

The importance of long axis function

-an echocardiographic study with respect to ageing,
response to treatment, prediction of survival
and effect of warm water immersion

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*“Erfaring er ikke hva som hender oss,
men hva vi gjør med det som hender oss”*

Aldous Huxley

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Abstract

Echocardiographic M-mode measurement of atrioventricular plane displacement (AVPD) and determination of annular velocity with Tissue Doppler imaging (TDI) is a reliable method to gauge ventricular long axis function for quantification of myocardial contractility and relaxation.

The aim of this thesis was to increase the understanding of the importance of long axis function with respect to ageing, response to pharmacological treatment, prediction of survival, and enhanced load condition caused by warm water immersion.

In 82 healthy subjects, we observed a decrease in systolic and diastolic long axis function with advancing age, whereas short axes function remained unchanged. A remodelling of the heart towards a more spherical shape was associated with age, and was also shown to be more pronounced in female subjects.

In 24 patients with dilated cardiomyopathy, we demonstrated a significant recovery of left ventricular systolic and diastolic long axis function after 6 months of treatment with the β_1 -adrenoceptor antagonist metoprolol. The improvement was observed both at rest and during pharmacological stress. The relative improvement at rest in the long axis function was 38%, compared with 20% in left ventricular ejection fraction (biplane Simpson).

In a multivariate regression analyse we found, in 228 patients with chronic heart failure, that systolic long axis function was an independent predictor of 10-year survival.

Acute immersion in warm water caused favourable hemodynamic effects in 18 patients with chronic heart failure. Despite increased preload, long axis function improved in both chambers, most likely caused by a combination of reduced heart rate and decreased afterload. Further, we observed in 12 of these patients, that repeated exposure to increased preload (8 weeks of hydrotherapy twice times weekly) was well tolerated.

In summary, these results emphasise that observation of long axis function give information about cardiac function that is not readily available in conventional measurements. Also, registration of long axis function appears to be superior to detect minor ventricular changes.

Svensk sammanfattning

Under en människas liv pumpar hjärtat drygt 2,5 miljarder gånger utan att vila. Kontraktionen (systolisk funktion) och relaxation (diastolisk funktion) sker genom samverkan mellan olika hjärtmuskelfibrer. Dessa fibrer har olika riktningar och medför att hjärtat rör sig i en kramande, längsgående och samtidigt roterande rörelse. Med tekniker så som t.ex. ultraljud och Doppler kan den systoliska och diastoliska funktionen bedömas.

Fokus i denna avhandling har varit att studera betydelsen av hjärtats funktion i längsaxeln, som speglar funktionen i de innersta muskelfibrerna i hjärtat, och jämföra denna funktion med den mer välstuderade kramande rörelsen i kortaxeln (ejektionsfraktionen=EF). Både friska individer och patienter med kronisk hjärtsvikt har undersökts.

Hos friska individer observerade vi att både diastolisk och systolisk längsaxel funktion reduceras med åldern, medan EF var oförändrad.

Patienter med hjärtsvikt förbättrade sin längsaxel funktion betydligt efter behandling med betablockerare och i större grad än EF.

Vidare fann vi att mätning av den systoliska längsaxel funktionen var den bästa prediktorn för överlevnad hos patienter med hjärtsvikt.

I en studie noterade vi att hjärtsviktpatienter mår bra av att träna i varmt vatten, trots att det hydrostatiska trycket bidrar till ökad volymsbelastning på hjärtat. Jämfört med förhållande på land sågs bland annat en tydlig förbättrad längsaxel funktion, något som kan förklara varför patienterna mår bra i vattnet.

Resultaten i denna avhandling betonar att längsaxel funktionen bidrar till information som inte är tillgänglig i traditionella mätningar. Funktionen i längsaxeln kan upptäcka små förändringar i hjärtat och uppvisar ett starkt samband med mortalitet. Förståelsen av hjärtats funktion och sjukdomar kan därför fördjupas om sådana mätningar utnyttjas rutinmässigt.

List of papers

List of papers

This thesis is based on following five papers, which will be referred to by their Roman numerals:

- I. Gender and age related differences in left ventricular function and geometry with focus on the long axis. Grüner Sveälv B, Fritzon G, Andersson B. *Eur J Echocardiogr.* 2006 Aug;7(4):298-307.
- II. Pronounced improvement in systolic and diastolic ventricular long axis function after treatment with metoprolol. Grüner Sveälv B, Scharin Täng M, Waagstein F, Andersson B. *Eur J Heart Fail.* 2007 Jun-Jul;9(6-7):678-83.
- III. Ventricular long axis function is of major importance for long-term survival in heart failure patients. Grüner Sveälv B, Lavik Olofsson E, Andersson B. *Heart.* 2008;94:284-9.
- IV. Warm water immersion improves biventricular function in heart failure patients. Grüner Sveälv B, Cider Å, Scharin Täng M, Angwald E, Kardassis D, Andersson B. *Submitted.*
- V. Exposure of enhanced venous return and preload during hydrotherapy are well tolerated in patients with chronic heart failure. Grüner Sveälv B, Cider Å, Scharin Täng M, Angwald E, Kardassis D, Andersson B. *In manuscript.*

Abbreviations

Abbreviations

AF	Atrial fibrillation
AVP	Atrioventricularplane
B-AR	β -adrenergic receptor
CHF	Chronic heart failure
CO	Cardiac output
CR	Contractile reserve
DSE	Dobutamine stress echocardiography
TDI	Tissue Doppler imaging
EF	Ejection fraction
FS	Fractional shortening
DCM	Dilated cardiomyopathy
LAX	Long axis
LV	Left ventricle
LVEDFV	Left ventricular early diastolic filling velocity
LVOT	Left ventricular outflow tract
MAP	Mean arterial pressure
M-mode	Motion-mode
MV	Mitral valve
PCWP	Pulmonary capillary wedge pressure
PWD	Pulsed wave Doppler
PV	Pulmonary vein
RV	Right ventricle
SAX	Short axis
SBP	Systolic blood pressure
SV	Stroke volume
SVR	Systemic vascular resistance
TV	Tricuspid valve
TVTI	Tissue velocity time integral
VTI	Velocity time integral

Introduction

The history of echocardiography

The development of non-invasive methods to investigate the heart is attributed to the Swedish physician Inge Edler and his co-worker Carl Helmuth Hertz. In early 1953, these two pioneers discussed the possibility of using ultrasound to assess heart function [1]. Edler was then working at the University Hospital in Lund and responsible for deciding which patients qualified for surgery to treat combined mitral valve disease. Hertz developed a camera that could display the motion mode (M-mode) of echo signals, and the first echocardiogram (or ultrasoundcardiogram as it was then known) was performed on 29 October 1953. Edler's work inspired new innovations in the field, and more than 25 million echocardiographic investigations are now performed worldwide each year using high-technological ultrasound machines [2].

Dilated cardiomyopathy (DCM)

Echocardiography appears to be the most helpful tool to diagnose different forms of myocardial disease such as dilated cardiomyopathy (DCM).). DCM is the cause of heart failure in approximately 20 % of all cases, a disorder characterized by impaired ventricular function Left ventricle (LV) is often more impaired than right ventricle (RV), and the ventricles, LV mostly, are dilated. Autoimmune reaction, infection and inflammation have been recognized in patients with DCM [1]. It has been suggested that various viruses play a role in the pathogenesis of idiopathic DCM and the dominating virus has been found to be parvo virus [2] and coxsackie virus [3].

The world health organization has defined DCM into two different forms [4]: idiopathic when the reason for heart disease is unknown, and ischemic in case of infarction and/or coronary artery stenosis.

The disadvantage of a driven heart

During a human life, the heart muscle beats more than two and a half billion times without rest. Even if this function is impaired, this tirelessly muscle always tries to satisfy the demand of blood to the body. In order to maintain an adequate cardiac output, despite a fatigued heart, an unfavourable mechanism leads to an increased

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neurohormonal activation [5] and this will eventually lead to an impaired ventricular function [6]. Neurohormones have been shown as powerful predictors of morbidity and mortality in patients with chronic heart failure [6-8]. Drug therapy aim to prevent the neurohormonal activation and to control fluid balance. Beta-adrenoreceptor (β -AR) antagonists have demonstrated significant reduction in morbidity and mortality [9, 10], probably caused by improvement in systolic and diastolic function [11] and reduction of LV volumes [12-14]. Beta blockers decrease the level of neurohormones [15] and preserve the sensitivity of the β -AR [16], leading to improvement in left ventricular function [17-20]. The positive effects of beta blockers regarding a decline in auto antibodies against cardiac receptors [21], is a factor that could play role in treatment of heart failure. Treatment such as angiotensin receptor blockers or angiotensin converting enzyme inhibitors is given in order to block the renin angiotensin aldosterone system [22]. The renin angiotensin aldosterone system causes vasoconstriction and increased salt and water retention [23].

Exercise

Exercise is an important complement to medical treatment, to prevent and reduce symptoms, improve functional capacity [24], lower the morbidity [25] and mortality [26, 27]. Physical inactivity contributes to many metabolic alterations (Figure 1), and is recognized as a factor for cardiovascular risks. However, regular exercise is required to maintain the positive effect [28]. It has also been suggested that physical exercise could replace percutaneous transluminal coronary angioplasty since both interventions improved myocardial perfusion Kendziorra, 2005 #286}.

Introduction

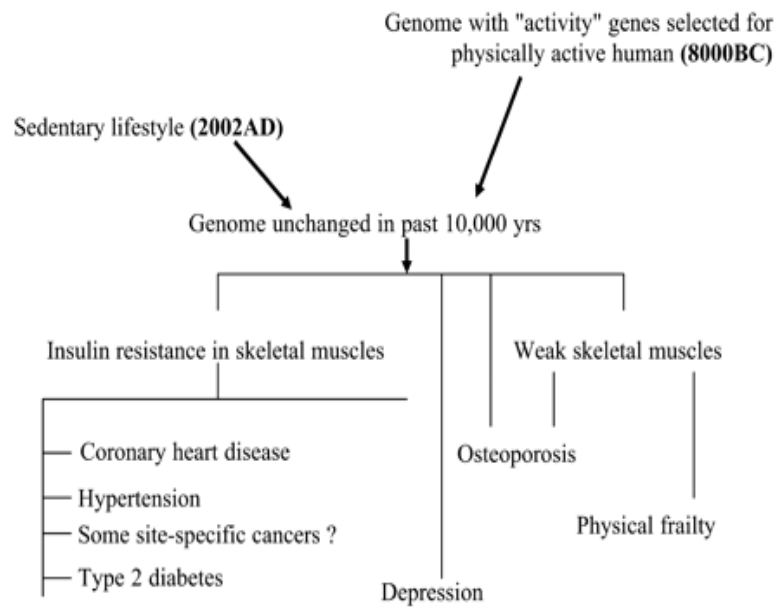


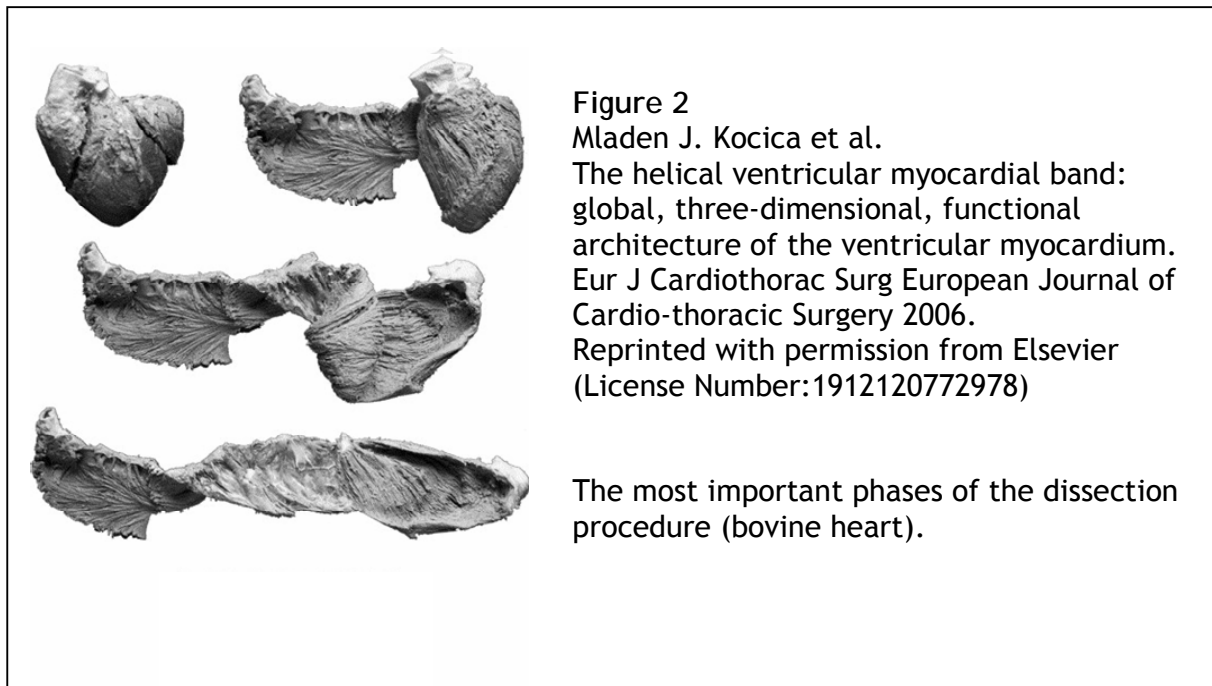
Figure 1. Frank W. Booth et al. *“Waging war on physical inactivity: using modern molecular ammunition against an ancient enemy”*
J Appl Physiol 2002. Reprinted with permission from J Appl Physiol.

Hydrotherapy

Since exercise has been shown as an independent cardio protective factor [28], it is of immense importance to offer suitable individually prescribed exercise. Hydrotherapy, exercise in warm water, (34°C), is an opportune exercise form [29] for patients suffering from disabilities that make exercise on land difficult. Whole body immersion cause, due to the hydrostatic pressure, a shift of blood from the periphery to the intrathoracic circulation, and due to this increased venous return by hydrostatically induced volume shift, it has been questioned if hydrotherapy is an appropriate exercise form for patients with chronic heart failure (CHF) [30]. The stretching of cardiac myocytes prior to contraction represents the preload of the heart. An increase in end-diastolic volume consequently increases preload. Warm water immersion (WWI) will result in vasodilatation caused by relaxation of the smooth muscle in the vessel wall. This will be followed by a decrease in peripheral resistance which might result in decreased afterload. Also renal vascular resistance will decline and suppress the renal sympathetic nerve activity leading to increased renal plasma flow [31, 32] and increase in diuresis. Supporting this statement, we and other research groups [33-36] have found beneficial acute hemodynamic effects in patients with CHF during WWI.

The myocardial band

The architectural organisation of the heart muscle are twofold, both complex, but also very simple and elegantly constructed. The heart is represented by a single ventricular myocardial band [37]. By unfolding this twisted band, the aortic and pulmonal valve will compose the beginning and the end of the band, see Figure 2. Contraction and relaxation of co-operating fibres located in different layers of this twisted band constitute an important mechanism for the ventricular function. Commonly, three different myocardial layers are considered to be distinguished through the ventricular mass. Since the heart consists of one single band [38, 39], the separations of these three layers are gradual with no cleavage. Subepicardial fibres are arranged in an oblique direction, middle layer in a more transversal direction, and deep subendocardial layers in a longitudinal direction [40]. Collaboration of abovementioned muscle fibres compose the systolic and diastolic ventricular function in a combined action of shortening and lengthening of these different muscle fibres [41, 42].



Assessment of ventricular function

Today, ventricular function can be assessed with several non invasive techniques. Single-photon emission computed tomography is a feasible method to get information about myocardial perfusion, left ventricular function and volumes [43]. Magnetic resonance imaging is, without doubt, a unique non-invasive technique with excellent spatial resolution that allows assessment of the cardiac anatomy, perfusion, function and metabolism [44, 45]. Two-dimensional echocardiography (2D) is recommended for volume determination and to assess LV remodelling with the biplane Simpson´s method [46]. Nevertheless, all methods have disadvantages, both single-photon emission computed tomography and magnetic resonance imaging are expensive and time consuming. 2D echocardiographic method needs good image quality in order to outline the endocardial border and to evaluate ejection fraction (EF) and volumes.

Earlier evaluation of longitudinal ventricular function

In 1932, Hamilton and Rompf [47] studied the movements of the basal parts of the heart. The hearts in centre of attention were from frogs, turtles and dogs. In all three animals they observed that the base of the heart moves downward to the

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apex during systole and that apex remained almost stationary. As already mentioned, Edler was the first physician to identify and record the mitral valve motion with echocardiography [48]. He inspired Feigenbaum and co-workers [49] to further investigate the motion of the annulus, the ring that connect the leaflets. They identified an ultrasound echo from the mitral ring, and the first description of systolic and diastolic motion of human atrioventricularplane displacement (AVPD) was performed by Zaky, Grabhorn and Feigenbaum.

Longitudinal function

Motion and velocity at any point of the AVP reflect longitudinal contraction or relaxation between the annulus and apex [50], and can be seen as a piston-like movement. The movement of the mitral ring towards the apex in systole increases the volume and decreases the pressure in left atrium, allowing systolic inflow from the pulmonary vein into the left atrium. In diastole, the mitral ring moves towards the atrium. The movement of the mitral annulus towards apex plays a major role in LV long axis (LAX) function and can easily be measured with M-mode technique [51-61]. With the development of newer and relatively preload independent techniques, such as tissue Doppler imaging (TDI) and strain rate, the interest of LAX function has experienced a renaissance [62-70]. More attention has therefore been paid to contraction and relaxation of subendocardial longitudinal muscle fibres in the deep layers [40, 71]. These muscle fibres contribute to shortening of the LAX and were first described by Leonardo da Vinci [72].

Even though 2D recorded LVEF incorporate information on longitudinal shortening, this method is not sensitive enough to detect minor ventricular changes [73, 74].

The valvular apparatus

The movement of the AVP depends on the longitudinal arranged fibres of the papillary muscle and consequently to the condition of the valvular apparatus. The mitral subvalvular apparatus consists of the papillary muscle and chordae. The first order chordae is stiff and prevent leaflet prolapse. The second order chordae is more elastic and play part in the ventricular mechanism and in preservation of LV systolic pump function [75]. Hence, it is of importance to preserve the longitudinal arranged fibres of the papillary muscle when repairing a defective mitral valve.

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The tricuspid valve is constructed in same way as mitral valve and prevents backflow from right ventricle to right atrium during systole. The papillary muscle contract together with right ventricular wall [76]. The tricuspid annular motion is possible to measure [77-79] in the same way as mitral annular motion and the method display low inter- and intraobserver variability [80].

Due to predominately longitudinal and oblique fibres in RV, the motion of RV LAX has higher amplitude and peak velocities compared with LV LAX.

The debate of long and short axis contribution to cardiac pumping

The significance of LAX function begins to be evident, nevertheless, discussions are ongoing about long and short axis contribution for the total LV filling and emptying [81-85]. Carlsson and co-workers [86] have recently found, in an magnetic resonance imaging study, that LAX function is the primary contributor to LV pumping, and accounts for approximately 60% of the stroke volume (SV). The largest differences in epicardial volume, and consequently contribution to SV, was found at the base of the ventricle, in healthy subjects, in athletes and in patients with DCM. However, there are still queries to be answered [87] if LAX function really contribute to that extent.

Response of dobutamine

Inotropic agents, as dobutamine, are given as a temporary support to patients with severe depressed myocardium. Dobutamine is predominately a β_1 adrenergic agonist with α_1 -receptor properties that counteract with β_2 , giving a moderate vasodilatation.

A prerequisite for inotropic support is the presence of contractile reserve (CR). It has been shown, by evaluation CR of AVPD, that myocardial viability in patients with acute myocardial infarction will result in a spontaneous recovery [88]. The response of pharmacological stress with low dose dobutamine on longitudinal function, assessed by tissue Doppler, has been described earlier [89, 90] and healthy subjects show a significant increase in AVPD during low doses of dobutamine [91]. The AVPD has also been shown to be significantly lower in patients compared to controls, while no significant differences were found at peak dobutamine-atropine infusion [92].

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Clinical implications of long axis function.

The correlation between the AVPD and traditional echocardiographic methods in evaluating systolic function has been found acceptable with good reproducibility both between inter- and intra observer [54, 93].

Patients with CHF show significant reduced AVPD compared with healthy subjects. Alam and Höglund [54] demonstrate a close correlation between AVPD and LVEF, and that an AVPD less than 7 mm reflects a severe depressed LV function (EF<30%). Mortality increases with depressed AVPD [57], and give important information about the condition of the LV [60, 94, 95].

Besides recording of systolic motion, diastolic function can be obtained [55, 96]. It has been demonstrated that the diastolic improvement during titration with a selective β_1 - receptor blocker, metoprolol, turn out to be more prominent and it was possible to observe improvement already after the first dose of treatment, while systolic recovery appears later [73]. Consequently, detection of early therapeutic effects can be obtained by using this technique. Henein et al [41, 42, 68, 97-102], have in several articles described the abnormal pattern and disturbance in timing of the AVPD in patients with heart failure, and that disturbed LAX function is a sensitive indicator of a pathophysiological function [103].

Exercise increases the displacement in healthy subjects, while patients with coronary artery disease show a decrease in displacement that correlates with the location of the stenosis [61]. Furthermore, coronary revascularisation increases the AVPD [91, 97] and patients with atrial fibrillation (AF) [104] improve their LAX function with 57% after electrical cardioversion [105].

However, it should also be noticed that varying results in previous studies indicates that longitudinal function is not a mirror of circumferential or global LV function [106, 107, 108]. A nonlinear relation between circumferential midwall and longitudinal LV systolic function in patients with hypertension has recently been found by Ballo et al.[108].

Aims of the thesis

The primary aim of this thesis was to evaluate, with echocardiography, the implication of longitudinal cardiac movement for ventricular systolic and diastolic function.

The studies are designed to:

- I. Identify the influence of age and gender on systolic and diastolic LV function and geometry with focus on the LV LAX function.
- II. Evaluate the effect of long term treatment with beta-blocker on systolic and diastolic LV LAX function in patients with dilated cardiomyopathy, and to observe if contractile reserve, with low dose dobutamine, could be used to predict treatment effect.
- III. Assess the importance of RV and LV LAX function for prediction of survival in patients with idiopathic heart failure.
- IV. Evaluate the acute effect of warm water immersion (34°C) on RV and LV systolic and diastolic LAX function in patients with chronic heart failure.
- V. Evaluate the effect of repeated preload exposure due to hydrotherapy in patients with chronic heart failure.

Methods

Study population

In accordance with principles set out by the Declaration of Helsinki [109], all subjects involved in this thesis gave informed consent to participate. The study protocols were approved by the Ethical Committee at the Medical Faculty, at the University of Gothenburg.

Healthy subjects.

In study I, subjects were recruited from the local census registries of Gothenburg, and the adjacent community Mölndal. Equal number of healthy men and women, in three different age groups: 20-29 (n=29), 50-59 (n=24) and 60-69 years (n=29) were recruited. One birthday per month was selected by random. Each person was asked to participate in the study by telephone and to provide information about concomitant diseases and medications. If the subject could not be contacted, was unwilling to participate, or had a disease that might influence cardiovascular function, another person born on the same day was contacted. In total 399 individuals were contacted, and 108 among them agreed to participate in the study. They underwent a physical examination, including an electrocardiogram, and filled out a questionnaire regarding background data and symptomatology. Routine blood assays such as haemoglobin, electrolytes status, liver enzymes, blood glucose and thyroxine hormones were analysed. Chest x-rays were performed in subjects older than 50 years. Finally, 82 subjects were eligible.

Patients

Study II included 24 patients with stable CHF in functional class II-III according to New York Heart Associations (NYHA) and with a LVEF between 13 and 49%, measured by equilibrium radionuclide angiography (ERNA). Eleven patients were randomized to placebo and 13 to metoprolol treatment. The study was performed at Sahlgrenska University Hospital and was a sub study in a double blind randomized placebo controlled multicenter trial [18]. Echocardiography was performed in patients before treatment, after six months of metoprolol/placebo treatment and after an additional 6 months of open treatment when all patients received metoprolol.

Methods

Study III included 228 patients hospitalized due to idiopathic heart failure. Nineteen hospitals in the western region of Sweden participated. Information about overall mortality was obtained from the Swedish national population registry 10 years after the initial investigation. Data on heart transplantation was obtained from the national transplantation registry.

In study IV and V, patients were recruited from Sahlgrenska University hospital. Patients with stable CHF, NYHA class II-III with a LVEF<45%, were included.

To study the acute effect of WWI, 18 patients were investigated on land and in warm water (study IV). In 12 of these patients, echocardiography was performed on land and water at baseline, after 8 weeks without hydrotherapy (control phase) followed by 8 weeks with hydrotherapy twice weekly, 45 minutes each time (study V).

Echocardiographic procedure

The different methods used in this thesis are presented in Table 1.

Echocardiographic examinations were performed in studies I and II using Acuson 128 XP with a 2.5 MHz or 3.5 MHz transducer (Mountain View, CA, USA). In study III, we used the local echocardiographic equipment at each hospital and in study IV and V Siemens Sequoia 512 with a 3v2c transducer (Mountain View, CA, USA). In study I-III subjects were investigated in a comfortable left lateral (decubitus) position and recordings were obtained, if possible, during relaxed end-expiratory apnea. In study IV and V, the patients were investigated in a slight sloping position at land, and in the same position in the swimming pool with the water level up to the sternal notch. The examinations were stored on videotape, strip-charts at 50 - 100 mm/s or digitally on magnetic optical disks. ECG recording was obtained throughout the studies, whereas phonocardiography of the second heart sound was recorded in study I and II.

Echocardiographic procedure of long axis function

To assess systolic and diastolic LAX function, pulsed-wave TDI and M-mode were performed, (see an example in Figure 4). The longitudinal motion was obtained from apical four and two chamber view with the cursor positioned from apex to the insertion of the right and left AVP. Calculations of ventricular systole were performed after isovolumetric- and before post systolic contraction. At least three cardiac cycles were analysed and averaged.

Each study was analysed by one person; study I (GF) and study II, III, IV and V (BGS).

Methods

Figure 3 illustrates the AVPD with M-mode where maximal velocities were calculated from the steepest parts of systolic and diastolic movements. Amplitudes, time intervals, and velocities were digitized and processed off line by a specially designed computer software program (CAS-Cardiac Analysis Software, Sahlgrenska University Hospital Sweden).

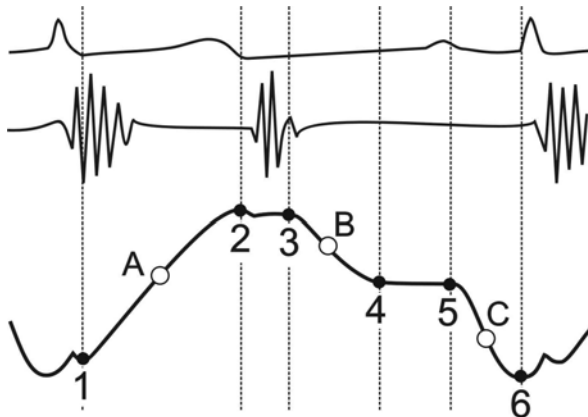


Figure 3.
The atrioventricular plane displacement derived from M-mode. Eur J Echocardiogr. 2006 Aug;7(4). Reprinted with permission from the editor.

O:A-C): The steepest part of systolic and diastolic curve from where maximal velocities are calculated.
1) start of LV contraction;
2) end of LV contraction;
3) start of early diastolic filling;
4) end of diastolic filling, beginning of diastasis; 5) end of diastasis, beginning of atrial contraction; 6) end of atrial contraction.

Table 1. Overview of study populations and methods used in this thesis.

Study	I (n=82)	II (n=24)	III (n= 228)	IV (n=18)	V (n=12)
M-mode, LAX	2 sites and 4 sites in the youngest group	4 sites	3 sites	3 sites	3 sites
End diastolic length	LV AVP-FS	LV AVP-FS			
TDI, LAX LVEF	M-mode	2D biplane 2D biplane	M-mode	5 sites 2D biplane	5 sites 2D biplane
Volume/Dimension	2D biplane		M-mode	2D biplane	2D biplane
Pulsed wave Doppler Pressure				MV, LVOT, PV TV gradient and "PCWP"	MV, LVOT, PV TV gradient and "PCWP"
Ergospirometry				Max. exercise Peak VO ₂	Max. exercise Peak VO ₂

2 sites= left ventricular septal and lateral, 3 sites= left ventricular septal, lateral and right ventricular lateral, 4 sites= left ventricular septal, lateral, inferior and anterior, 5 sites= left ventricular septal, lateral, inferior anterior and right ventricular lateral. LVEF; left ventricular ejection fraction, LAX, long axis; LVOT, left ventricular outflow tract; MV, mitral valve, PCWP, Pulmonary capillary wedge pressure; PV, pulmonal vein; TDI, tissue Doppler imaging; TV, tricuspid valve.

Methods

Echocardiographic procedure of LV end diastolic length

In order to consider the end diastolic length, the AVP-Fractional Shortening (FS) was calculated. The systolic amplitude was divided with the length from the epicardium in apex to point 5 (after early diastolic filling and before atrial contraction [73, 110]).

Tissue Doppler Imaging

Left and right ventricular myocardial velocities were recorded with a sample volume of 2.0 mm. Three velocity signals during each cardiac cycle were measured: systolic velocity (Sv) directed toward the transducer, early diastolic (Ev) and atrial diastolic (Av) velocities away from the transducer (Figure 4). Annular systolic motion was also measured by integration of the systolic wave velocity curves (area), tissue velocity time integral (TVTI) [50, 111]. The calculations were performed on line.

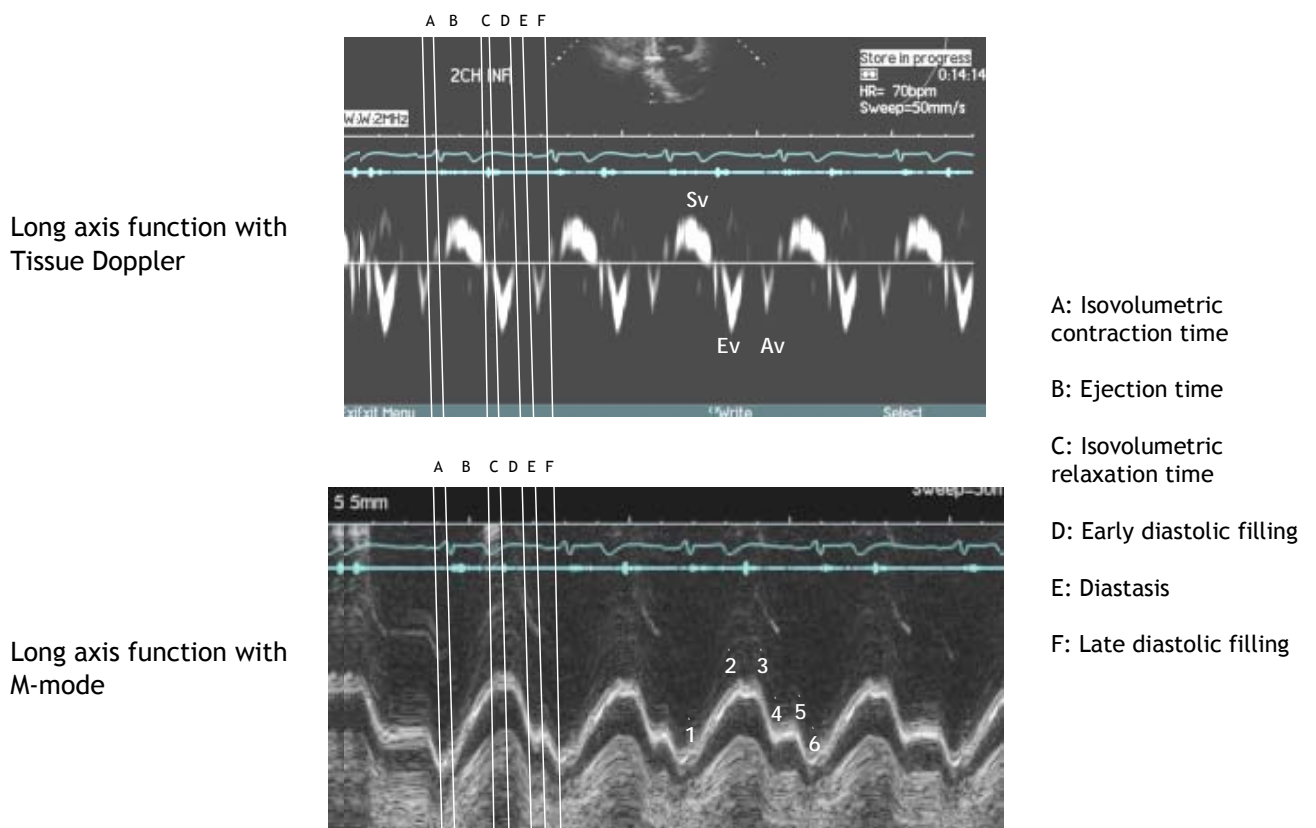


Figure 4.

Long axes function recorded with tissue Doppler imaging :Sv; systolic velocity, Ev; early diastolic velocity and Av; atrial diastolic velocity.

Long axes function recorded from M-mode: 1) start of LV contraction; 2) end of LV contraction; 3) start of early diastolic filling; 4) end of diastolic filling, beginning of diastasis; 5) end of diastasis, beginning of atrial contraction; 6) end of atrial contraction.

Methods

Short axis function derived from one dimensional echocardiography

Dimensions were measured using the methodology of leading edge. EF and FS data were recorded from parasternal short axis (SAX) views with M-mode technique, in accordance with the recommendations of the American Society of Echocardiography [112]. FS= left ventricular enddiastolic dimension (LVEDD) - left ventricular endsystolic dimension (LVESD) / LVEDD. Dimensional data were used for conversion to volumes by the Teichholtz formula. EF = left ventricular enddiastolic volume (LVEDV) - left ventricular endsystolic volume (LVESV) /LVEDV.

Left ventricular volume

Two-dimensional bi-plane recordings (4 and 2 chamber views) were performed for calculations of LV end-diastolic and end-systolic volumes. LVEF was calculated with the method of disc, modified Simpson rule, in one representative heart beat, and in accordance with the recommendations of the American Society of Echocardiography [113, 114].

Pulsed wave Doppler

Pulsed wave Doppler was carried out in a five chamber view for calculation of SV and cardiac output (CO, L/min) [115] by registration of velocity time integral (VTI, cm) from left ventricular outflow tract (LVOT, mm). Cardiac output was calculated from the formula : $SV = (LVOT \text{ area} \times VTI) \times HR$, where LVOT area was calculated as: $3.14 \times (LVOT \text{ dimension}/2)^2$ [116].

Diastolic transmitral flow velocities were recorded from apical four chamber view with the sample volume at the tips of the mitral leaflet. Peak velocity of E (early diastolic filling) and A (late diastolic filling) wave were measured and VTI was traced.

Estimated Pulmonary Capillary Wedge Pressure (PCWP)

Estimation of pulmonary capillary wedge pressure was achieved as described by Nagueh [117]. Formula used for estimated PCWP = $1.91 + ((E \text{ mitral Doppler}/E \text{ lateral}) \times 1.24)$.

Methods

Validity

There exist no golden standard for performance of LAX function; hence, it might not be correct to appraise the validity. Although the coefficient of variation (CV%) is rather high with respect of agreement between M-mode recorded AVP and EF (CV18.2%), measured with the golden standard ERNA, figure 5AB, there are still a very good correlation between these parameters.

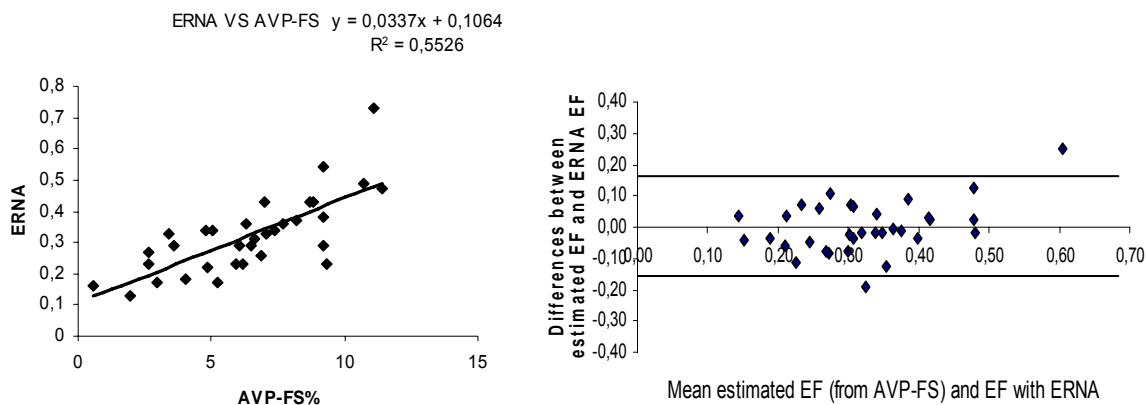


Figure 5A. Correlation between AVP and ERNA (from study II)

Figure 5B. Bland-Altman plot of mean EF derived from AVP-FS and ERNA EF (fig. 5A)
Mean EF 0.32 ± 0.10
Mean differences 0 ± 0.083 ($2SD \pm 0.166$)
CV 18.2%

Reproducibility (intra-observer)

Regarding LAX recordings, the intra-observer (BGS) coefficient of variation using the cardiac analyse software system was; systolic amplitude, mm (CV =4.7% $r=0.99$); systolic velocity, mm/s (CV=9.7%, $r=0.92$); and early diastolic filling velocity, mm/s (CV= 9.2%, $r=0.92$).

Intra and inter-observer variability

The Intra and inter-observer variability in our laboratory is good, especially regarding young healthy subjects, table 2.

Table 2. Intra-variability between patients and inter-observer variability within two observers (MST and BGS) in young healthy individuals.

Table 2.

	r	CV
EF %	0.95 ***	1.47
LVEDV (ml)	0.94 ***	5.14
LVESV (ml)	0.86 ***	5.62
E (m/s)	0.99 ***	2.60
A (m/s)	0.90 ***	3.77
LVOT VTI (cm)	0.98 ***	2.15
TDI Sv (cm/s)	1.00***	1.27
TDI Ev (cm/s)	0.99 ***	1.56
TDI Av (cm/s)	0.98 ***	2.57
AVP (mm)	0.99 ***	1.66

*** p<0.001

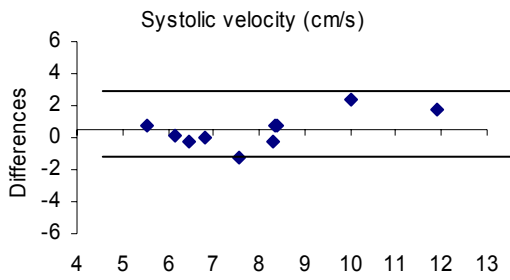
A, late filling velocity at atrial contraction; AVP, atrioventricular plane; E, early diastolic filling velocity ; EDV, enddiastolic volume; EF, ejection fraction; LV, left ventricular; LVOT, left ventricular outflow tract, S, systolic; TDI, tissue Doppler imaging; VTI, velocity time integral. n=6

Reproducibility and short-term variation in stable heart failure patients

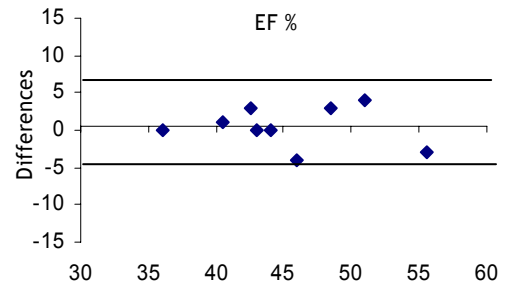
We have found in our laboratory, using Siemens Sequoia 512, that systolic and diastolic echocardiographic variables are steady during one month in patients with stable heart failure without changes in medical treatment. Figure 6 A-C and table 3 shows, within the patient, the agreement according to Bland-Altman plots on different methods to evaluate systolic function.

Table 4 shows the intra-observer and intra-patients variability in standing position on land and in warm water in patients with CHF.

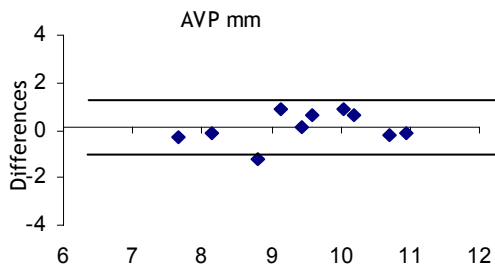
Methods



6A Bland-Altman plot shows:
Systolic velocity from TDI
Mean systolic velocity (cm/s) 7.95 ± 1.92
Mean Differences 0.47 ± 1.07 (2SD ± 2.14)
CV 9.5%



6B Bland-Altman plot shows:
Ejection fraction (biplane)
Mean EF 0.45 ± 0.06
Mean differences 0.04 ± 0.03 (2SD ± 0.06)
CV 4.2%



6C Bland-Altman plot shows:
Atrioventricularplane-displacement from M-mode.
Mean AVPD (mm) 9.47 ± 1.06
Mean Differences 0.12 ± 0.65 (2SD ± 1.30)
CV 6.1%

Table 3. Intra-patient variability in different echocardiographic variables, within one month

	r	CV
Ejection fraction(%)	0.90 **	4.2
LVEDV (ml)	0.88 **	8.3
LVESV (ml)	0.91 **	10.2
Transmitral Doppler E (m/s)	0.85 **	10.5
Transmitral Doppler A (m/s)	0.16	12.9
TDI Sv (cm/s)	0.91 ***	9.5
TDI Ev (cm/s)	0.80 **	8.3
TDI Av (cm/s)	0.79 **	14.7
Long axis systolic ampl.	0.75 *	6.1
Long axis early diastolic filling ampl.	0.78**	10.1
Long axis atrial contraction ampl.	0.82 **	6.1
Heart rate	0.88 **	4.6

$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Abbreviations see table 2. n=10

Methods

Table 4. Intra-observer and intra-patients variability in standing position on land and in warm water

Measurements Standing position n=12	Intra-observer variability (BGS)			Intra-patient variability A vs B		
	CV (%)	r	P	CV (%)	r	p
SV (mL) land	3.12	0.99	<0.001	13.9	0.82	<0.01
SV (mL) WWI	5.2	0.99	<0.001	8.1	0.92	<0.001
LVAVP (mm) land	5.8	0.98	<0.001	15.3	0.94	<0.001
LVAVP (mm) WWI	5.7	0.96	<0.001	7.7	0.94	<0.001
LVEF (%) land	10.0 (n=9)	0.92	<0.001	6.9	0.85	<0.001
LVEF (%) WWI	9.8 (n=9)	0.82	<0.01	8.5	0.83	<0.001
LVEDV (mL) land	10.2 (n=9)	0.90	<0.01	13.1	0.88	<0.001
LVEDV (mL) WWI	20.0 (n=9)	0.75	<0.05	12.8	0.84	<0.01
LV TVTI s land				10.6	0.89	<0.001
LV TVTI s WWI				7.3	0.83	<0.01
RV TVTI s land				6.3	0.95	<0.001
RV TVTI s WWI				10.7	0.77	<0.01

AVP, atrioventricular plane; LV, left ventricular; LVEDV, left ventricular enddiastolic volume; LVEF, left ventricular ejection fraction; r, correlation; RV, right ventricle; SV, stroke volume; TVTI, tissue velocity time integral; WWI; warm water immersion.

Ergospirometry

In study IV and V, patients underwent a maximal ergometer exercise test. In an upright position, a ramp protocol was utilised with a 10-Watt increase every minute until exhaustion. Peak oxygen uptake (VO₂ peak) was measured breath-by-breath using a V max-29, (Sensor Medics, USA, Fenton, MO). Inspiratory flows and expiratory oxygen (O₂) and carbon dioxide (CO₂) concentrations were determined. Rate of perceived exertion was assessed on the Borg scale graded between 6 and 20 and dyspnea was assessed with Borg category ratio (CR10) scale [118].

Hydrotherapy

The training programme comprised of 45-min sessions in a heated pool (33-34°C), twice weekly over an 8-week period. The patients trained as a group following a low to moderate exercise level, i.e. 40-70% of maximal heart rate reserve. The basis posture was standing with water just below neck level. The exercise regime was designed to include muscles utilised in activities of daily living such as walking, dressing and household activities. The programme focused on peripheral muscle training but central circulatory exercises were also included. The physiotherapist used music to facilitate the correct pace of exercise.

Methods

BNP

BNP were collected in chilled tube containing ethylene diamine tetraacetic acid (EDTA), centrifuged at 4°C and stored at minus 70°C. The plasma BNP concentration was measured using an immunoradiometric method (Shionogi, Osaka, Japan) [119].

Statistical methods

Data were analysed using SPSS 9-11 for Windows (Chicago, Ill, USA) and a SigmaStat statistical software package (Jandel Corporation, Chicago, Ill, USA).

If not specified in the text, data are expressed as median or mean±SD, and in graphs as mean±SEM.

To analyse the relation between different variables, Spearman's correlation coefficient was used. The Bland and Altman method was performed to determine inter- and intravariability [120], and paired data were analysed with paired sample T-test.

In study I, the relation between age and different variables was evaluated by linear regression and ANOVA. Mann-Whitney test was performed in comparison between genders. A multivariate logistic regression analysis was used to evaluate possible clinically independent predictors of echocardiographic variables.

In study II, Wilcoxon non-parametric analyses were performed within the groups, while Mann-Whitney test was performed in the comparison between the groups.

In study III, Cox regression analyses were obtained for prediction of 10 years survival. Survival curves were constructed by the Kaplan-Meier method, and differences in mortality were compared with the log-rank test. Hazard ratios (HR) were estimated with 95% confidence intervals (CI).

In study IV, Wilcoxon non-parametric analyses were performed within land and water, and in study V, the differences between groups were analysed with one-way ANOVA (analysis of variance).

Results

Results

Paper I

We found that the most prominent age related differences were observed in LV LAX function, whereas minor alterations were noticed in SAX function. Both systolic and diastolic LAX function decreased with advancing age; maximal systolic velocity ($r=0.61$, $p<0.0001$) and maximal early diastolic filling velocity ($r=0.87$, $p<0.0001$). The length of the LAX decreased with age, figure 7, while the relative contraction amplitude was maintained. LV global and SAX measurements revealed significant differences between genders, males having generally larger dimensions, even when correcting for body surface area. Females exhibited a more pronounced remodelling process with advancing age.

To evaluate different clinical factors affecting systolic and diastolic function, a multivariate logistic regression analysis was performed. Age was independently associated with several variables, including maximal systolic velocity and maximal early diastolic filling velocity.

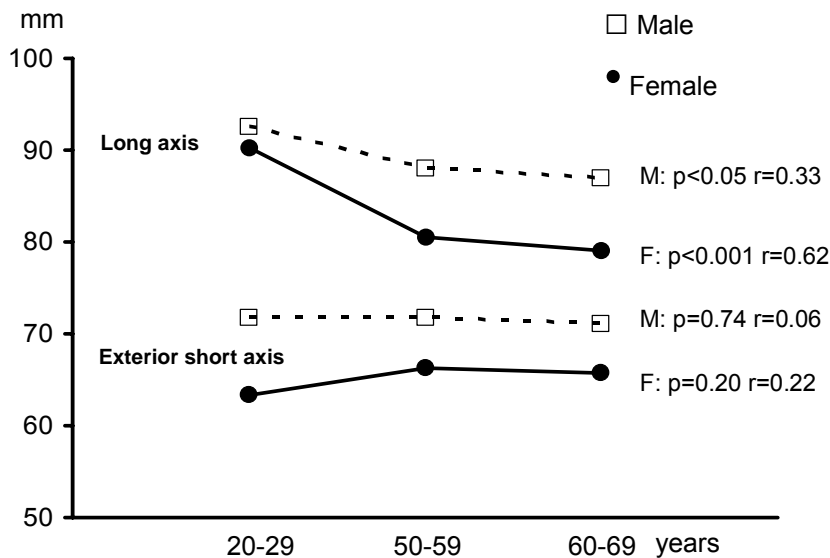


Figure 7. Gender and age specific differences in end diastolic dimensions.

Results

Paper II

We observed a pronounced effect on systolic and diastolic LAX function after treatment with metoprolol, table 5. The improvement in LV LAX function was 38% after 6 months beta-blockade, as compared with 20% improvement in LVEF ($p<0.05$). However, LAX CR at baseline was not able to predict long-term treatment response to metoprolol. LAX CR at baseline was lower than the long-term treatment response to metoprolol (Figure 8).

Table 5. Systolic and diastolic long axis function at rest and during dobutamine stress before and after 6 months with beta-blockade

(n=24)	Rest		Dobutamine	
	baseline	6months	baseline	6months
Heart rate (bpm)	74±12	57±10***	99±12###	76±15***###
Diastasis (ms)	147±87	307±145***	100±66##	187±88***###
Atrial fraction (%)	86±64	63±25*	106±105	71±33*
Atrial contraction vel. (mm/s)	-53±21	-52±17	-77±23###	-66±16*##
Early diastolic vel. (mm/s)	-27±21	-31±17	-47±20###	-39±21#
AVP-FS (%)	5.6±2.4	7.7±2.6***	6.7±2.9###	8.4±3.2***
Systolic vel. (mm/s)	28±9	33±13**	44±17###	50±21*###

AVP-FS, atrioventricularplane-fractional shortening; vel, velocity. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, baseline vs. 6 months; # $p<0.05$, ## $p<0.01$, ### $p<0.001$, rest vs. stress. Values are presented as mean±SD

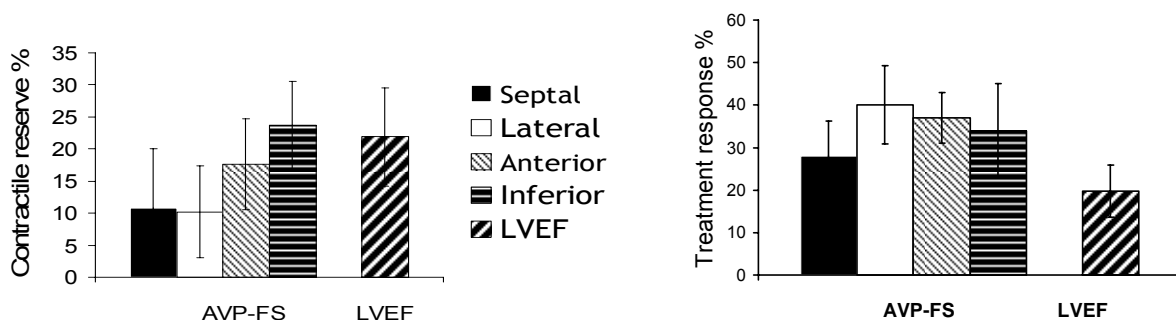


Figure 8. Response to dobutamine before treatment (contractile reserve), and response after 6 months treatment with metoprolol (treatment response). AVP-FS, atrioventricularplane-fractional shortening; LVEF, left ventricular ejection fraction.

Results

Paper III

Prediction of mortality

During the 10 years of follow-up 110 patients died and 7 patients had heart transplantation. In the total study population, several echocardiographic LAX and SAX variables were significantly associated with 10 years mortality in univariate analysis, table 6. However, only LV LAX systolic amplitude remained as a significant prognostic variable in the multivariate analysis, table 6. Gender, age, and heart rate did not predict mortality in this study. Also after adjustment for age, gender, heart rate, systolic blood pressure and FS; LV LAX systolic amplitude was shown as a significant prognostic variable, HR 0.89 [0.80-0.98], $p=0.02$.

Survival was significantly better for patients with the highest (>8.7 mm) versus lowest (<4.8mm) LAX systolic amplitude ($p<0.001$), figure 9. Similar findings were observed with respect to SAX FS. However, there was no significant difference in survival between the two quartiles with highest SAX FS. Concerning patient with AF, significant independent predictors of mortality were left atrial dimension, ($p<0.05$) and RV LAX early diastolic filling velocity ($p<0.05$), table 7. After adjustment for age, gender, heart rate, systolic blood pressure and SAX FS; RV LAX early diastolic filling velocity, HR 0.84 [0.71-0.99], ($p<0.05$) and left atrial dimension HR 1.54 [1.14-2.07], ($p<0.01$) were independently predictive of 10 years mortality for patients with AF.

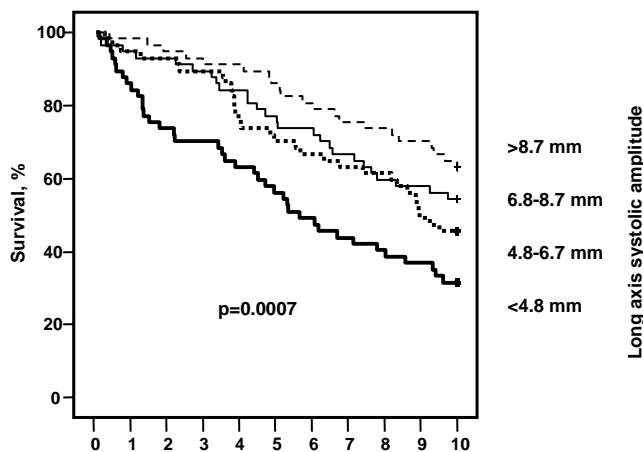


Figure 9. Association between mortality and ventricular long axis function
Survival curves are displayed for each quartile of left ventricular long axis systolic amplitude. There was an overall difference between the curves as assessed by the log-rank test ($p=0.0007$). Survival between quartiles was estimated by Cox regression analysis, the fourth quartile being the reference. Q1:<4.8mm; Q2:4.8-6.7mm; Q3:6.8-8.7mm; Q4:>8.7mm.

Q3 vs. Q4, HR 0.72 [0.41-1.29], $p=0.27$.

Q2 vs. Q4, HR 0.76 [0.57-0.99], $p=0.049$

Q1 vs. Q4, HR 0.72 [0.60-0.86], $p< 0.0001$.

Results

Table 6. Predictors of 10-year mortality in 228 patients with CHF

	Univariate association		Multivariate association	
	p	HR 95% CI	p	HR 95% CI
Gender	0.20	0.76 [0.50-1.16]	0.32	
Age	0.55	0.99 [0.97-1.01]	0.53	
Heart rate (beats/min)	0.42	1.02 [0.97-1.08]	0.51	
SBP (mmHg)	0.002	0.93 [0.89-0.98]	0.21	
LA (mm)	0.001	1.22 [1.08-1.36]	0.30	
LVEDD(mm)	<0.0001	1.30 [1.20-1.42]	0.06	
SAX FS (%) n=199	<0.0001	0.72 [0.65-0.81]	0.16	
LVLAX syst ampl (mm)	<0.0001	0.83 [0.77-0.89]	0.024	0.80 [0.66-0.97]
LVLAX syst vel (cm/sec)	<0.0001	0.71 [0.60-0.83]	0.12	
LVLAX EDFV (cm/sec)	0.014	0.88 [0.79-0.97]	0.30	
RVLAX syst. ampl. (mm)	<0.0001	0.93 [0.89-0.97]	0.60	
RVLAX syst.vel (cm/sec)	0.007	0.90 [0.84-0.97]	0.24	
n=206				
RVLAX EDFV (cm/sec)	0.001	0.88 [0.81-0.94]	0.09	

EDFV=early diastolic filling velocity; LA=left atrium; LVEDD=left ventricular enddiastolic dimension; LVLAX=left ventricular long axis, RVLAX=right ventricular long axis; SAX FS=short axis fractional shortening; SBP=systolic blood pressure. n=228 if nothing else is shown

Univariate and multivariate Cox regression analysis of 10 years mortality. Calculations were performed on continuous data. Changes of 5 units were used for age, heart rate, systolic blood pressure, left atrial dimension, LV enddiastolic dimension, and SAX fraction shortening. Remaining variables have low numeric value and changes are expressed for one unit.

Results

Table 7. Predictors of 10-year mortality in 63 patients with CHF and AF

	Univariate association		Multivariate association	
	p	HR 95% CI	p	HR 95% CI
Gender	0.40	0.69 [0.28-1.67]	0.86	
Age	0.78	0.97 [0.79-1.20]	0.28	
Heart rate (beats/min)	0.89	0.99 [0.91-1.09]	0.66	
SBP (mmHg)	0.39	0.96 [0.88-1.05]	0.82	
LA (mm)	0.11	1.20 [0.96-1.51]	0.04	1.42 [1.02-1.98]
LVEDD(mm)	<0.0001	1.58 [1.27-1.96]	0.21	
SAX FS (%)	0.002	0.72 [0.58-0.88]	0.57	
LVLAX syst ampl (mm)	0.04	0.80 [0.64-0.99]	0.94	
LVLAX syst vel (cm/sec)	0.039	0.67 [0.46-0.98]	0.43	
LVLAX EDFV (cm/sec)	0.26	0.89 [0.72-1.09]	0.85	
RVLAX syst. ampl. (mm)	0.031	0.89 [0.81-0.99]	0.65	
RVLAX syst.vel (cm/sec)	0.087	0.86 [0.72-1.02]	0.41	
RVLAX EDFV (cm/sec)	0.002	0.79 [0.68-0.92]	0.03	0.68 [0.48-0.97]

EDFV=early diastolic filling velocity; LA=left atrium; LVEDD=left ventricular enddiastolic dimension; LVLAX=left ventricular long axis, RVLAX=right ventricular long axis; SAX FS=short axis fractional shortening; SBP=systolic blood pressure
n=63

Relation between LV long-axis and short-axis function

In patients with the most severe LV function (below 6.8 mm), we observed a significant relation between longitudinal systolic motion and circumferential shortening. In contrast, there was no relation between longitudinal systolic motion and circumferential shortening in patients in the range >6.8 mm.

Results

Paper IV

We found that WWI caused favourable hemodynamic effects in patients with stable CHF. Despite increased left ventricular volumes, WWI resulted in significantly enhanced biventricular function (Figure 10A-B and Table 8).

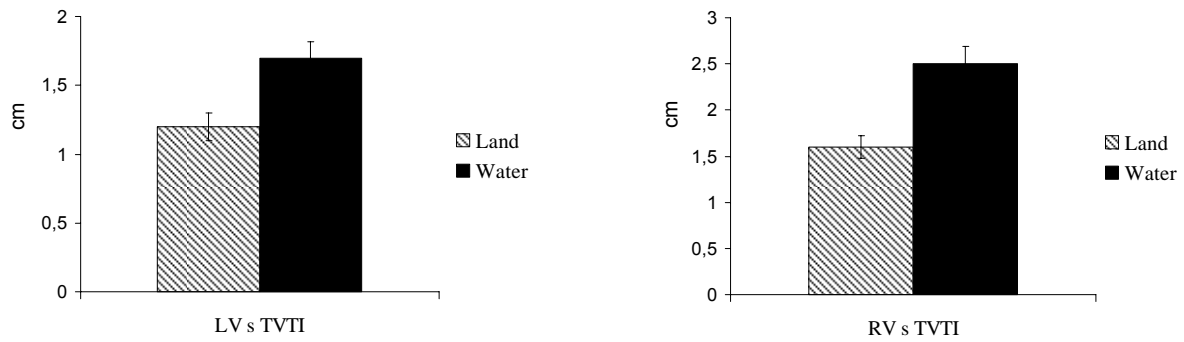


Figure 10 A-B. Left and right systolic ventricular tissue velocity time integral on land and in warm water. Left ventricular systolic tissue velocity time integral (LV s TVTI) 1.2 ± 0.1 cm vs 1.7 ± 0.1 cm, *** $p < 0.0001$. Right ventricular systolic tissue velocity time integral (RV s TVTI) 1.6 ± 0.1 cm vs 2.5 ± 0.2 cm, *** $p < 0.0001$. Data are mean \pm SEM.

Results

Table 8. Land vs warm water immersion

18 patients	Land	Warm water	P value
LVOT VTI (cm)	12.8±3.8	18.9±4.5	0.000
MV VTI (cm)	15.5±6.6	21.1±6.1	0.000
SV (mL)	43.9±13.6	64.4±16.5	0.000
HR (bpm)	73±12	66±11	0.000
CO (L/min)	3.1±0.8	4.2±0.9	0.000
E/A ratio	0.72±0.37	1.21±0.75	0.010
TDI Sv (cm/sec)	9.1±2.3	8.9±1.9	NS
TDI Ev (cm/sec)	8.3±1.8	9.6±1.8	0.017
TDI Av (cm/sec)	10.0± 2.4	10.9±2.8	NS
LV S TVTI (cm)	1.2±0.4	1.7±0.5	0.000
LV AVP (mm)	5.5±2.1	8.2±2.7	0.001
RVTDI Sv (cm/sec)	14.3±2.0	13.7±3.6	NS
RVTDI Ev (cm/sec)	12.1±2.7	12.7±2.3	NS
RVTDI Av (cm/sec)	16.6±4.7	15.0±5.6	NS
RV S TVTI (cm)	1.6±0.5	2.4±0.8	0.000
RV AVP	14.7±6.0	15.2±5.3	NS
TV gradient	19.8±10.3	24.1±13.4	NS
Syst/diast PV	1.2±0.43	1.0±0.3	0.02
PV PW A (m/sec)	0.21±0.04	0.27±0.06	0.002
LVEF (%)	31±9	35±8	0.028
LVEDV (mL)	122.8±36.1	153.1±55.5	0.002
LVESV (mL)	85.4±32.3	100.0±39.7	0.007
SVR (RU)	31±7	22 ±5	0.006
MAP (mmHg)	92±14	86±16	0.000
PCWP (mmHg)	10.0±5.8	12.4±5.2	0.008
SBP (mmHg)	126±23	123±25	NS
DBP (mmHg)	75±11	68±12	0.002
Atrial contr. to AVPD (%)	75±47	49±9	0.026

A, late filling velocity wave at atrial contraction; AVP, atrioventricular plane; CO, cardiac output; DBP, diastolic blood pressure; E, early diastolic filling velocity wave; EDV, enddiastolic volume; EF, ejection fraction; HR, heart rate; LV, left ventricular; LVOT, left ventricular outflow tract; MAP, Mean arterial pressure; MV, mitral valve; PCWP, pulmonary capillary wedge pressure; PV, pulmonary vein; PW, pulsed wave; RU, resistant unit; RV, right ventricle, S, systolic; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; TDI, tissue Doppler imaging; TV, tricuspid valve; TVTI, tissue velocity time integral; v, velocity; VTI, velocity time integral; WWI; warm water immersion.

Results

Paper V

We found that eight weeks of repeated hydrotherapy was well tolerated in patients with stable heart failure. There were no sign of changes in volumes, systolic or diastolic function on land or in water after 8 weeks of repeated hydrotherapy. The significant favourable hemodynamic effects during WWI were present also after frequent exposure of enhanced preload and filling pressure. A trend towards decreased HR was observed on land after 8 weeks of hydrotheraphy (from 73 bpm to 67 bpm, $p=0.075$).

Cardiopulmonary exercise test

Maximal ergometer exercise test was neither improved nor worsen after 8 weeks of hydrotherapy. Heart rate, systolic and diastolic blood pressure, peak VO_2 , and ventilation remained unchanged.

BNP

There were no significant differences in BNP (ng/L) during the study period. At baseline, the level was 169 ± 158 ng/L, after 8 weeks of control period 134 ± 102 ng/L and after 8 weeks of hydrotherapy 147 ± 125 ng/L.

Discussion

This thesis focused on the superiority of long axis function to observe ventricular changes due to ageing, response to pharmacological treatment, prediction of survival and increased load condition.

We found a significant decline in systolic and diastolic LAX function due to age. A pronounced improvement in systolic ventricular LAX function was observed after treatment with metoprolol, and to a greater extent than LVEF. LV LAX systolic amplitude was the only independent prognostic variable predicting 10 years of survival and right and left ventricular LAX function improved significantly during WWI.

Normal ageing process

A structural remodelling of the heart seems to be a normal ageing process, particularly in women. We found that women increase their LV mass with age, while male's heart mass remained relatively constant. This is in line with Kitzman's study [121] on 765 human autopsies. We observed that left ventricular LAX length decrease with age indicating a remodelling of the heart from ellipsoid to a more spherical left ventricular shape. Similar detection has been reported in a magnetic resonance image performed study by Hees et al. [122]. It has also been shown, after myocardial infarction, that increased LV sphericity independently could predict a decrease in 10 year survival rate [123]. However, whether there are differences between males and females can not be determined. In the mentioned study, 80% were, not surprisingly, men. Subsequently it is difficult to discriminate whether increased sphericity were associated with decreased survival rate in both genders.

In older hearts fibrosis is more frequently found in the subendocardial layer of the ventricular wall [124]. This could explain our observed decrease in systolic and diastolic LAX velocities and amplitudes during age.

Recovery of long axis function

In this thesis we can conclude that LAX function has a remarkable capacity of recovery. The improvement during metoprolol therapy was 38% after 6 months treatment, in comparison with 20% improvement in LVEF [125]. This pronounced LAX improvement could be explained by a restoration of the affected longitudinal subendocardial muscle fibres, which are extremely sensitive to increased load pressure and reduced perfusion.

The role of subendocardial function

It has been reported by Beau and his colleagues [126] that down regulation of myocardial β -adrenergic receptor (β -AR) do not exist uniformly. He observed, in the failing heart, that despite significant reduction of total β -receptor density, no significant reduction was observed in the subepicardium, whereas β -receptors were significantly reduced in the subendocardium. It has also been shown, in failing myocardium, that phosphodiesterase inhibitor decrease cyclic adenosine monophosphate and phosphodiesterase activity in the endocardial, but not epicardial layers [127]. This is probably mediated by increased wall stress and decreased coronary reserve in the subendocardium. Recovery of these conditions could explain the increased possibility to improve subendocardial function. Long-term metoprolol therapy is associated with an increase in myocardial β -receptor density, and Heilbrunn et al [16] found that long-term treatment with metoprolol restored the β -AR to a normal level. Further, Bristow shows [128], that the β_1 : β_2 ratio in failing human myocardium is ~60:40 in comparison with the normal ratio of ~80:20. Assuming that the β -receptor in the subendocardium, before treatment with β -blocker is significantly reduced compared with the epicardium, it is not unlikely that the restoration is more prominent in the deep layer.

Wall stress

Other explanations for the subendocardial improvement could be facilitated perfusion due to higher perfusion pressure [17]. Prolongation of diastolic time periods probably leads to a facilitated myocardial perfusion promoting calcium transport into the sarcoplasmic reticulum.

Contractile reserve

Significant enhancement in systolic motion of AVP from rest to stress with low dose dobutamine was used to define CR. To further explore the mechanisms of therapy patients were divided into three groups dependent on the increase in LVEF after 6 months treatment with metoprolol (data not presented in paper II). Good responder were defined as an increase in global LVEF more than 6 unit (n=8), moderate responder improve 2-6 unit (n=7) and poor less than 2 unit improvement (n=7).

Contractile reserve and treatment respond of AVP-FS was normalised for mean AVP-FS at baseline and expressed in percent ($\Delta\text{AVP-FS} / \text{mean AVP-FS at baseline} \times 100$).

We observed, in the septal part of AVP, that CR at baseline and the improvement after 6 months treatment with metoprolol was significant higher in good compared with poor responders, figure 11. Septum's ability to disclose significant differences in CR and treatment effect in good, moderate and poor responder is purely hypothetical. Divergent observations have been found regarding the fibre architecture of intraventricular septum. It has been reported that longitudinal fibres are absent in septum [129] whereas circumferential musclefibres dominate, leading to a more transverse contraction. This could explain why septum, which prove to have the lowest longitudinal displacement, was able to discriminate between CR and treatment response. Several authors have shown that the CR of foremost circumferential musclefibres, assessed by dobutamine stress, [125, 130-132] are able to predict outcome after treatment with beta-blockade.

Another reflection is the role of septum's biventricular systolic and diastolic function. The contraction of septum is performed during simultaneous drawing towards opposite direction, and could also be an explanation for the reduced displacement. Septum thickens on its transverse axis, contributing equally to RV and LV function [133]. The fact that RVEF has been shown as an independent predictor of death [134-136], demonstrate the significance of the RV and might contribute to septum's ability in this aspect.

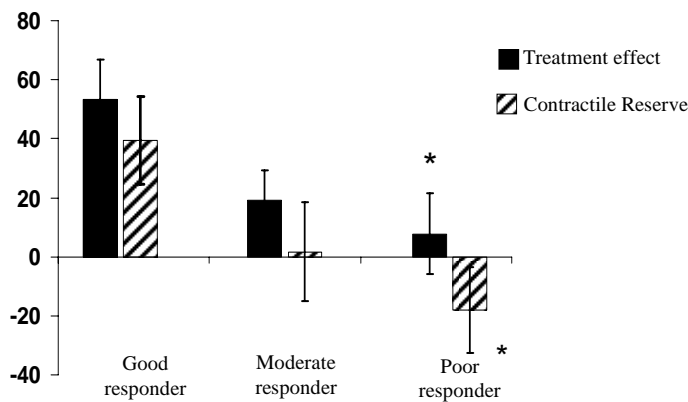


Figure 11. AVP-FS in the septal region, showed significant differences between good and poor responders with respect to CR at baseline and treatment effect. * $p < 0.05$. Data are presented as mean \pm SEM.

Long axis function for prediction of survival

The basal portion of the ventricle is connected with longitudinal subendocardial muscle fibres that are sensitive to ischemia [137] and increase in wall stress. Even though 2D recorded LVEF incorporates information on longitudinal shortening, this method is not sensitive enough to detect minor ventricular changes [73, 74]. Likewise, it has been observed, that mortality decreased in a linear fashion with increasing LVEF up to 45%, with no further reductions in mortality when EF was $>45\%$ [138]. In this thesis we observed that LAX function was a more powerful predictor of outcome compared to other echocardiographic parameters. This finding is supported by Nikitin [74] who reports that LAX systolic velocity was the most potent predictor of outcome compared with other variables, including LVEF (modified Simpson's rule). Further, it has been reported that LAX early diastolic velocity is the superior prognostic parameter [64].

There is not a straight linear relationship between SAX and LAX function. We observed a significant relation between LAX systolic amplitude and FS, in patients with most impaired LV function (LAX systolic amplitude below 6.8 mm). In contrast,

there was no relation in patients with LAX systolic amplitude >6.8 mm. This might explain the varying results in previous studies and indicates that LAX function is not a mirror of SAX or global LV function [106, 107].

Right ventricular function and atrial fibrillation

In a few studies, RVEF has been found to be superior to LVEF in predicting mortality in chronic heart failure [134, 139]. Due to the complex geometry of the RV, radionuclide angiography has been employed for evaluation of RV volume and function. However, also with this method there are significant difficulties in delineating RV cavity from the right atrium and the great arteries. Further, patients with AF are often excluded from studies due to their irregular heart rhythm. There are also considerable obstacles when using 2D echocardiography for assessment of RV volumes, and RVEF is usually not used to report RV function in the clinical setting [77]. In contrast, the motion pattern of the tricuspid LAX function is easily registered and could be used to assess ventricular function [140]. In an article by Field et al. [141], RV myocardial performance index (Tei index) was associated with adverse outcome in a population of heart failure including patients with AF. Increased ventricular stiffness or decreased relaxation will impede filling of blood into the chambers, and in combination with an increased RV afterload this will cause both diastolic and systolic RV dysfunction [142]. By nature of RV anatomy, this chamber is also extremely sensitive to changes in afterload, and thus to pulmonary artery pressure.

Warm Water Immersion

WWI cause a move of blood from the periphery to the intrathoracic circulation and due to this hydrostatically induced volume shift, water immersion could be a challenge for patients with CHF [30, 36]. Nevertheless we found, during WWI, that systemic vascular resistance (SVR) and HR reduced, which could explain the improved systolic and diastolic function observed in both left and right ventricular LAX function and in LVEF.

The most important effects of WWI are a reduction in heart rate, increase in preload and decrease in afterload. According to the Bainbridge reflex [143], it could be expected that the increase in preload should cause an increase in heart rate during WWI [144]. However, in our study heart rate decreased, possibly caused by an enhanced

parasympathetic activity [35]. Further, it has been hypothesized [145] that ventricular volume expansion during WWI stimulates cardiopulmonary baroreceptors, causing a reduction in sympathetic nervous system activity.

Water temperature

Tei *et al* [34] observed, during and after WWI and sauna bath, an increase in heart rate and PCWP during thermal exposure. Water temperature in this study was 41 °C compared with 34 °C in our study. An explanation for the diverging results might be that whole body heating results in cardiovascular stress and heat stress has been shown to increase sympathetic activation [146]. As water temperature in our study is considered to be thermoneutral, we believe this to be an important contributor to the results.

Time in water

The autonomic system responds to changes in vascular pressure and stretch and modulates circulatory changes through baroreceptor signals [147]. Considering the short time of WWI (20-30 minutes), the pronounced reduction in heart rate is therefore most likely activated through autonomic nervous regulation.

Intravascular volume is controlled by complex systems that involve renal, autonomic, and neurohormonal activities [31, 32]. Increased BNP leads to vasodilatation and an increased glomerular filtration rate [148, 149], these reflexes are activated to reduce preload.

Body position

Body position is important when considering water immersion. We have used the standing position, which is common when physical training is applied as part of physiotherapy. In addition, our experimental protocol was comfortable for the patients compared to other studies where the subjects were exposed to heart catheterization [150] or investigated with transesophageal echocardiography [30].

Post systolic contraction

We made an interesting observation in patients with left bundle branch block [151]. Standing on land, there was a pronounced post systolic contraction. Post systolic contraction is a delayed ejection motion of the myocardium [152, 153], a phenomenon related to ischemia and intra-ventricular dyssynchrony [154]. During WWI, the abnormal contraction was abolished.

Hydrotherapy

The buoyancy of the water facilitates exercise and hydrotherapy has been found to be excellent [29] for patients suffering from disabilities that hinder exercise on land. We found that 8 weeks of hydrotherapy are well tolerated in patients with CHF, although they were exposed to repeated increased venous return and enhanced preload. We could not observe any adverse effect or permanent remodelling of the heart. The positive response of acute WWI was significant also after frequent exposure of hydrostatic pressure and their physical capacity was maintained. On the other hand, we could not observe any improvement in exercise tolerance, peak VO_2 or cardiac function after 8 weeks of hydrotherapy twice a week. One explanation for this could be insufficient time of exercise. A previous study [29] has shown that hydrotherapy three times weekly improved the functional capacity while patients randomized to the control group deteriorated. Surprisingly, patients in this study maintained their physical capacity during the control phase. A reason could be that they felt care for and optimistic towards the approaching hydrotherapy, it can therefore not be excluded that patients unconsciously became more active ahead of the training regime.

Conclusions

This thesis focused on determining the significance of long axes function and thus subendocardial function. Long axes function was superior to short axes function in identifying age-related differences in healthy individuals. In patients with chronic heart failure, we demonstrated that long axes function was considerably improved after treatment with metoprolol and also during warm water immersion. Further, left ventricular long axes function was the only independent prognostic variable for 10-year survival in patients with idiopathic heart failure. Thus, the importance of long axes function is now clearer and we conclude that long axes function is of significance for ventricular function.

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Acknowledgement

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Albert Einstein

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Sören Kierkegaard

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