months training was not related to the increase of VO₂max. The authors suggest that the increased exercise capacity is the result of peripheral adaptations such as a decrease in left ventricular afterload.

In the present study patients with lower VO₂max had higher NT-proBNP levels. In multivariate analysis however NT-proBNP levels did not independently predict exercise capacity in a model including E/E'. This could be related to the fact that levels of NT-proBNP are determined by increased LV wall stress which is in turn related to LV filling pressures and LV function.

VO₂max and inflammation

Data on the relationship between exercise capacity and inflammatory markers, especially circulating, are scarce. Rahimi et al studied 209 patients with established CAD and found an inverse correlation between hsCRP and an estimation of exercise capacity. (21) In the present study hsCRP levels were not significantly different between the VO₂max quartiles. Proinflammatory cytokines however were significantly higher in patients with low exercise capacity and they independently predicted VO₂max in multivariate analysis. Lommi et al studied 58 patients, 44 had heart failure, and found inverse relations between 6 minutes walking distance and sTNFr 2 and IL-6. (22) A potential explanation for the relationship between proinflammatory cytokines and exercise capacity is their involvement in the pathogenesis of skeletal muscle pathology causing deconditioning. Larsen et al studied 15 men (LVEF 33±5 %, VO₂max < 20 ml/kg/min) and evaluated the effect of 3 month aerobic exercise training on muscle fibre distribution, muscle characteristics and the relationship between muscle changes and cytokine levels. (23) Some of the changes in muscle morphometry were weakly correlated to IL-6, suggesting a link between cytokines and skeletal muscle pathology. Conraads and co-workers evaluated cytokines in 23 heart failure patients (EF 27%, 52% CAD) at baseline and

after 4 months exercise training. (24) They found significant correlations between peak VO₂ and TNF α and sTNFr 2. Moreover the training program improved peak VO₂ and diminished cytokines among the CAD patients. These authors suggest that the anti-inflammatory effect of exercise training could reverse the detrimental consequences of heart failure induced muscular adaptations. Whether the link between elevated cytokines and lower exercise capacity in the present study are muscular adaptations is far from proven but is an attractive hypothesis.

LIMITATIONS

A minority of the patients had clinical, electrocardiographic or scintigraphic signs of myocardial ischemia during exercise testing. Ischemia could have influenced exercise results but quantitative perfusion analysis showed no relevant differences regarding reversible myocardial ischemia between the VO₂max quartiles. Pulmonary and muscular function was not evaluated but patients with severe chronic obstructive pulmonary disease and patients with orthopaedic problems limiting exercise were not included. Patients were on optimal medical treatment; ACE-inhibitors, AT-II-receptor blockers and aldosterone antagonists could have influenced the neurohumoral axis; also statin treatment could have influenced inflammatory status. Blood samples were taken on day 2; exercise testing was done one day 1; some studies reported elevation of NT-proBNP as a result of exercise induced ischemia, however the duration of this possible effect has not been evaluated.

CONCLUSION

In patients with known or suspected CAD, VO_2 max was independently determined by inflammatory markers on top of tissue Doppler derived cardiac factors assessing LV filling and longitudinal global systolic function.

ACKNOWLEDGEMENTS

Roche Diagnostics provided NT-proBNP reagent as an unrestricted grant.

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General Discussion and Future Perspectives

GENERAL DISCUSSION

This thesis focuses on the growing patient population of coronary artery (CAD) disease patients with heart failure. Many of these patients survived a myocardial infarction and gradually developed signs and symptoms of heart failure. As it involves an elderly population, often with comorbidities such as diabetes mellitus, pulmonary disease, neurologic deficits, musculoskeletal conditions, it is important to rely on noninvasive techniques for diagnosis, prognostication, therapy choice and follow-up.

Parts 1 and 2 were devoted to the clinical applications of noninvasive imaging techniques. In Part 1 echocardiography was used for diagnostic purposes, in Part 2 we discussed the role of echocardiography, scintigraphy and Multi-slice Computed Tomography in the selection of patients for biventricular pacing. In Part 3 the role of prognosticators such as fasting blood glucose and exercise testing combined with spirometry was emphasized.

In *Part 1* we studied the role of echocardiography as a means to estimate filling pressures noninvasively. Since the original validation in the mid eighties, the peak systolic pressure gradient across a regurgitant tricuspid valve has been increasingly used to estimate right ventricular systolic pressure. More recently, since the introduction of Tissue Doppler Imaging (TDI), the ratio of transmitral early peak velocity (E) over early diastolic mitral annulus velocity (E') was validated as an estimation of left ventricular (LV) end-diastolic pressure. Although both parameters are being used extensively in clinical practice, published data on reference values incorporating the influence of aging were scarce. Therefore, in *Chapter 1.1*, we

studied the effects of aging on the transtricuspid Doppler gradient and on the E/E' ratio in 249 normotensive healthy individuals. We found that both the transtricuspid gradient and the E/E' ratio increased with aging. Moreover linear regression analysis showed that E/E' was an independent predictor of the transtricuspid gradient. Aging is accompanied by an increased vascular loading on the heart, causing a change in LV geometry, an increase in LV mass, slowed ventricular and myocardial relaxation, altered diastolic tone and altered passive myocardial properties. (1) These alterations lead to increased diastolic filling pressures elicited by stress and exercise. (2) When disease and age advance, elevated diastolic filling pressures will even be observed in the resting state. These changes, together with pulmonary alterations, could be responsible for the equivalent increase of right ventricular systolic pressure at older age. The results of our analysis support the need for additional studies in healthy individuals in order to establish age specific reference values. Especially in the old and very old, other (higher) cut-off values should probably be used to identify individuals with pathologically elevated right and left ventricular filling pressures. In *Chapter 1.2* we studied the effects of age, gender and LV hypertrophy on E/E' in normals and in patients with LV hypertrophy due to hypertension. Age was the strongest determinant of E' and E/E' suggesting that both in normals and patients with LV hypertrophy age dependent cut-off values should be taken into consideration. In normals there was also a relationship between gender and E/E'; women had higher values than men across all age groups but the differences were small. The effect of LV mass was only modest after correction for age and gender. Both *Chapters 1.1* and *Chapter 1.2* strongly support the need for age dependent reference values. Using a dichotomic cut-off value for the E/E' ratio was a valid initial step, but not designed to be used in a growing population of older individuals.

After having established reference values, we applied non-invasive estimation of LV filling pressures in a clinical setting. In *Chapter 1.3*, we applied the E/E' ratio in a population of patients with established coronary artery disease and ischemic mitral regurgitation. This form of mitral regurgitation is not caused by a structural defect of the valve itself but by changes in ventricular structure and function related to ischemia and remodeling. It is well known that patients with a more severe degree of ischemic mitral regurgitation have a worse prognosis. We observed a high prevalence of significant mitral regurgitation, especially in CAD patients with a low LV ejection fraction. We were able to show that patients with the highest degree of mitral regurgitation and the lowest ejection fraction had the highest E/E' values. The higher filling pressures in these patients might be associated with a worse prognosis. Further studies are needed to clarify this issue.

Table: E/E' values according to age categories based on Chapters 1.1, 1.2, 1.3

	E/E'		
	Normals	Hypertension + LV hypertrophy	CAD patients
Age category			
< 45 years	7.9 ± 2.0	9.3 ± 2.3	9.5 ± 2.4
45 – 54 years	9.0 ± 2.3	10.5 ± 2.2	11.7 ± 4.0
55 -64 years	10.4 ± 3.2	11.1 ± 3.1	12.6 ± 4.3
65 -74 years	10.5 ± 3.2	12.6 ± 3.9	13.6 ± 4.6
> 74 years	10.9 ± 2.0	13.6 ± 3.9	14.2 ± 4.4

Despite advances in pharmacological treatment, some heart failure patients with ischemic cardiomyopathy remain highly symptomatic. In selected patients Cardiac Resynchronization Therapy (CRT) will improve symptoms, favour reverse

remodelling and reduce cardiac events. If classic selection criteria (NYHA III-IV, broad QRS, poor LV function) are used then up to 30% of the patients with a biventricular pacemaker do not respond favourably. In *Part 2* we applied several noninvasive imaging modalities to help identifying potential responders. In *Chapter 2.1*, using TDI we investigated potential differences between patients with an ischemic and patients with a nonischemic cardiomyopathy. Mechanical activation times were longer in patients with an idiopathic cardiomyopathy. The area of latest mechanical activation in patients with an ischemic cardiomyopathy was most frequently located in the lateral wall whereas in ischemic patients the location was more spread. Our results were recently confirmed by a Magnetic Resonance Imaging study. (3) These findings underscore the importance of an individual approach for every patient. Accepting a “standard” posterolateral LV lead position in every single patient will not automatically result in optimal pacing in some CAD patients.

Not all heart failure patients have an impaired systolic function. In *Chapter 2.2* we report on the prevalence of mechanical dyssynchrony in heart failure patients with a preserved LV function. We found that the prevalence of mechanical dyssynchrony in these patients is generally low. However, in the subgroup of heart failure patients with a preserved LV function and a wide QRS, the prevalence of mechanical dyssynchrony was as high as in patients with a broad QRS and poor LV function. Further studies are needed to investigate the potential role of biventricular pacing in heart failure patients with a preserved LV systolic function.

In *Chapter 2.3* we used a scintigraphic technique to describe the prevalence of nonviable tissue in CRT candidates and found that 30% of these patients have no

viable tissue in the inferolateral wall. Recently Bleeker et al found similar results, using Magnetic Resonance Imaging. (4) Since nonviable tissue is electromechanical nonfunctional, placement of the LV lead in this area could lead to ineffective pacing. Based on *Chapters 2.1 and 2.3* we proposed a triad of questions that has to be answered before referring a highly symptomatic heart failure patient with ischemic cardiomyopathy and broad QRS for CRT implantation; First what is the area of latest mechanical activation? TDI will provide an answer. Second: does the area of latest mechanical activation contain viable tissue? Nuclear imaging techniques or MRI will answer this question. But even if the area of latest mechanical activation is viable than implantation of an LV lead will only be successful via the transvenous approach if this target area is drained by a suitable cardiac vein. So the third question to be answered is: what about cardiac venous anatomy?

In *Chapter 2.4* we provide an answer using another noninvasive imaging modality: Multislice Computed Tomography (MSCT). We demonstrated that patients with a history of a myocardial infarction were less likely to have a Left Marginal Vein. We also showed that 64 MSCT is an ideal tool to depict the cardiac veins noninvasively, at the outpatient clinic. If no suitable tributary of the Coronary Sinus is demonstrated with MSCT than a surgical approach could be more successful than the endocardial technique to insert the LV pacemaker lead.

In Part 3 we switch from noninvasive evaluation with imaging modalities to noninvasive prognosticators such as fasting blood glucose and exercise testing combined with spiroergometry. Exercise testing can be used as a diagnostic tool to detect ischemia and arrhythmia but if combined with spirometry it also offers

important information on the patients' functional status and prognosis. Moreover it is an objective tool to evaluate the effect of therapeutic interventions.

In this part of the thesis we tried to gain insight in some of the determinants of exercise capacity as evaluated with spirometry in a clinical setting. It is widely accepted that patients with diabetes mellitus have a worse prognosis. In *Chapter 3.1* we showed that in patients with coronary artery disease, heart failure and a poor left ventricular ejection fraction, diabetes patients had indeed the worst prognosis but patients with fasting blood glucose levels between 110 and 126 mg/dl (impaired fasting glucose) also had a less favourable prognosis compared to patients with fasting blood glucose levels < 110 mg/dL. This underscores the recent observations that there is a spectrum of patients from normoglycaemic to diabetes mellitus patients and that the risk for cardiovascular events increases gradually along this spectrum along with the fasting blood glucose levels.

Exercise performance is the result of interaction between the cardiovascular, pulmonary and musculoskeletal systems. Attempts to correlate the most widely used parameter of LV systolic function, LV ejection fraction, have found only weak correlations between $VO_2\text{max}$ and ejection fraction. More recently several authors have reported significant correlation between exercise capacity and more sensitive markers of LV systolic function reflecting longitudinal suction: TDI derived systolic velocities. Exercise capacity is also determined by diastolic parameters, including E/E' . In pathological conditions, neurohormones such as NTproBNP and inflammation could also have an effect on $VO_2\text{max}$. In *Chapter 3.2* we investigated the role of inflammatory markers and NTproBNP (on top of TDI derived markers of

systolic and diastolic function) on the exercise capacity of coronary artery disease patients with a preserved LV systolic function. Even in patients with a normal ejection fraction, small differences in longitudinal suction as evaluated with sensitive TDI techniques had an influence on exercise capacity. Longitudinal myocardial velocities, E/E', fasting blood glucose and inflammation were all independently associated with VO₂max in these patients.

FUTURE PERSPECTIVES

In an era of subspecialisation (5,6), increasing invasive cardiologic interventions and growing numbers of device implantations, the future 's looking bright for a novel subspeciality within cardiology: that of the noninvasive cardiology. (7) Emerging technologies such as high-end echocardiographic platforms (including tissue Doppler and 3D applications), gated SPECT, PET, multidetector row CT and MRI allow noninvasive evaluation of cardiac function and structure. The integration of these imaging modalities into clinical cardiologic practice requires specific training and close collaboration between cardiologists, radiologists and specialists in nuclear medicine. (8) The noninvasive cardiologist working in a large cardiovascular center will have to keep up the pace with several novel imaging modalities that will be introduced into clinical practice:

- Multi-modality imaging and fusion imaging such as PET-CT and SPECT-CT allow a combined evaluation of structure and function. PET-CT for instance could be used in the selection of CRT patients to evaluate viability in the area of latest mechanical activation and to identify a suitable cardiac vein for LV lead implantation. SPECT-CT might facilitate the decision to treat a stenosis in a specific coronary artery if associated ischemia is demonstrated (9,10).

- Noninvasive targeted molecular imaging will allow us to directly track biochemical processes and signalling events that precede the pathophysiological changes of e.g. atherosclerosis. (11)
- High- end echocardiographic platforms that have the size of a notebook are becoming commercially available. These small portable echomachines will have all features including Tissue Doppler Imaging. Measuring the E/E' value in the emergency department, outpatient clinic or at the ward will be just as easy as using a stethoscope. (12)
- Three-dimensional echocardiography will improve the accuracy to calculate left and right atrial and ventricular dimensions, mass and ejection fraction. (13)
- Contrast media, especially developed for cardiac purposes, will allow a more sensitive analysis of regional wall motion abnormalities, a reliable identification of intracardiac thrombi and evaluation of myocardial perfusion

Combining cardiovascular imaging modalities with exercise testing will also be the responsibility of the noninvasive cardiologist. Some pathologic cardiovascular conditions are not present at rest but become detectable during stress. The most physiologic way of stressing the heart is exercise. Bicycle or treadmill testing combined with gated SPECT is being used routinely in many centers to increase sensitivity and specificity of standard exercise testing to detect ischemia. Recently semi-supine exercise echocardiography has also gained interest, especially for the evaluation of dynamic mitral regurgitation in patients with coronary artery disease. (14) Other indications of semisupine exercise echocardiography might include other valvular lesions and hypertrophic cardiomyopathy to evaluate dynamic intraventricular gradients. A recent publication validates the use of E/E' to estimate

LV filling pressures during exercise. (15) Using spirometry in all patients referred for stress testing combined with imaging will provide new insights in the pathophysiology of exercise intolerance and introduce novel markers that allow a better prognostification of patients unable to reach a true maximal exercise.

The real challenge for the clinical and noninvasive cardiologist will be about making the right choices. Working as a gatekeeper, it will be his responsibility to select the most appropriate technique to unravel a patients' problem and to propose a valid treatment option, within the technological boundaries of a specific hospital setting. To achieve this goal he will combine "old fashion" clinical skills and knowledge on the latest state-of-the-art noninvasive evolutions. Finally, it will require a lot of flexibility and creativity to reach these goals within a cost-effective manner.

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Summary

Aging is accompanied by structural and functional cardiac changes that are reflected by echocardiographic parameters. Left ventricular end-diastolic pressure, estimated with the E/E' ratio and right ventricular systolic pressure, estimated with the transtricuspid regurgitation gradient, increase in older subjects. Age appears to be strongest determinant of E' and E/E' whereas the effects of gender and left ventricular hypertrophy are only moderate. These findings support the need for age specific reference values and cut-off values. In coronary artery disease patients, the E/E' ratio is determined by the degree of left ventricular systolic dysfunction and by the severity of mitral regurgitation. Ischemic mitral regurgitation is frequently observed in patients with an ischemic cardiomyopathy; patients with poor LV systolic function and mitral regurgitation grade III-IV have the highest E/E' value.

If classic criteria (poor LV function, broad QRS, NYHA III-IV) are used to select heart failure patients for cardiac resynchronization therapy, than the success rate is only 70%. The answers to a triad of additional questions, especially in patients with an ischemic cardiomyopathy, might increase the number of responders. First, using tissue Doppler imaging, the degree of intraventricular dyssynchrony and the region of latest mechanical activation has to be determined. In patients with an ischemic cardiomyopathy this area is not always the lateral wall as in patients with an idiopathic cardiomyopathy. Almost 50% of patients with an ischemic cardiomyopathy and broad QRS have significant intraventricular dyssynchrony but also half of the patients with preserved LV function and broad QRS have significant asynchrony. Second, viability of myocardial tissue has to be evaluated. Using SPECT, 30% nonviable tissue was observed in the inferolateral wall of CRT candidates with CAD. Third, when an area of latest mechanical activation containing viable tissue is

identified then transvenous positioning of the LV lead will only be possible if a suitable cardiac vein is present. Multi-slice Computed Tomography allows noninvasive evaluation of the cardiac venous system. Knowledge on the cardiac veins is especially important in CAD patients with a history of myocardial infarction because patients with anterolateral infarctions are often missing the left marginal vein.

Nondiabetic patients with an ischemic cardiomyopathy have a worse prognosis if their fasting blood glucose levels are between 110 and 126 mg/dL compared to normoglycemic patients. In patients with a preserved LV systolic function, exercise capacity is not only predicted by fasting blood glucose but also by E/E', longitudinal strain and biomarkers representing inflammation.

Samenvatting

Verouderen gaat gepaard met structurele en functionele cardiale veranderingen die gereflecteerd worden door echocardiografische parameters. De linker ventriculaire (LV) einddiastolische druk, geschat met de E/E' waarde, en de rechter ventriculaire systolische druk, geschat met de gradient over een lekkende tricuspidalisklep, nemen toe bij oudere individuen. Leeftijd blijkt de belangrijkste determinant te zijn van E' en E/E' terwijl de effecten van geslacht en linker ventrikelhypertrofie eerder bescheiden zijn. Deze bevindingen ondersteunen de noodzaak tot leeftijds-specifieke referentie-waarden en drempelwaarden. Bij patiënten met coronair lijden, wordt de E/E' verhouding bepaald door de ernst van de linker ventriculaire dysfunctie en de ernst van de mitralisklepinsufficiëntie. Ischemische mitralisklepinsufficiëntie wordt frequent gevonden bij patiënten met een ischemische cardiomyopathie; patiënten met een slechte LV functie en mitralisklepinsufficiëntie graad 3-4 hebben de hoogste E/E' waarde.

Indien klassieke criteria (slechte LV functie, breed QRS, NYHA III-IV) worden gebruikt om hartfalen patiënten te selecteren voor cardiale resynchronisatietherapie dan is het slaagpercentage slechts 70%. De antwoorden op een drietal bijkomende vragen, voornamelijk bij patiënten met een ischemische cardiomyopathie, kunnen het aantal responders doen toenemen. Ten eerste kan gebruik makende van tissue Doppler imaging, de ernst van intraventriculaire dyssynchronie en de regio van laatste mechanische activatie worden bepaald. Bij patiënten met een ischemische cardiomyopathie is dit niet altijd de laterale wand zoals bij patiënten met een idiopatische cardiomyopathie. Bijna 50% van de patiënten met een breed QRS hebben significante dyssynchronie maar ook de helft van de patiënten met bewaarde LV functie en breed QRS hebben significante asynchronie. Ten tweede dient de

viabiliteit van het myocard te worden geëvalueerd. Gebruik makende van SPECT, werd 30% niet-viabel weefsel geobserveerd in de inferolaterale wand van CRT kandidaten met coronair lijden. Ten derde, wanneer een viabel gebied dat laatst wordt geactiveerd is geïdentificeerd dan zal transveneuze plaatsing van een LV draad enkel mogelijk zijn indien een geschikte cardiale vene aanwezig is. Multi-slice Computed Tomography laat een niet-invasieve evaluatie toe van het cardiaal veneus systeem. Kennis van de cardiale venen is voornamelijk belangrijk bij coronaire patiënten met een voorgeschiedenis van acuut myocardinfarct omdat bij patiënten met anterolaterale infarcten de linker marginale vene vaak ontbreekt.

Niet-diabetische patiënten met een ischemische cardiomyopathie en een nuchtere bloedsuikerspiegel tussen 110 en 126 mg/dL hebben een slechtere prognose dan normoglycemische patiënten. Bij patiënten met een bewaarde LV systolische functie wordt de inspanningscapaciteit niet alleen bepaald door de bloedsuiker spiegel maar ook door E/E' , longitudinale suctie en inflammatie markers in het bloed.

List of publications

A1 Publications

1. Relationship between arterial elasticity indices and carotid artery intima-media thickness.

D. Duprez, M. De Buyzere, T. De Backer, **N. Van de Veire**, D. Clement, J. Cohn
Am J Hypertens 2000; 13: 1226-1232

2. Decreased carotid artery distensibility as a sign of early atherosclerosis in viscose rayon workers.

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3. Vascular changes in workers exposed to carbon disulfide

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4. Images in cardiology: coincidental diagnosis of a myxoma during abdominal ultrasound.

N. Van de Veire, A. Heyse, D. Vanhercke
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5. Role and limitations of cardiac time intervals.

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6. Global and regional parameters of dyssynchrony in ischemic and non-ischemic cardiomyopathy.

N. Van de Veire, J. De Sutter, G. Van Camp, P. Vandervoort, P. Lancellotti, B. Cosyns, P. Unger, T.C. Gillebert
Am J Cardiol 2005 95; 421-423

7. Effects of age, gender and left ventricular mass on septal mitral annulus velocity (E') and the ratio of transmitral early peak velocity to E' (E/E')

J. De Sutter, J. De Backer, **N. Van de Veire**, A. Velghe, M. De Buyzere, TC Gillebert
Am J Cardiol 2005;95:1020-1023

8. Prevalence of mechanical dyssynchrony in patients with heart failure and preserved left ventricular function. (a report from the Belgian Multicenter Registry on Dyssynchrony)

J. De Sutter, **N. Van de Veire**, L. Muyldermans, T. De Backer, E. Hoffer, M. Vaerenberg, B. Paelinck, P. Decoodt, L. Gabriel, T. Gillebert, G. Van Camp
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9. Incremental prognostic value of combined perfusion and function assessment during myocardial gated SPECT in patients aged 75 years or older.

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J Nucl Cardiol 2005; 12: 662-670

10. Relationship between QRS duration, left ventricular volumes and prevalence of nonviability in patients with coronary artery disease and severe left ventricular dysfunction.

O. De Winter, **N. Van de Veire**, F. Van Heuverswijn, G. Van Pottelberge, TC. Gillebert, J. De Sutter
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Int J Cardiovasc Imaging, 2006, March 16 (Epub ahead of print)

12. Coronary risk factors and inflammation in patients with coronary artery disease and internal cardioverter defibrillator implants.

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14. Diabetes and impaired fasting glucose as predictors of morbidity and mortality in male coronary artery disease patients with reduced left ventricular function.

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Nucl Med Com, 2006; 27: 529-534

19. Prospective evaluation of the oxygen uptake efficiency slope as a submaximal predictor of peak oxygen uptake in older patients with ischemic heart disease
C. Van Laethem, **N. Van de Veire**, J. Bartunek, G. De Backer, M. Goethals, J. De Sutter, M. Vanderheyden.

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20. Maximum oxygen uptake at peak exercise in elderly patients with coronary artery disease and preserved left ventricular function: The role of inflammation on top of tissue Doppler derived systolic and diastolic function.

N. Van de Veire, O. De Winter, J. Philippé, M. De Buyzere, D. Bernard, M. Langlois, TC Gillebert, J. De Sutter

Am Heart J 2006; 152: 297.e1-297.e7

21. Neurohumoral and inflammatory activation in coronary artery disease patients treated with statins.

N. Van de Veire, J. Philippé, O. De Winter, M Langlois, D Bernard, J. De Sutter
Heart 2006 ; accepted for publication

22. VE/VCO₂-slope and Oxygen Uptake Efficiency Slope in patients with coronary artery disease and intermediate peakVO₂

N. Van de Veire, C. Van Laethem, J. Philippé, O. De Winter, G. De Backer, M. Vanderheyden, J. De Sutter

Eur J Cardiovasc Prev Rehab, accepted for publication

23. Noninvasive evaluation of the cardiac venous system in coronary artery disease patients using 64-slice Computed Tomography

N. Van de Veire, J. Schuijff, J. De Sutter, D. Devos, A. de Roos, E. van der Wall, M Schaliij, J. Bax

J Am Coll Cardiol 2006; accepted for publication

24. Intra- and interatrial asynchrony in patients with heart failure.

K. Van Beeumen, M. Duytschaever, R. Tavernier, **N. Van de Veire**, J. De Sutter
Am J Cardiol 2006, accepted for publication

25. Triplane tissue Doppler imaging to evaluate mechanical dyssynchrony before and after cardiac resynchronization in a patient with congenitally corrected transposition of the great arteries.

N. Van de Veire, N. Blom, E. Holman, M. Schaliij, J. Bax

J Cardiovasc Electrophys 2006; accepted for publication

26. Optimal use of echocardiography in cardiac resynchronization therapy

G. Bleeker, C.M. Yu, P. Nihoyannopoulos, J De Sutter, **N Van de Veire**, E Holman, M Schaliij, E. van der Wall, JJ Bax

Heart, accepted for publication

A2 Publications

1. Right sided endocarditis: Tempus fugit! A case report.

N. Van de Veire, A-K Ascoop, M. De Pauw, J. De Sutter, TC Gillebert
Eur J Echocard 2006; 7: 235-238

A3 Publications

1. Intima-media dikte: een morfologische screeningsparameter voor cardiovasculair risico

N. Van de Veire, T. De Backer, D. Duprez, M. De Buyzere, D.L. Clement
Tijdschr. voor Geneeskunde 1999; 55: 1137-1142

2. Therapeutisch beleid bij arteria-carotisstenose: medicamenteuze of heelkundige aanpak?

N. Van de Veire, D. Duprez, M. De Buyzere, D.L. Clement
Tijdschr. voor Geneeskunde 2001; 57: 490-496

A4 Publications

1. Verslag van het symposium van de Young Cardiologists' Club op de 24ste Wetenschappelijke Vergadering van de Belgische Vereniging voor Cardiologie

N. Van de Veire
Tijdschr Cardiol 2005;17:44-47

Bookchapters

Role of echocardiography before CRT implantation, can we predict non-responders?

G. Bleeker, **N. Van de Veire**, M. Schalijs, J. Bax
In Cardioslim 2006, S. Barold, editor, in press

Dankwoord

Dit proefschrift zou nooit tot stand zijn gekomen zonder de hulp en inzet van heel wat mensen. In de eerste plaats wil ik de honderden patiënten bedanken die belangeloos en zonder enige vorm van financiële vergoeding aan een of meerdere studies hebben deelgenomen die aan de grondslag liggen van deze thesis. Het is dankzij deze patiënten dat klinisch wetenschappelijk onderzoek mogelijk wordt; het is ook voor hen dat dit werk werd gerealiseerd.

Prof De Sutter, beste Johan, dat deze thesis na 3 jaar tot een goed einde werd gebracht is voor het grootste deel te danken aan de onderzoekslijn die door jou de voorbije jaren was opgebouwd. De echocardiografische database, de inspanningsfysiologische en nucleaire database, de HF65 plus studie, de Belgische multicenter studie over dyssynchronie, het zijn allemaal projecten die jij hebt opgestart en die een onuitputtelijke bron waren om verschillende wetenschappelijke hypothesen te toetsen. Ik heb jou de voorbije jaren leren kennen als een empathisch arts, een gedreven en integere wetenschapper en een getalenteerd echografist, altijd bereid om je kennis te delen. Je menselijke aanpak, met de nodige dosis relativiseringsvermogen en een gezonde portie humor zorgden steeds voor een aangename werksfeer waarin het onmogelijke mogelijk werd, kortom jij was de ideale promotor.

Prof Gillebert, ik dank U om binnen de Dienst Cardiologie de nodige tijd en ruimte te hebben gecreëerd die mij hebben toegelaten dit onderzoeksproject te realiseren.

Dank aan de medewerkers van het Laboratorium voor Echocardiografie UZ Gent: Dr An-Kristin Ascoop, Dr Julie De Backer en alle verpleegkundigen voor hun inzet; Bart Middernacht en Veronique Moerman, voor de hulp bij het analyseren van de echo-beelden. Verder wil ik alle leden van de Belgian Working Group on Noninvasive Cardiac Imaging danken voor de samenwerking naar aanleiding van de Belgian Multicenter Registry on Dyssynchrony.

Dr Olivier De Winter, het was een plezier om met jou samen te werken. Honderden SPECT's werden door jou vakkundig gescoord en je praktische tips bij het realiseren van abstracts, posters en manuscripten waren bijzonder welkom. Prof Christophe

Van De Wiele, dank voor je adviezen, zowel de nucleaire-geneeskundige als de meer filosofische.

Veel tijd heb ik doorgebracht in het Centrum voor Evaluatie en Revalidatie van Hartlijders o.l.v. Prof Guy De Backer. Tijdens mijn wekelijkse zoektocht naar patiënten kon ik steeds rekenen op de enthousiaste medewerking van Dr Ivan Elegeert, Dr Sofie De Biscop, Dr Anja Velghe (Geriatric) en Dr An-Kristin Ascoop. Ook de receptionistes en de (sociaal) verpleegkundigen (bijzondere dank aan Norma, Annick, Els en Petra) hebben meer dan een steentje bijgedragen.

Lic Marc De Buyzere, samen met Prof Daniel Duprez heb jij mij geïntroduceerd in de wereld van het wetenschappelijk onderzoek. Ik wil je danken voor het streng maar rechtvaardig nalezen van de manuscripten en voor de distributie van de bloedstalen die door de prikploeg werden afgenomen. Prof Jan Philippé en de medewerkers van de dienst Klinische Biologie, UZ Gent wil ik danken voor de bepalingen van de inflammatoire biomarkers, alsook Dr Dirk Bernard en Prof Michel Langlois, AZ Sint Jan Brugge, voor de NT-proBNP en hsCRP bepalingen.

Isabel, jouw nauwgezette follow-up van de HF65plus patiënten roepen alweer nieuwe onderzoeksvragen op die verdere analyse zullen vergen.

De informatica-kennis van Ingenieur Krista Van Vlaenderen zorgde ervoor dat alle databasen op wietjes liepen en “bugs” onmiddellijk werden verholpen.

Linda Packet, dank voor je onmisbare hulp in de wondere wereld van de universitaire administratie. Alleen jij kan het mysterieuze SAP volledig doorgronden!

Prof Bax, beste Jeroen en iedereen op de afdeling hartziekten van het LUMC (afdelingshoofd prof E.E. van der Wall), dank voor de geboden kansen en de onvergetelijke tijd dat ik deel mocht uitmaken van “de tuin” in Leiden. Ik ben er zeker van dat we ook in de toekomst gezamenlijke research-projecten tot een goed einde zullen brengen.

Verder wil ik alle stafleden, collega's assistenten, verpleegkundigen en administratieve medewerkers van de afdeling Hart- en Vaatziekten UZ Gent bedanken voor de "kleine dingen" die me vaak heel hard hebben geholpen om één en ander rond te krijgen.

Dank aan het Fonds voor Wetenschappelijk Onderzoek – Vlaanderen voor het aspiranten-statuut dat mij de financiële mogelijkheid bood onderzoek te verrichten.

De leden van de Examencommissie en in het bijzonder de leden van de Leescommissie, ben ik erkentelijk voor hun inspanningen en suggesties.

Tot slot wil ik mijn ouders danken voor alle kansen die ze mij geboden hebben, de logistieke maar vooral de emotionele steun ook op momenten dat het niet altijd liep zoals gepland. Het doctoraat is nu klaar, nu nog even cardioloog worden ...

Leiden, september 2006

Curriculum Vitae

The author of this thesis was born on June 23th 1975 in Ghent, Belgium. His Latin-Sciences secondary school certificate was obtained at Sint-Lievenscollege Gent in 1993. He studied medicine at the Faculty of Medicine and Health Sciences of Ghent University and became a Bachelor of Medicine in 1996, *maxima cum laude*. In 1997, he followed an intensive Erasmus course on cardiovascular diseases at the Wallenberg Laboratory, Sahlgrenska University Hospital, Göteborg University, Sweden. He earned his Medical Degree, *summa cum laude*, in 2000. His training in Internal Medicine started in 2000. Residencies in general internal medicine, cardiology, gastroenterology, pneumology, and nephrology were completed at AZ Sint-Elizabeth Zottegem, AZ Sint-Lucas Ghent and the University Hospital Ghent. Since October 2003 he started training in Cardiology. As a student he performed research at the Department of Cardiovascular Diseases of the University Hospital Ghent (Prof dr D. Duprez and Prof dr D.L. Clement). In September 1998 he won the Poster Award at the Joint Scientific Meeting of the Dutch and Belgian Society of Hypertension, Mondorf, Luxemburg. Between October 2003 and September 2006 he was a Research Assistant of the Fund for Scientific Research – Flanders (F.W.O.-Vlaanderen) and conducted clinical research at Ghent University (supervisors Prof dr J De Sutter and Prof dr TC Gillebert). Topics of interest included clinical applications of non-invasive cardiac imaging modalities, exercise physiology and biomarkers in elderly heart failure patients with coronary artery disease. In October 2004 he was awarded a Travel Grant from the Young Cardiologists' Club of the Belgian Society of Cardiology and in October 2005 he won the YCC award for his work on the echocardiographic evaluation of mechanical dyssynchrony. Between January 1st 2006 and September 30th 2006 he was a research fellow at the Department of Cardiology, Leiden University Medical Center, The Netherlands (Head: Prof dr E.E. van der Wall). In Leiden he performed research in the field of noninvasive cardiac imaging modalities (supervisor Prof dr J.J. Bax) including 3-D echocardiography, tissue Doppler applications and Multislice Computed Tomography. In April 2006 he was awarded the Poster Price (First Price) at the Spring Meeting of the Dutch Society of Cardiology for his work on cardiac veins using MSCT. Between October 2006 and March 2008 he will complete his training as a cardiologist at the University Hospital Ghent.

