Right Heart Function in Health and Disease

A Doppler Echocardiography And Doppler Tissue Imaging Study.

Per Lindqvist

Umeå 2005
The heart on the cover page was drawn by my daughter, Alice

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CONTENTS

ABSTRACT .................................................................................................................. 4
LIST OF PAPERS ......................................................................................................... 5
ABBREVIATIONS ....................................................................................................... 6
A SHORT PERSONAL REFLECTION ...................................................................... 8
INTRODUCTION ......................................................................................................... 9
  Right heart anatomy ............................................................................................... 9
  Right heart physiology ......................................................................................... 10
  Right heart patho-physiology ............................................................................. 11
  Ventricular interaction ......................................................................................... 14
  Assessment of right heart function .................................................................... 15
    Radionuclide techniques ................................................................................. 15
    Computed tomography .................................................................................... 16
    Cardiac catheterisation .................................................................................... 16
    Magnetic resonance imaging ......................................................................... 17
    Doppler echocardiography ............................................................................. 17
    Doppler tissue imaging .................................................................................. 20
OBJECTIVES ........................................................................................................... 21
SUBJECTS AND METHODS ....................................................................................... 22
  Study populations ............................................................................................... 22
  Methods and measurements ............................................................................... 26
    2D/M-mode echocardiography ...................................................................... 27
    Doppler echocardiography ............................................................................. 29
    Doppler tissue imaging .................................................................................. 30
    Cardiac catheterisation .................................................................................... 33
    Statistics ........................................................................................................... 33
RESULTS .................................................................................................................. 34
  Right ventricular inflow and outflow tract systolic function in pulmonary hypertension ........................................................................................................... 34
  Right heart function in healthy subjects ............................................................. 35
  Right heart function in systemic sclerosis .......................................................... 39
  Right heart function in pulmonary hypertension ............................................... 43
  Right ventricular isovolumic contraction velocity and right ventricular state of contractility ........................................................................................................ 44
  Right ventricular isovolumic contraction velocity and right ventricular filling pressures ......................................................................................................... 45
GENERAL DISCUSSION ............................................................................................ 47
CONCLUSIONS ......................................................................................................... 63
ACKNOWLEDGEMENTS ............................................................................................ 65
REFERENCES ............................................................................................................ 68
ABSTRACT

Background: It is well known that performance of the right ventricle (RV) determines exercise capacity and may confer prognostic information in different cardiopulmonary diseases. To allow optimal patient management, ideal methods to assess right heart function are therefore important. Echocardiography is an attractive investigation for that purpose, although limited by the anatomical and functional complexities of the RV.

The aim of the present thesis was to present applicable methods useful in clinical practice by traditional 2D/Doppler echocardiography and Doppler tissue imaging (DTI) in the assessment of global and regional RV function in both health and disease.

Methods: The studies were performed on 4 different groups; (1) 255 healthy subjects (125 females), (2) 92 consecutive patients with different cardiac diseases (36 females), (3) 26 patients with systemic sclerosis, (SSc) (21 females) and (4) 26 consecutive patients with heart failure (8 females) undergoing cardiac catheterisation.

Results: RV outflow tract fractional shortening (RVOT fs), which is a new method in the assessment of RV function, correlated significantly with RV systolic long axis motion (r= 0.66, p< 0.001), pulmonary artery acceleration time (r= 0.80, p< 0.001) and RV-right atrial peak systolic pressure drop gradient (r= -0.53, p< 0.001). Furthermore, RVOT fs was reduced in patients with pulmonary hypertension whereas RV systolic long axis motion was not in difference. This finding was confirmed after comparing RV function with invasive pressures.

In healthy subjects, while the systolic myocardial velocities were preserved over age, the peak isovolumic contraction velocity (IVCv) was weakly increased with advanced age (r= 0.34, p< 0.01). Furthermore, both global and regional E/A ratios were reduced (r= -0.57, r= -0.67, p< 0.001 for both) with age whereas no alteration was found in the myocardial isovolumic relaxation time (IVRt). In patients with systemic sclerosis (SSc) both global (64± 23 vs. 39± 12 ms, p< 0.001) as well as regional (83± 40 vs. 46± 24 ms, p< 0.001) IVRt were prolonged.

After evaluating echocardiographic parameters with invasive pressures we found a significant correlation between DTI derived IVRt and pulmonary artery systolic pressures (r= 0.83, p< 0.01) while the IVCv was related to the state of contractility (r= 0.77, p< 0.001). Furthermore, an IVCv below 6 cm/s was shown to be an accurate marker of increased right atrial pressure (>6 mm Hg).

In conclusion, RVOT fs can be used as a complementary measurement of RV systolic function, being more sensitive to elevated pulmonary artery systolic pressures than the systolic longitudinal RV motion. Right heart function, mainly the diastolic function, is relatively weakly influenced by age compared to the left heart function. In patients with SSc, we found diastolic disturbances, including a prolonged IVRt and proposed the findings to be early markers related to intermittent pulmonary hypertension. This observation was strengthened after evaluating IVRt against invasive pulmonary artery systolic pressures. IVCv can be used to determine the state of RV contractility and also be used to identify patients with elevated filling pressures. The presented methods can be used to detect early signs of RV dysfunction which might prohibit right heart failure. All presented methods are non-invasive, reproducible, easy obtainable, and thus useful in clinical practice.

Key Words: Echocardiography, Doppler tissue imaging, Right ventricle, cardiac catheterisation, isovolumic relaxation, isovolumic contraction
LIST OF PAPERS

This thesis is based on the following original papers and will be refereed in the text by their Roman numerals.


II. P Lindqvist, A Waldenström, M Henein, S Mörner, E Kazzam. Regional and Global Right Ventricular Function in Healthy Individuals Aged 20 to 90 years: A pulsed Doppler tissue imaging study. Umeå General Population Heart Study. Accepted for publication in Echocardiography 2004.

III. P Lindqvist, C Caidahl, G Neuman-Andersen, C Ozolins, S Rantapää-Dahlqvist, A Waldenström, E Kazzam. Disturbed right ventricular diastolic function in systemic sclerosis. Submitted


## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>RV</td>
<td>Right ventricle</td>
</tr>
<tr>
<td>LV</td>
<td>Left ventricle</td>
</tr>
<tr>
<td>RA</td>
<td>Right atrium</td>
</tr>
<tr>
<td>LA</td>
<td>Left atrium</td>
</tr>
<tr>
<td>FAC</td>
<td>Fractional area change</td>
</tr>
<tr>
<td>IVRt</td>
<td>Isovolumic relaxation time</td>
</tr>
<tr>
<td>IVCt</td>
<td>Isovolumic contraction time</td>
</tr>
<tr>
<td>EJt</td>
<td>Ejection time</td>
</tr>
<tr>
<td>RVOT</td>
<td>Right ventricular outflow tract</td>
</tr>
<tr>
<td>RVIT</td>
<td>Right ventricular inflow tract</td>
</tr>
<tr>
<td>PHT</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>DTI</td>
<td>Doppler tissue imaging</td>
</tr>
<tr>
<td>IVCv</td>
<td>Myocardial peak velocity during the isovolumic contraction phase</td>
</tr>
<tr>
<td>E</td>
<td>Peak velocity in early diastole</td>
</tr>
<tr>
<td>A</td>
<td>Peak velocity during atrial systole</td>
</tr>
<tr>
<td>Ev</td>
<td>Myocardial peak velocity in early diastole</td>
</tr>
<tr>
<td>Av</td>
<td>Myocardial peak velocity during atrial systole</td>
</tr>
<tr>
<td>E/A</td>
<td>Ratio of the E and A velocity</td>
</tr>
<tr>
<td>Sv</td>
<td>Myocardial peak systolic velocity</td>
</tr>
<tr>
<td>SSc</td>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>PCG</td>
<td>Phonocardiogram</td>
</tr>
<tr>
<td>BSA</td>
<td>Body surface area</td>
</tr>
<tr>
<td>PACt</td>
<td>Pulmonary artery acceleration time</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>FS</td>
<td>Fractional shortening</td>
</tr>
<tr>
<td>RBBB</td>
<td>Right bundle branch block</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection fraction</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>TR</td>
<td>Tricuspid regurgitation</td>
</tr>
<tr>
<td>PASP</td>
<td>Pulmonary artery systolic pressure</td>
</tr>
<tr>
<td>S₂</td>
<td>Second heart sound</td>
</tr>
</tbody>
</table>
A SHORT PERSONAL REFLECTION

In 1988 I was introduced to the field of echocardiography and was fascinated by the moving heart seen on the ultrasound screen.

However, I found it strange that the function of the right heart was less investigated compared to the left. I realized that not much was actually known about the function of the right heart and therefore, put an “extra eye” and may be 5 more minutes on viewing “the ignored right heart”. I then understood that the function of the right heart is important for overall cardiac function. I decided to further devote my interest in science to it and started a research project while my ambition was to make the assessment of right heart function possible in clinical practice. Today the importance of accurate assessment of RV function is well established.

I’ve tried to evaluate easy methods bearing in mind the respect for all complexities. I hope you find the book useful.

Per
INTRODUCTION

Right heart anatomy

The right ventricle (RV) is placed just beneath the sternum in an anterior position to the left ventricle (LV). The muscle mass of the RV is approximately 1/6 of the LV and this is explained by different loading conditions as it is pumping towards approximately 1/6 the pressure and resistance of the LV. While the LV, under normal conditions, is thick walled and is ellipsoid in shape, the RV is thin walled (3-4 mm) and crescent shaped (1). Furthermore, the RV is anatomically, structurally and functionally divided into two parts, the inflow (IT)- and outflow tract (OT) separated by a thick intra cavitary muscle band called crista supraventricularis (2). A second intra cavitary muscle band runs from septum to the anterior RV wall and is called the moderator band that is attached to the RV outflow tract (3). The apical part of RV is heavily trabeculated and virtually an immobile part of the ventricle.

The IT is mainly composed of circumferential fibres in the subepicardium and longitudinal fibres at the subendocardium. At the OT, both subendocardial and subepicardial fibres run longitudinally, overlain by fibres running at right angle to the outlet long axis, which can be traced to the crista supraventricularis and to the anterior sulcus, serving to bind the two ventricles together. As the inflow and outflow long axis are at right angles to each other, the inflow long axis fibres are perpendicular to those on the diaphragmatic surface, hence running parallel to the outflow with little change in direction (4). The architecture of the outflow tract is described as a bulbar musculature, anatomically and functionally different from the rest of the RV (3, 5). The functional role of the outflow tract is still not fully understood (6) but it has been proposed that it could protect the pulmonary circulation during pressure rise in the RV (5, 7).
Right heart physiology

The overall thin RV is capable of filling and pumping blood at the same rate and volume as the thick walled LV. This is possible considering the characteristics of the venous system and the pulmonary circulation compared to the pulmonary veins and the systemic circulation (8).

- Pulmonary artery pressure and pulmonary vascular resistance are approximately 1/6 of the corresponding systemic values.
- The pulmonary artery pulse amplitude is lower than the systemic pulse amplitude.
- The pulmonary arterial distensibility is higher than systemic arterial distensibility.
- Pulmonary arteries do not exhibit increasing stiffness between central and peripheral sites.
- The peripheral pulse wave reflection in the pulmonary arteries is lower than in the systemic circulation

The RV wall motion is complex (9, 10). During systole, at the inflow tract there is a longitudinal shortening from base to apex and a radial motion towards the common septum. Additional circumferential motion gives a rotation or a squeeze of the ventricle (11). During the phase of isovolumic contraction the ventricle moves in a circumferential direction which is related to the action from subepicardial fibres. The longitudinal shortening of the ventricle occurs mainly during the ejection phase due to the contraction of subendocardial fibres. The ejection of the RV outflow tract occurs approximately 25 ms. after the contraction of the inflow tract which gives an overall peristaltic ventricular motion (5). The contribution of septal motion to RV function in the normal heart and in disease states is not fully understood, but it contributes to both the LV and RV function (12) and is a major determinant of maximal RV function (13).
Right heart pathophysiology

Right heart response to acute and chronic pressure overload

The RV is a thin walled chamber which makes it sensitive to alterations in the pulmonary artery pressure. However, the relationship between the pulmonary artery pressures and RV function is complicated (2, 14). The effect of age, gender, primary pulmonary or secondary pulmonary hypertension, acute or chronic elevation of pulmonary pressures, coexisting volume overload, type of myocardial disease and the presence of elevated right atrial pressure may all be important coexisting factors (15-17). In health the RV ejects to a low impedance vasculature. However, the RV chamber can compensate and adapt when afterload increases slowly, by dilating and developing hypertrophy. The change in the ventricular shape often results in reduced compliance and inability to increase cardiac output (18). In more rapid and pronounced elevation in pulmonary artery pressures, for example in pulmonary embolism, the RV enlarges and if not treated rapidly may cause elevated RV end diastolic and right atrial (RA) pressures leading to severe tricuspid regurgitation and right heart failure. This situation is commonly related to an adverse outcome (19).

Right heart and myocardial blood flow

Maintenance of coronary flow is crucial when RV systolic pressure is elevated. In pulmonary hypertension, RV myocardial oxygen demand is increased and right coronary artery (RCA) perfusion pressure may be unchanged or decreased. Furthermore, as RV perfusion occurs during both diastole and systole, the systolic portion of flow will be diminished as a result of elevated chamber pressures (20, 21). Involvement of RV is present in approximately 40-50% of patients with acute inferior myocardial infarction and may result in haemodynamic compromised situation with a poor clinical outcome. Acute RCA occlusion proximal to the RV branch often results in RV free wall dysfunction. The ischemic RV is stiff, dilated and volume dependent resulting in RV dysfunction. Patients with RV myocardial infarction often respond to volume treatment and early reperfusion enhances the
recovery of RV performance and significantly improves the clinical outcome and improves survival (22).

Right heart function in pulmonary disease

Pulmonary disease affects the RV function by elevation in pulmonary artery pressures and resistance. In patients with chronic obstructive pulmonary disease, (COPD) a wide range of resting pulmonary pressures and grades of RV dysfunction have been reported (23-25). However, depressed RV function may be found in patients with COPD, especially during exercise (26). Previous studies have shown a fall in long axis function in patients with cystic fibrosis (27) and RV diastolic dysfunction in patients with COPD and pulmonary embolism (28).

Right heart function in heart failure and valvular diseases

The RV function is a major determinant of symptoms and exercise capacity in heart failure (29) with poor outcome in patients with RV and RA dilatation (30, 31). A rise in pulmonary pressures related to a longstanding severe mitral and aortic valve disease commonly affects the RV EF. Consequently, tricuspid annulus may dilate and a volume overload due to severe tricuspid regurgitation may result. However, successful treatment of valvular or myocardial disease may improve RV function. Studies have shown that a doubling in the RV afterload (from 25 to 50 mm Hg) decreases RV EF with approximately 10% (from 55 to 45%). A doubling in LV afterload (from 125 to 250 mm Hg) gives a similar reduction in LV EF (15). Mitral valve diseases generally influence the pulmonary pressures and RV function more than aortic valve diseases. PA pressures may normalise within 6 months after successful mitral valve surgery. However, it may stay elevated in patients where severe longstanding pulmonary hypertension (PHT) is found before operation (15). This can be explained by the structural changes of the pulmonary vessels, which may normalise slowly after operation or may be irreversible (32). Therefore, early detection of PHT is important in optimizing patient management. A reduced long axis motion is a mandatory finding after open heart surgery (33), the reason for that is not fully explained. Pericardectomy with loss of lubricating surface at the anterior
surface of the heart, ischemic damage due to poor RV preservation during surgery and right atrial damage due to placement of bypass cannulae are possible factors (34).
Ventricular interaction

Ventricular interaction occurs during pressure and/or volume overloading and refers to the effects of one ventricle transmitted to the other through:

- Septum
- Muscle fibres
- Pericardium
- Blood supply by the coronary arteries
- Pressure-volume changes within the chest cavity

Diastolic interaction

Diastolic interaction may occur on moment-to-moment and beat-to-beat basis when LV filling is reduced during inspiration as an enlarging RV encroaches on the LV by flattening the septum and increasing the pericardial pressures (35). A similar phenomenon has been demonstrated during application of positive end expiratory pressure (PEEP) in mechanical ventilation. High levels of PEEP cause a significant increase in pulmonary artery pressure and RV dilation in association with a decline in LV peak filling rate. Studies have also shown that acute RV volume and pressure overloading result in an upward and leftward displacement of the LV pressure-volume curve, with reduced compliance and altered septal configuration (35). Furthermore, increase in the RV size that occurs during RV ischemia and application of PEEP causes a significant upward shift in the LV diastolic pressure-volume relationship, consistent with reduced LV compliance.
**Systolic interaction**

Systolic ventricular interaction may occur when an increased LV systolic pressure produces an immediate increase in RV systolic pressure. Releasing a partial constriction of the pulmonary artery not only decreases the RV systolic pressure but also the LV systolic pressure (35). As preload is not altered only systolic ventricular interdependence could explain this interaction. A similar interaction is seen after releasing aortic constriction. The systolic bulging of the septum towards RV or LV due to primary ventricular pressure overload generates a significant proportion of stroke volume (35).

**Assessment of right heart function**

*Radionuclide techniques*

Three different techniques have been used to measure the RV EF and regional wall motion abnormalities.

- Gated equilibrium radionuclide angiography (RNA)
- Gated first-pass RNA
- First pass RNA

Comparing these 3 methods with ultra-fast computed tomography estimated RV EF, the strongest correlation was found with gated first-pass RNA. On the other hand, poor correlation was found with gated equilibrium and first-pass RNA. Comparison between gated equilibrium and gated first-pass RNA to cine-magnetic resonance imaging (MRI) showed good correlation between gated first pass and MRI when a two-region–of interest was used. Limitations are the inability to separate the atrium and the ventricle, radiation, high cost, time for acquisition and processing (36).
Computed tomography

Ultra fast cine computed tomography (CT) provides an excellent avenue for assessment of cardiac morphology and comparison to actual RV volumes are shown to be very accurate (37). The method permits high spatial, temporal and contrast resolution for delineation of endocardial and epicardial borders. Furthermore, stroke volume can be determined by planimetry of tomographic volumes applying the Simpson’s rule. Application of this method makes no assumptions of the RV geometry, as commonly done by other methods (37).

Cardiac catheterisation

Determination of intra cardiac pressures and volumes based on invasive technique was previously the most common method in the assessment of cardiac function. Pressures can be obtained at different levels in the right side of the heart. An additional thermo-dilution catheter provides possibility to assess cardiac output. From the cardiac pressure analysis of both the positive and negative derivate from ventricular pressure curve can be done to determine both contractility and relaxation. Absolute and relative contra indications and risk with invasive method are well known limitations. The method can be considered as one of the gold standards (38). However, cardiac catheterisation is today rarely used for the assessment of RV function.
Magnetic resonance imaging

Magnetic resonance imaging has several advantages compared to other techniques, making it suitable for RV imaging. The technique does not require any contrast or use of radiation and calculations of volumes do not depend on geometric assumptions. The natural contrast between blood and tissue allows accurate assessment of regional RV wall motion and chamber size. Recently, it has been shown that myocardial deformation can be assessed by depositing the planes or “tags” after detection of QRS from ECG to capture motion throughout the cardiac cycle (15). Limitations are long acquisition and processing time. Furthermore, availability and cost are other limitations.

Doppler Echocardiography

The use of echocardiography is today well established worldwide. As the RV is positioned close to the sternum and being complex in its geometric shape, assessment by 2-dimensional echocardiography is difficult despite the improvement in image acquisition. Volume- and ejection fraction calculations based on 2-dimensional echocardiography have been reported but are based on mathematical assumptions of RV geometry (39, 40) not attractive in clinical situations. The area change measurement may reflect global and regional wall motion but this technique is mainly a measurement of the inflow tract of the RV (41-43).

By using Doppler echocardiography, estimation of pulmonary artery pressure can be done. The most common way to determine this is by measuring the peak retrograde pressure drop across the tricuspid valve regurgitation (TR) and pulmonary valve regurgitation (PR). The calculation of the pressure gradients can be done by using the modified Bernoulli formula ($\Delta P = 4V^2$). Additional estimation of right atrial pressure can be done from measuring the inferior vena cava dimensions and the hepatic venous flow curve can be used to estimate the pulmonary artery systolic pressure and mean pulmonary pressure (44). Furthermore, pulmonary artery flow acceleration time (PACt) and the RV isovolumic relaxation time (IVRt) are additional methods for estimating pulmonary artery pressure. Among these methods, assessment of TR is most commonly used in clinical practice (45).
A new method in the assessment of RV function utilizes the sum of the isovolumic time intervals divided by the ejection time. This index is called the myocardial performance index (MPI) or Tei index, which is proposed to be correlated to the pulmonary pressures (46).

Due to the RV complexity, the use of 2 dimensional measurement of the systolic long axis motion of the RV free wall has been found to be attractive due its simplicity (47, 48) and shown to correlate with radionuclide angiography derived ejection fraction (31). A limitation in measuring the long axis motion is the lack of information about the outflow tract function and septal contribution (Figure 1).
Figure 1. Echocardiographic views of the right ventricle (RV). A = the RV viewed from apical four chamber view with the right atrium (RA) and the inflow tract of the RV. B = the RV is viewed from parasternal short axis view with RV outflow tract (RVOT), RA, pulmonary valve (PV), tricuspid valve (TV) and aortic valve (AV) visualised.

The systolic long axis amplitude has been shown to be only weakly related to pulmonary artery systolic pressures (49, 50). Annular motion, assessed by 2D/M-mode echocardiography or Doppler tissue imaging (DTI) can also be used to measure the RV diastolic function (51).
Three-dimensional echocardiography may have a potential advantage in determining RV volumes. Image reconstruction can be performed both on-line and off-line (52, 53). However, the technique is very time consuming and therefore remains far from being clinically applicable.

**Doppler tissue imaging and strain echocardiography**

Doppler tissue imaging (DTI) is a new echocardiographic tool in the assessment of ventricular function. The method is available in most modern ultrasound systems and can provide accurate information about myocardial motion throughout the cardiac cycle (54, 55). In contrast to traditional pulsed Doppler echocardiography, which detects high velocity with low frequency, Doppler tissue imaging reflects low velocity with high frequency. To display tissue velocities, two relatively simple alterations in the Doppler signal are required: (i) the high pass filter is bypassed and (ii) lower gain amplification is used to eliminate the weaker intensity blood flow signals (56). Tissue velocities can be displayed with spectral pulsed, colour-encoded M-mode or two dimensional- mode, with pulsed Doppler measuring peak velocities and colour Doppler mean velocities (54). Doppler tissue imaging is proposed to be less preload dependent compared to traditional pulsed Doppler technique (57). Recently, strain and strain rate techniques have been shown to quantify regional deformation, but this technique is mainly derived from mechanical engineering and is today not widely used in clinical practice (58). However, pulsed Doppler technique is the simplest and most robust to use, with high temporal resolution and being on-line informative (59). The major disadvantage of pulsed DTI is poor spatial resolution due to movement of the heart while the sample volume is fixed (60).
OBJECTIVES

I. To explore a new and simple method for the assessment of right ventricular function by measuring the outflow tract fractional shortening (RVOT fs).

II. To investigate right ventricular function in healthy subjects using Doppler tissue imaging and conventional 2D/Doppler echocardiography.

III. To evaluate right ventricular function in patients with systemic sclerosis using Doppler tissue imaging.

IV. To evaluate the use of Doppler tissue imaging derived isovolumic relaxation time to estimate the pulmonary artery pressure, by comparison with simultaneous invasive pressures.

V. To evaluate the use of Doppler tissue imaging derived isovolumic contraction velocity to estimate right ventricular contractile function, by comparison with simultaneous invasive pressures.
SUBJECTS AND METHODS

Study populations

Study I

The study population consisted of 92 consecutive subjects referred for echocardiographic examination (mean age 67±14 years, range 19-95, 56 males). For comparative purposes, 20 healthy controls (mean age 46±12 years, 10 males) were studied.

Study II

Umeå General Population Heart Study

Every resident in Sweden has a national registration number that includes the date of birth. The numbers are registered and controlled by the Swedish tax authority in a national register, including vital statistics and which by law, must be kept up to date. The registration number consists of the date of birth plus four digits where the third digit indicates female (even) or a male (odd). On this basis, one thousand (500 females) subjects born at five years intervals (e.g. 1905, 1910, 1915 up 1975, a total of fifteen age groups) were randomly drawn from the register. Information about the nature of the project and invitation to participate were sent to those subjects. Inclusion criteria were absence of any known cardiovascular or systemic disease and absence of any medication which could influence cardiac function. This was further checked by a telephone interview. A specially designed questionnaire was sent to all subjects before enrolment. Subjects with diabetes, hypertension, hyperlipidemia, history of rheumatic fever, transient ischemic attack, stroke and intermittent claudication were excluded. Three hundred subjects (ten from each age group, with equal sex distribution) were included. Despite these precautions, 45 subjects had to
be excluded after the examinations; 23 had blood pressure > 160/90 mm Hg, 3 had moderate aortic stenosis, 13 had abnormal ECG (3 LBBB, 4 RBBB, 6 LAH) and 6 were on anti-hypertensive therapy.

The upper limit for blood pressure in our study population was 160/90 mm Hg chosen because of the very wide age span (61). The remaining 255 subjects (mean age ± SD, 58± 19 years, and range 22-89, 125 females) constituted the study population. All subjects were coded and analyse were made blindly. All subjects gave informed consent for the study, which was approved by the ethics committee of Umeå University.

Study III

Twenty-six consecutive patients (21 females) with systemic sclerosis (SSc) according to the previously defined criteria for SSc (62) were studied. Eighteen of the patients fulfilled the criteria for limited disease (lcSSc), and 2 patients had the diffuse cutaneous type (dcSSc) (63). Six of the SSc patients with high titres of RNP antibodies also fulfilled the criteria for mixed connective tissue disease (MCTD) (64). The mean age of the studied group was 56±15 (range 26-78) years and the disease had been recognized for 11.8±8.7 (range 1-35) years. The extent of skin involvement was assessed according to the modified Rodnan model C with 8 unilateral sites and a maximum of 16 points (65). All patients except for one had Raynaud’s phenomenon (66). Seven of the patients were severely affected with digital pitting scars or ulcers, and 2 had had fingers amputated. Six patients were receiving medical treatment with ACE inhibitors and/or beta-blockers. For comparison, 25 healthy subjects (21 females) with a mean age of 56±16 (range 25-76) years were used as controls. All the patients and controls gave their consent to participate in the study, which was approved by the local ethics committee. Seven of the patients and four of the controls were smokers.
Studies V and IV

The study population consisted of 26 consecutive patients (18 males) referred for cardiac catheterisation. Mean age was 52±12 years (range 23-75). The underlying diagnoses were: hypertrophic cardiomyopathy (HCM) (n=2), dilated cardiomyopathy (DCM) (n=10), previous transplanted hearts (n=4), systemic hypertension (n=1), mitral valve prosthesis dysfunction (n=1), heart failure due to longstanding aortic stenosis (n=1), mitral valve disease (n=2), ischemic heart disease (n=1) and primary pulmonary hypertension (n=4). All were in sinus rhythm and patients with complete right bundle branch block were excluded. Medication: Nine were on diuretics, 12 were on ACE-inhibitor, 12 were on beta blockers, 1 was on digitalis and 6 were on calcium antagonists (Table 1). All the patients gave their consent to participate in the study, which was approved by the local ethics committee.
Table 1. Patient characteristics in studies V and VI

<table>
<thead>
<tr>
<th></th>
<th>DCM</th>
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<th>sPHT</th>
<th>pPHT</th>
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<td>6</td>
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<td>Age (years)</td>
<td>49±9</td>
<td>56±8</td>
<td>60±8</td>
<td>30±9</td>
<td>64±6</td>
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<td>HR (bpm)</td>
<td>62±12</td>
<td>76±14</td>
<td>89±16</td>
<td>74±14</td>
<td>73±1</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>118±21</td>
<td>152±31</td>
<td>131±26</td>
<td>120±30</td>
<td>128±16</td>
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<td>DBP (mm Hg)</td>
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<td>92±2</td>
<td>77±13</td>
<td>68±13</td>
<td>85±7</td>
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<td>Gender (m/f)</td>
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<td>4/0</td>
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<td>BSA (m²)</td>
<td>2.07±0.26</td>
<td>2.15±0.17</td>
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<td>1.75±0.21</td>
<td>2.15±0.21</td>
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<td>NYHA (I/II/III/IV)</td>
<td>0/4/5/1</td>
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<td>0/2/2/2</td>
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<tr>
<td>PASP (mm Hg)</td>
<td>47±32</td>
<td>32±3</td>
<td>71±39</td>
<td>90±26</td>
<td>42±0</td>
</tr>
<tr>
<td>RAMP (mm Hg)</td>
<td>7±5</td>
<td>6±2</td>
<td>12±7</td>
<td>14±10</td>
<td>8±4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35±11</td>
<td>54±15</td>
<td>31±23</td>
<td>72±7</td>
<td>43±19</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>71±11</td>
<td>52±11</td>
<td>50±7</td>
<td>43±12</td>
<td>54±18</td>
</tr>
<tr>
<td>RVS long axis (mm)</td>
<td>18±5</td>
<td>17±2</td>
<td>16±9</td>
<td>13±7</td>
<td>13±1</td>
</tr>
</tbody>
</table>

DCM= dilated cardiomyopathy; sPHT= secondary pulmonary hypertension; pPHT= primary pulmonary hypertension; HR= heart rate; SBP= systolic blood pressure; DBP= diastolic blood pressure; BSA= body surface area; PASP= pulmonary artery systolic pressure; RAMP= right atrial mean pressure; LVEF= left ventricular ejection fraction; LVDD= left ventricular diastolic diameter; RVS= right ventricular systolic.
Methods and measurements

Ultrasound systems in the studies

Study I. Echocardiography was performed using the commercially available system (ATL HDI Ultramark 9, Philips Ultrasound, Bothell, Wash, U.S.A) equipped with a 2.0-3.0 MHz phased array transducer. Patients were examined in the left lateral decubitus position. All echocardiographic examinations were performed by the same investigator.

Study II. The examinations were performed with the subjects in the left lateral decubitus position and recordings were taken during expiration. A commercially available ultrasound system (Acuson Sequoia, Mountain View, Calf, U.S.A) equipped with a multi frequency phased array transducer (3V2c) and pulsed DTI technique was used. The echocardiographic examinations were performed by three experienced investigators.

Study III. Echocardiography was performed using an Acuson 128 XP Ultrasound system (Acuson Co, Mountain View, CA, U.S.A) equipped with a 2.5-4.0 MHz (V4c) transducer and Doppler Tissue Imaging (DTI) technology. The examinations were performed with the subject lying in left lateral decubitus position and tracings recorded at the end expiratory phase. All echocardiographic examinations were performed by the same investigator.

Study IV and V. Two-dimensional and Doppler echocardiographic examinations were performed simultaneously with cardiac catheterisation. The patients were in stable haemodynamic condition. The echocardiographic examinations were performed with the subjects in the supine position. A commercially available ultrasound system (HP, Sonos 5500, Andover, Mass. U.S.A) equipped with a multi frequency phased array transducer (S4, 2-4 MHz and S3, 1-3 MHz) and pulsed DTI
technology was used. One experienced investigator performed all the echocardiograms.

In the Studies II, III, IV and V, a phonocardiogram was applied to detect the pulmonary component of second heart sound (S₂) to determine the end of systole.

2D/M-mode echocardiography

Two-dimensional echocardiograms from the parasternal short axis view were obtained at the level of the aortic root and the RV outflow tract level 4 was studied (RVOT) (1). M-mode recordings of the RV outflow tract were obtained and dimensions were measured at end diastole (onset of the q wave) and end systole (end of T-wave) using endocardial leading edge methodology. Right ventricular outflow tract fractional shortening (RVOT fs) was calculated as the percentage fall in RV outflow tract diameter in systole with respect to that in diastole. Furthermore, from the same position, the RV anterior free wall systolic motion and the end diastolic wall thickness were measured. RV long axis function was recorded from the apical 4-chamber view with the M-mode cursor positioned at the free wall angle of the tricuspid valve annulus. Systolic RV long axis amplitude was measured from end systole (pulmonary component of S₂) to end diastole (q wave). Furthermore, early diastolic and late atrial amplitudes were also measured (67). From the same transducer position RV end diastolic and systolic areas were manually measured and the RV fractional area change (RV FAC) was calculated (Figure 2).
Figure 2. Right ventricular inflow tract (upper left) with normal long axis motion (lower left). Right ventricular outflow tract (upper right) with normal fractional shortening (lower right).

From M-mode echocardiography recordings, the following measurements were made according to the recommendations of the American Society of Echocardiography (68). The internal left ventricular (LV) end diastolic and end systolic diameters, ventricular septal and posterior wall thickness at end diastole were measured. Left ventricular fractional shortening was calculated as the fall in systolic diameter divided by the end diastolic diameter. The LV volume was measured and the ejection fraction was calculated using the modified Simpson’s rule from the apical four- and two-chamber views (69). The left atrial (LA) and right atrial (RA) areas were traced manually and measured at end systole from the apical four-chamber view.
Doppler echocardiography

Mitral and tricuspid flow velocities were obtained from apical 4-chamber view, with the sample volumes placed at the tips of the respective valve leaflets. The presence of valvular regurgitation was determined by colour Doppler. Tricuspid peak regurgitation velocities were recorded using the continuous wave Doppler technique and the Bernoulli’s modified equation (AP= 4V²) was used to estimate the right ventricular - right atrial peak pressure gradient. The pulmonary artery flow velocity was recorded from the parasternal short-axis view with the sample volume placed at the central position of the valves. From the mitral- and tricuspid blood flow velocity profiles, the following measurements were made partly according to the recommendations of the American Society of Echocardiography (70):

1/ Peak early (E) and late (A) diastolic velocities and E/A ratio were calculated.
2/ E-wave deceleration time (E-DT).
3/ Isovolumic relaxation time (IVRt) was measured as the time interval from pulmonary component of S₂ to the onset of E-wave.
4/ The mitral and tricuspid filling time was measured as the time interval from the onset of E-wave to the cessation of A-wave.

From the pulmonary artery flow we measured:

1/ The acceleration time (PACt) defined as the interval from onset to peak velocity.
2/ The pre-ejection period (PEP) was measured as the time from the onset of Q wave from the ECG to the onset of ejection.
3/ The ejection time (EJt) was measured as the time between the onset to end of the ejection flow. All measurements were obtained from three beats.
Doppler tissue imaging

Myocardial systolic and diastolic velocities were recorded using the pulsed wave DTI technique. Velocities were obtained from the apical 4-chamber view. The sample volume was placed at the basal, mid segmental and apical level of the RV free wall (71, 72). Pulsed Doppler tissue imaging was used to measure myocardial velocities and time intervals, as previously suggested (55, 73).

From DTI recordings (Figure 3A and B), the following measurements were made:

1/ Peak isovolumic contraction velocity (IVCv).
2/ Peak systolic velocity (Sv).
3/ Peak early (Ev) and atrial (Av) diastolic velocities and the E/A ratio were calculated.
4/ Isovolumic contraction time (IVCt), as the time interval from the end of atrial (Av) to the onset of systolic flow (Sv) components.
5/ Ejection time (EJt) was measured from the onset of ejection to its end,
6/ Isovolumic relaxation time (IVRt), as the time interval from pulmonary component of S₂ to the onset of early diastolic velocity (Ev). The measurements were taken from three beats.
Figure 3A. Myocardial velocities and timings from Doppler tissue imaging. 
Ev = early diastolic velocity; Av = atrial velocity; IVCv = isovolumic contraction velocity; Sv = systolic velocity during the ejection phase; IVCt = isovolumic contraction time, time interval between 1 and 2; EJt = ejection time, time interval between 2 and 3; IVRt = isovolumic relaxation time, time interval between 3 and 4.
Figure 3B. Schematic presentation of the relation between Doppler tissue imaging tracings and invasive pressure. Myocardial velocities and timings from Doppler tissue imaging; Ev= early diastolic velocity; Av= atrial velocity; IVCv= isovolumic contraction velocity; Sv= systolic velocity during the ejection phase; IVCT= isovolumic contraction time; EJt= ejection time; IVRT= isovolumic relaxation time.
Cardiac catheterisation

One experienced investigator performed all the cardiac catheterizations. Briefly, a balloon catheter was inserted through the right internal jugular vein or right brachial vein (Becton Dickinson Criticath SP 5107 HTD catheter). Pressures were registered with a Cathcor® system 3.3 (Siemens Elema AB, Electro-medical systems divisions, Solna, Sweden). Pressure in the studies was taken at pulmonary artery, right ventricle and right atrium.

Statistics

All data analysis was performed using the Statistical Package for Social Sciences (SPSS 10.1 and 11.5, SPSS Inc., Chicago, Illinois, USA). All data are presented as mean ±SD. Pearson’s correlation and linear regression analyses were performed to display certain relationships. Student’s paired t-test was used to compare values within groups whereas unpaired Student’s t-test was used to compare two groups. Mann-Whitney non-parametric test was used when appropriate. Stepwise multiple regression analysis was performed to assess the influence of age, systolic and diastolic blood pressure, body surface area and heart rate on RV diastolic function in healthy subjects. A p-value less the 0.05 was considered as significant.

Reproducibility of the measurements

Reproducibility of data that were analysed by repeating measurements by the same investigator (intra-observer) and independently by a second investigator (inter-observer) from 10 consecutive tracings, Studies II, III, IV and V. The measurements were done from MO discs copied to an ultrasound machine. In Study I 13 paper printouts were randomly selected for analysing inter-and intra-observer variability. Furthermore, in study I we investigated the beat to beat variability within 20 minutes by two different investigators. Variability was expressed as the coefficient of variation (CV) which is calculated as standard deviation of the difference from 2 observers divided by mean value from the same two observations, expressed as percentage.
RESULTS

Right ventricular inflow and outflow tract systolic function in pulmonary hypertension

Whereas the longitudinal systolic free wall motion showed no relationship to the pulmonary artery pressure, the fractional shortening at the outflow tract were significantly correlating to the pulmonary artery systolic pressure (Studies I and V). In patients with different cardiac diseases, the tricuspid regurgitation estimated RV-RA pressure gradient was elevated and the RVOTfs, the long axis amplitude and the pulmonary acceleration time were all decreased compared to the healthy controls. The RVOTfs correlated positively with RV long axis amplitude ($r= 0.66$, $p< 0.001$), PA acceleration time ($r= 0.80$, $p< 0.001$) and inversely with the tricuspid regurgitation estimated RV-RA pressure gradient ($r= -0.53$, $p< 0.001$). Importantly, in patients with elevated RV-RA pressure drop (> 35 mmHg) RVOTfs was reduced and PA acceleration time was shorter compared to patients while the RV systolic long axis amplitude was not different (Table 2) (Figure 4).

Table 2. Right ventricular systolic function and pulmonary artery pressures

<table>
<thead>
<tr>
<th></th>
<th>≤ 35 mm Hg</th>
<th>&gt; 35 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVOT fs (%)</td>
<td>43±18</td>
<td>26±10 *</td>
</tr>
<tr>
<td>RVLX (mm)</td>
<td>18±7</td>
<td>15±7 ns</td>
</tr>
<tr>
<td>PACt</td>
<td>104±31</td>
<td>66±15 *</td>
</tr>
</tbody>
</table>

RVOTfs= right ventricular outflow -tract fractional shortening; RVLX = right ventricular long axis excursion; TR = tricuspid regurgitation; RV = right ventricle; RA = right atrium; PACt = pulmonary artery acceleration time. *p<0.001; ns=not significant;
After evaluating RVOT fs and simultaneously obtained invasive pulmonary artery pressures, (Study IV) RVOT fs correlated inversely with pulmonary artery systolic pressures (PASP) (r = -0.47, p < 0.05) whereas RV fractional area change (RVFAC) and RV systolic long axis amplitude did not.

In this study thirteen recordings were randomly selected for offline analysing of intra- and inter-observer variability. Furthermore, another 13 registrations obtained within approximately 20 minutes by two different observers to determine beat-to-beat inter-observer variation. Intra-inter and beat-to-beat variability of RVOT fs varied from 15 to 19 %.

**Right heart function in healthy subjects**

*Regional myocardial function assessed with Doppler tissue imaging.*

Recordings of the RV free wall function were measurable in 98% of the subjects from the basal level, in 79% at the mid cavity level but only in 44% at the apical level. Isovolumic contraction velocities were 27% higher at the base compared to the apical level and the systolic myocardial velocities were 38% higher at the basal
level than at the apical level. The same pattern was found in the diastolic velocities. RV systolic and diastolic velocities were not different between the basal and mid cavity levels but apical E/A ratio was significantly higher compared to the basal one. The isovolumic contraction and relaxation time intervals were significantly longer at both the mid cavity and the apical level compared to the basal level. Inversely, ejection time was found to decrease from the basal to the apical level. Reference values for segmental pulsed Doppler imaging peak velocities and time intervals are presented in Tables 3 and 4.

Table 3. Regional myocardial velocities and time intervals in 255 healthy subjects from UGPHS.

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Mid</th>
<th>Apical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>IVCv, cm/s</td>
<td>15.1±6.1</td>
<td>15.5±6.0</td>
<td>11.0±4.4*</td>
</tr>
<tr>
<td>Sv, cm/s</td>
<td>15.2±2.8</td>
<td>14.5±2.6</td>
<td>9.3±2.6*</td>
</tr>
<tr>
<td>Ev, cm/s</td>
<td>14.5±3.5</td>
<td>14.1±3.7</td>
<td>10.8±2.8*</td>
</tr>
<tr>
<td>Av, cm/s</td>
<td>16.2±3.1</td>
<td>16.6±5.5</td>
<td>10.9±2.9*</td>
</tr>
<tr>
<td>E/A</td>
<td>0.97±0.37</td>
<td>0.94±0.39</td>
<td>1.27±0.93†</td>
</tr>
<tr>
<td>IVRt, ms</td>
<td>53±28</td>
<td>58±38‡</td>
<td>99±47‡</td>
</tr>
<tr>
<td>IVCt, ms</td>
<td>91±26</td>
<td>100±30*</td>
<td>114±36*</td>
</tr>
<tr>
<td>EJt, ms</td>
<td>263±35</td>
<td>259±38</td>
<td>220±51*</td>
</tr>
</tbody>
</table>

IVCv= isovolumic contraction velocity; Sv= systolic velocity; Ev= early diastolic velocity; Av= atrial velocity, IVRt= isovolumic relaxation time; IVCt= isovolumic contraction time; EJt= ejection time; P-value * < 0.001; †< 0.01; ‡ < 0.05, all compared to the base.
Table 4. Regional myocardial velocities and their time intervals in different ages.

<table>
<thead>
<tr>
<th></th>
<th>Young (20-39, n=80)</th>
<th>Middle aged (40-59, n=80)</th>
<th>Elderly (60-79, n=75)</th>
<th>Old (&gt;80, n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean±SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVCv, cm/s</td>
<td>12.3±4.0</td>
<td>15.1±4.8‡</td>
<td>17.7±7.9†</td>
<td>15.2±4.6</td>
</tr>
<tr>
<td>Sv, cm/s</td>
<td>15.5±2.6</td>
<td>14.9±2.7</td>
<td>15.4±3.2</td>
<td>14.9±2.0</td>
</tr>
<tr>
<td>Ev, cm/s</td>
<td>16.1±3.1</td>
<td>14.6±3.2†</td>
<td>13.0±3.5†</td>
<td>12.1±2.9‡</td>
</tr>
<tr>
<td>Av, cm/s</td>
<td>13.4±3.9</td>
<td>15.8±3.9†</td>
<td>18.9±5.6†</td>
<td>20.0±4.7†</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3±0.4</td>
<td>1.0±0.2*</td>
<td>0.7±0.2*</td>
<td>0.6±0.1*</td>
</tr>
<tr>
<td>IVRt, ms</td>
<td>53±26</td>
<td>51±28</td>
<td>55±29†</td>
<td>54±25</td>
</tr>
<tr>
<td>IVCt, ms</td>
<td>90±22</td>
<td>88±21</td>
<td>91±28</td>
<td>112±39†</td>
</tr>
<tr>
<td>EJt, ms</td>
<td>260±31</td>
<td>262±34</td>
<td>269±38</td>
<td>267±38</td>
</tr>
<tr>
<td>Mid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVCv, cm/s</td>
<td>12.7±4.2</td>
<td>16.7±6.2‡</td>
<td>17.4±7.0†</td>
<td>14.7±2.4</td>
</tr>
<tr>
<td>Sv, cm/s</td>
<td>13.6±2.6</td>
<td>12.2±2.6†</td>
<td>13.4±3.3</td>
<td>13.2±3.2</td>
</tr>
<tr>
<td>Ev, cm/s</td>
<td>15.8±3.2</td>
<td>14.0±3.9†</td>
<td>13.0±3.4†</td>
<td>11.9±2.2*</td>
</tr>
<tr>
<td>Av, cm/s</td>
<td>13.2±3.4</td>
<td>16.9±5.1*</td>
<td>19.2±6.2*</td>
<td>21.4±3.5*</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3±0.4</td>
<td>0.9±0.3*</td>
<td>0.7±0.2*</td>
<td>0.6±0.1*</td>
</tr>
<tr>
<td>IVRt, ms</td>
<td>52±37</td>
<td>53±34</td>
<td>69±42</td>
<td>62±33</td>
</tr>
<tr>
<td>IVCt, ms</td>
<td>98±25</td>
<td>101±29</td>
<td>98±29</td>
<td>125±54</td>
</tr>
<tr>
<td>EJt, ms</td>
<td>263±29</td>
<td>254±44</td>
<td>258±42</td>
<td>269±31</td>
</tr>
<tr>
<td>Apical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVCv, cm/s</td>
<td>10.6±5.2</td>
<td>12.4±3.4</td>
<td>11.9±3.9</td>
<td>11.0±0.9</td>
</tr>
<tr>
<td>Sv, cm/s</td>
<td>9.7±2.6</td>
<td>8.7±1.8</td>
<td>9.0±2.5</td>
<td>9.8±4.0</td>
</tr>
<tr>
<td>Ev, cm/s</td>
<td>12.0±2.9</td>
<td>10.7±2.3</td>
<td>9.8±2.5†</td>
<td>9.8±2.8</td>
</tr>
<tr>
<td>Av, cm/s</td>
<td>8.8±1.7</td>
<td>10.0±3.7</td>
<td>11.9±3.7†</td>
<td>11.4±2.3‡</td>
</tr>
<tr>
<td>E/A</td>
<td>1.4±0.4</td>
<td>1.6±1.8</td>
<td>0.90±0.4*</td>
<td>0.9±0.6‡</td>
</tr>
<tr>
<td>IVRt, ms</td>
<td>94±44</td>
<td>97±51</td>
<td>107±48</td>
<td>97±50</td>
</tr>
<tr>
<td>IVCt, ms</td>
<td>120±33</td>
<td>121±33</td>
<td>102±36</td>
<td>106±52</td>
</tr>
<tr>
<td>EJt, ms</td>
<td>217±49</td>
<td>231±31</td>
<td>215±56</td>
<td>245±69</td>
</tr>
</tbody>
</table>

IVCv= isovolumic contraction velocity; Sv= systolic velocity; Ev= early diastolic velocity; Av= atrial velocity; IVRt= isovolumic relaxation time; IVCt= isovolumic contraction time; EJt = ejection time; P-value ; *< 0.001; †< 0.01; ‡< 0.05, all compared with the young group.
Regional and global RV function and age in healthy subjects

By using pulsed Doppler tissue imaging, right ventricular peak systolic velocity, isovolumic contraction time and ejection time were not related to age in any of the segments. However, age was correlated to the diastolic myocardial velocities, inversely with Ev and directly with Av at all three levels. E/A ratio was therefore negatively correlated with age at all levels, again with the strongest relationship at the basal and mid cavity levels. Regional IVRt did not correlate with age in any segment of the RV, but IVCv at basal and mid cavity segment weakly increased with age (r = 0.34 and r = 0.30 respectively, p< 0.01). When traditional pulsed Doppler technique was used, the tricuspid peak early diastolic velocities fell whereas the peak atrial velocities, early diastolic deceleration time and isovolumic relaxation time increased with age. The E/A ratios were reduced with increasing age (Table 5).

Table 5. Global diastolic RV function and age

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Range</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E, cm/s</td>
<td>43±11</td>
<td>21-93</td>
<td>-0.39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>A, cm/s</td>
<td>31±10</td>
<td>8-71</td>
<td>0.35</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.53±0.80</td>
<td>0.62-4.29</td>
<td>-0.57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E-DT, ms</td>
<td>187±58</td>
<td>72-380</td>
<td>0.38</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RV-RA ΔP, mm Hg</td>
<td>22±6</td>
<td>7-44</td>
<td>0.29</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVRt, ms</td>
<td>31±16</td>
<td>5-90</td>
<td>0.29</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

E= early diastolic velocity; A= atrial velocity, E-DT= early diastolic deceleration time; IVRt= isovolumic relaxation time RV= right ventricle; RA= right atrium; ΔP= pressure gradient.

Relationship between regional and global RV diastolic function

Early diastolic RV myocardial velocities at the basal and mid-ventricular level correlated weakly with tricuspid E-wave velocity. Late atrial myocardial velocity at the base (r = 0.32, p< 0.001), the mid (r = 0.25, p< 0.001) and apical level (r = 0.20, p< 0.05), all correlated with the corresponding tricuspid flow A-velocity.

Myocardial E/A ratio and IVRt at the basal level (r = 0.58, p< 0.001, r = 0.25, p< 0.05 respectively) and mid cavity level (r = 0.46 and r = 0.23, p< 0.001 for both) correlated with the corresponding tricuspid flow measurements.
The IVCv significantly correlated with its corresponding Av at all three levels of the RV free wall, basal ($r= 0.74$, $p< 0.001$), mid ($r= 0.58$, $p< 0.001$) and apical level ($r= 0.47$, $p< 0.001$) (Figure 5).

**Figure 5.** The relationship between the isovolumic contraction velocity (IVCv) and the atrial contraction velocity (Av) at the basal level of RV.

**Reproducibility of the measurements**

The inter- and intraobserver variability, expressed as coefficient of variation, was within the interval of 7-12% for tricuspid flow measurements and 4-21% for DTI measurements.
Right heart function in systemic sclerosis

Contrary to previous reports, (74, 75) we did not find differences in LV dimensions, LV wall thickness, LV systolic or diastolic function in patients with SSc compared to controls. Right ventricular systolic function was not abnormal, regardless whether it was determined from M-mode, conventional Doppler or DTI recordings. However, the pulmonary artery acceleration time was reduced among the patients (119±34 vs. 141±29 ms, p< 0.05).

The disturbances were found due to the RV diastolic function (Table 6), as right ventricular IVRt, global (64±23 vs. 39±13 ms, p< 0.001) and regional (83±40 vs. 46±24 ms, p< 0.001), were prolonged (Figures 6A and B) whereas RV global E/A ratio was reduced (1.2±0.4 vs.1.7±0.6, p< 0.01). These diastolic abnormalities were still significant despite adjustments for heart rate, which was increased among patients. Right atrial end systolic area (15.9±3.7 vs. 13.0±2.3 cm², p< 0.01) and RV outflow tract wall thickness were also increased among patients. (5.8±1.7 vs. 3.7±1.1 mm, p< 0.001)
Table 6. Right ventricular diastolic function in patients with systemic sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>SSc</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=25)</td>
<td>(n=26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Conventional Doppler Measurements (Global Function)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF RR (ms)</td>
<td>949±126</td>
<td>870±141</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>TF filling time (ms)</td>
<td>548±104</td>
<td>454±122</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>TF filling time/RR (%)</td>
<td>58±7</td>
<td>52±7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>39±13</td>
<td>64±23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVRT/RR (%)</td>
<td>4.2±1.7</td>
<td>7.5±2.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E-velocity (cm/s)</td>
<td>40.2±9.8</td>
<td>41.9±11.6</td>
<td>0.58</td>
</tr>
<tr>
<td>A-velocity (cm/s)</td>
<td>25.9±7.5</td>
<td>36.0±12.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.7±0.6</td>
<td>1.2±0.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>187±60</td>
<td>188±52</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Doppler Tissue Imaging (Regional Function)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV RR (ms)</td>
<td>941±127</td>
<td>871±117</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>E-velocity (cm/s)</td>
<td>12.9±4.8</td>
<td>12.1±3.2</td>
<td>0.52</td>
</tr>
<tr>
<td>A-velocity (cm/s)</td>
<td>13.9±5.0</td>
<td>15.0±3.9</td>
<td>0.43</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.0±0.6</td>
<td>0.9±0.6</td>
<td>0.41</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>46±24</td>
<td>83±40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVRT/RR (%)</td>
<td>5.0±2.7</td>
<td>9.6±4.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Velocities in cm/s. E= early diastolic velocity; A= late atrial diastolic velocity; TF= tricuspid flow; RV= right ventricle, RR= R-R time interval; IVRT= isovolumic relaxation time, E/A= early diastolic to atrial component velocity ratio.
Figure 6. (A) DTI recordings from the RV free wall in a healthy subject. (B) DTI recordings from the RV free wall in a patient with SSc. Note the in-coordinated and prolonged wall motion during the isovolumic relaxations phase (IVRt) in the SSc patient (B).

The extent of RV diastolic dysfunction was not related to the duration of the disease, the SSc skin score or influenced by medication such as beta-blockers and/or ACE inhibitors. Furthermore, age, blood pressure, creatinine clearance, height, weight and body surface area did not differ between patients and controls. Thirteen (59%) of the patients (2 with diffuse, 3 with MCTD and 8 with limited type) had a diffusion capacity of carbon monoxide (DLCO) below 80% of the predicted value. Six of the patients showed signs of fibrosis from the high resolution computed tomography (HRCT) scans. (76) One had ground glass confined to lower parts of both lung lobes, one had reticular pattern fibrosis with mild honeycombing in the lower parts of both lower lung lobes, three had fibrosis in the lower parts of both lower lung lobes and one reticular pattern fibrosis at lower parts of both lower lung lobes.

*Inter- and intraobserver variability*

Parameters which differed significantly between patients and controls were controlled for their inter- and intra-observer variability. Ten randomly selected tracings were analyzed independently by two different observers and by the same observer on two different occasions. The coefficient of variation varied between 3%
and 14% for intra-observer variability and between 3% and 15% for inter-observer variability.

**Right heart function in pulmonary hypertension**

In Study III we found that IVRt was prolonged in patients with SSc and therefore suggested that it could be caused by an intermittent pulmonary hypertension due to Raynaud’s disease in the pulmonary arteries. We therefore evaluated the IVRt from DTI with simultaneous invasive pressures. A significant correlation was found between PASP and regional DTI IVRt at mid cavity level ($r=0.52$, $p<0.05$) which was improved at both base and mid cavity levels after correcting for heart rate, IVRt/RR% ($r=0.42$, $p<0.05$ and $0.71$, $p<0.01$, respectively). When only including patients with right atrial pressures < 8 mm Hg higher correlation coefficients were seen to myocardial basal IVRt/RR% ($r=0.65$, $p<0.05$) and mid cavity ($r=0.76$, $p<0.01$). Furthermore, when only patients with normal right atrial pressures (< 7 mm Hg) were taken into account the correlation further improved at both segments ($r=0.74$, $p<0.05$, $r=0.83$, $p<0.01$, Figure 7) RV-RA peak pressure gradient was highly significant correlated to PASP ($r=0.90$, $p<0.001$). However despite the catheter placement through the tricuspid valves the RV-RA peak pressure gradient was only detectable in 19 cases (73 %) while DTI derived IVRt at both segments was measured in almost all patients (96 %).
Figure 7. Relationship between DTI derived IVRt/RR (%) for the right ventricle and pulmonary artery systolic pressures in patients with normal right atrial pressures (<7 mm Hg).

**Reproducibility of IVRt**

Inter- and intraobserver variability in IVRt measurements were tested by repeated measurements in 10 consecutive tracings. Variability is expressed as the coefficient of variation. The inter- and intraobserver variability of DTI IVRt was 12.2% for both.

**Right ventricular isovolumic contraction velocity and right ventricular contractility**

Previous studies have shown that the wall motion during IVC is influenced by the state of contractility (77). We therefore tested the relation between peak myocardial IVCv and dP/dt/P\textsubscript{max}. In all patients, a significant relationship was found between dP/dt/P\textsubscript{max} and IVCv at mid cavity level of the right ventricular free wall (r= 0.59,
p< 0.01). Furthermore, when only patients with atrial pressure < 8 mm Hg were taken into account, the relationship at both basal and mid segmental levels were strengthened (r= 0.69, p< 0.01 and r= 0.77, p< 0.001, Figure 8). We found no relationship between RV systolic long axis motion, right ventricular area change, right ventricular outflow tract fractional shortening or Sv at any segment to dP/dt/P_max, neither in total group nor in the subgroup with atrial pressure < 8 m Hg. The IVCv at basal and mid segmental level did not correlate with pulmonary artery systolic pressure or pulmonary artery resistance, right ventricular end diastolic dimension or heart rate.

![Figure 8. The relationship between IVCv and RV state of contractility](image)

Right ventricular isovolumic contraction velocity and right ventricular filling pressures

Isovolumic contraction velocities measured at base and mid cavity level correlated inversely with right ventricular end diastolic pressure (r= -0.47 and
We also found a negative relation between right atrial mean pressure (RAMP) and IVCv at both segments ($r=-0.62$ and $-0.54$, $p<0.01$, for both, Fig 9). On the basis of the correlation between isovolumic contraction velocity at basal segment and right atrial mean pressure, we tested the sensitivity and specificity of a cut off value below 6 cm/s indicating an increased right atrial pressure (>6mm Hg). The sensitivity and specificity was 100% and 78%, respectively.

Figure 9. The relation between IVCv and RAMP in patients.
GENERAL DISCUSSION

Recent reports have shown the importance of preserved right ventricular function as it might determine the exercise capacity and be of prognostic importance in heart failure (78, 79) and pulmonary hypertension (80-82). Furthermore, in myocardial infarction, involvement of the RV predicts the outcome (83). Consequently, a reduced right ventricular function is a powerful predictor for an adverse outcome in different cardiopulmonary diseases (84) and accurate echocardiographic methods in its assessment are important to explore.

A major limitation in the assessment of the RV function relates to the regional, anatomical and functional complexities (42). Therefore, applicable methods by echocardiography that are suitable in clinical situations are lacking. In the assessment of cardiac function, it is important to be aware of the anatomical and functional principles. This correlates with the words of Sir Arthur Keith in 1918 (85).

“No physiological thinking can be true unless it gives a complete and final explanation of all point of structure”.

However, although being a helpful tool in clinical practice, echocardiography alone cannot explain all these points of structure.

The fibre architecture of the left and right ventricles are different (4, 86). Circumferential or spiral fibres compose the predominant muscle layer for the left ventricle and but also longitudinally directed fibres are in the subendocardial and subepicardial layers. In the right ventricle the fibre construction is different. At the infundibulum or outflow tract, both the subepicardial and subendocardial fibres run longitudinally. At the inflow tract, the subepicardial fibres run in a circumferential or spiral motion whereas the subendocardial ones run longitudinally (Figure 10).
Buckberg et al (11) described the arrangement of cardiac fibres in terms of two different myocardial muscle bands where the first is designated as the basal loop and second one as the apical loop. The basal loop is running in a transverse or circumferential motion of the ventricles and perpendicular to the long axis motion which is related to the apical loop. These two loops are being responsible for four cardiac motions including:

(I) Narrowing and (II) shortening, composing the systolic function, and (III) lengthening and (IV) widening composing the diastolic function. As result of contraction of the basal loop, which reflects the stiff outer shell, (ie. pericardium) it compresses the apical loop. The narrowing movement follows a sequential contraction of the right and left segments of the basal loop. Contraction of the right segment occurs first and is followed by contraction of the left segment. The contraction of the basal loop occurs during the isovolumic contraction phase. The

Figure 10. Fibre architecture in the left and right ventricles from Greenbaum et al. published in Br Heart J 1981;45:248-63. Reprinted with permission from BMJ publishing group.
next motion, which involves the apical loop, is a downward twisting of the
descending segment that ejects the ventricles. Later, an untwisting of the ascending
segment relates to early diastole and finally widening of the cavity, that is related to
diastasis and atrial contraction (11, 87, 88) (Figure 11).
Figure 11. Motion of the four segments and their time events. The motion during pre-ejection phase and late diastole representing narrowing and widening of basal loop. Reprinted from, Seminars in thoracic and cardiovascular surgery, Vol 13, No 4, Torrent-Guasp et al. The structure and function of the helical heart and its buttress wrapping. I The normal macroscopic structure of the heart. Copyright © 2001 by W.B Saunders Company. With permission from Elsevier.
The combination of longitudinal, oblique or radial and circumferential cardiac motion might be compared to wringing a wet scrubbing mop (Figure 12).

Figure 12. Cardiac function visualized as a squeezed mop.

Studies of the right ventricle have shown that under normal conditions the RV free wall of the inflow tract moves towards the common septum during emptying of the ventricle and the systolic wall motion at the outflow tract fulfils the emptying of the ventricle (2, 42). This complexity makes the assessment cumbersome, and volumetric calculation from different geometric planes become time-consuming and rely on mathematical models, being less suitable in clinical practice. Therefore absolute values in the assessments were considered preferable in the present studies. Most of the studies on RV function have regarded the ventricle as a single anatomic and functional unit, i.e. the inflow tract (43, 83, 89). However, the outflow tract or infundibulum has attracted recent attention and its role is now being discussed (6). In 1924 Sir Arthur Keith described the cavity of the infundibulum and summarised that its role was to serve as a protection for the pulmonary circulation during RV
pressure rise in systole (7). Similar theories have more recently been presented (5, 90). Furthermore, with elevated afterload conditions it has been shown that there are differences in function in which the outflow tract is more affected than the inflow tract (91, 92). We were able to confirm these observations by using regional assessment with simple M-mode echocardiography (Studies I and V). However, the relation between RV systolic function and pulmonary artery pressures is relatively weak and the systolic RV long axis systolic function may even increase in PHT (93).

The ageing right heart in a healthy population

The elderly population in western countries is increasing rapidly and it is estimated that by 2025 nearly one third will be 60 years or older (94). Increasing age is related to an increased risk of cardiovascular diseases and changes in the cardiovascular system in normal ageing are similar to some of the patho-physiological ones (95). Left ventricular hypertrophy, heart failure and atrial fibrillation increase dramatically with age (61) and it has been proposed that signs of heart failure with presence of normal ejection fraction may occur in about one-third of patients, proposed as being a result of “isolated” diastolic dysfunction. However, the true prevalence of diastolic dysfunction is uncertain with regard to the patient selection and to the diagnostic criteria (96). Furthermore, “diastolic dysfunction” seems to be more common in females and the reason remains unknown (97).

How much an orthodox echocardiography examination of diastolic ventricular function contributes to understanding the clinical syndrome of diastolic heart failure has been extensively discussed (98), and alternative diagnosis for the signs of heart failure can be obesity, pulmonary disease and coronary artery disease (99). As a result of increasing interest of right heart function, several studies have shown increasing age changes the right heart function, similar to the changes on the left heart side. This has not only been shown by measuring the global function from tricuspid flow with traditional pulsed Doppler but also within the myocardium with pulsed or colour Doppler tissue imaging (100-104). Most of these studies investigated small samples recruited on an ad-hoc basis. Our results were taken from a large healthy population that was equally distributed for both age and gender.
Compared to these studies, our results are in general in agreement with these but we could not show changes in the myocardial isovolumic time intervals, isovolumic relaxation (IVRt) and contraction (IVCt) time. Furthermore, we investigated the velocity of isovolumic contraction (IVCv), which was slightly increased with advanced age and also found it to be related to myocardial atrial contraction. Both these two parameters have recently been proposed to be sensitive markers early in the dyskinetic myocardium due to ischemia (105). Disturbances in these parameters have been seen in hypertrophic cardiomyopathy (106), cardiac amyloidosis (107), coronary artery disease (108), and pulmonary hypertension (109). Absence of influence of age influence on isovolumic periods by using Doppler tissue imaging, improves the interpretation in the assessment of RV dysfunction. Furthermore, DTI measurements of isovolumic events are well reproducible and useful in most of the patients.

Systemic and pulmonary artery pressure in the healthy population

WHO has proclaimed that 140/90 mm Hg is being the upper level for blood pressure and every patient identified having a blood pressure above that level should therefore be proposed as hypertensive. Larger studies have also shown that mild to moderate elevation of the systolic blood pressure are likely to develop clinical disease. (110)

However a causal value of more than 160/90 mm Hg was chosen as an level for exclusion. It is known that increasing age is associated to a greater extent, by central conduit vessel stiffness and therefore increasing systolic blood pressure whereas the diastolic pressure decreases after 50 years of age (95).

In our study we found elevated systolic and diastolic artery pressures in 23 subjects. A similar trend was also found for the PASP (Study II) which has previously been described (111, 112) and a PASP up to 40 mm Hg in the very elderly could be considered being normal (113). In our study one healthy control had a PASP above 40 mm Hg (83 years old women with PASP = 42 mm Hg).

As the healthy subjects were carefully selected from the population and none complained of any cardiovascular related dysfunction or were on medication for any
cardiovascular disease, we decided to exclude these with blood pressure above 160/90 mm Hg. However, none was excluded because of the PASP.

Right heart function in patients with systemic sclerosis

Pulmonary involvement is commonly seen in systemic sclerosis (SSc) and pulmonary hypertension (PHT) being one of the leading causes of death, especially in the limited type (64). Development of new and potent drugs has therefore increased the interest of pharmacological treatment. However, early detection of cardiopulmonary involvement in PHT is important for optimizing patient treatment and evaluating follow up results (114). Doppler echocardiography allows non-invasively estimation of systolic pulmonary artery pressure from the peak tricuspid regurgitation drop gradient (45). Reports in the literature suggest that this method is appropriate in 60-86% of the patients (115), and may be improved by using contrast (116). In clinical practice, the quality of signal generation and determination of peak velocity is difficult, especially in patients with mild to moderate PHT. It must also be remembered that Doppler echocardiography is reported to underestimate the real pulmonary pressure when obtained from a single measurement of tricuspid regurgitation peak gradient (117, 118). Data from our study in patients with SSc relate to an estimation of pulmonary artery systolic pressure (PASP) obtained from one single measurement at rest, which could also be a reason for an error, as single measurement and exercise have been found to influence estimations of pulmonary pressure (118). We were not able to see any difference in the tricuspid regurgitation peak gradient compared to controls. On the other hand, we could demonstrate that while LV and RV systolic functions were preserved, the RV diastolic function was disturbed. This was evidenced by disturbed relaxation and abnormal filling properties together with RV hypertrophy and right atrial dilatation. One of the important findings was the significant prolongation of the isovolumic relaxation time (IVRt). We suggest that these abnormal findings could be related to mild or intermittent pulmonary hypertension.
Right ventricular relaxation

The abnormal findings in the studies on patients with systemic sclerosis were related to the RV diastolic function. Therefore a clear understanding of its physiology and patho-physiology is important. As previously described, diastolic dysfunction is being increasingly accepted as a cause of exercise limitation and clinical signs of heart failure, whether or not ejection fraction is normal. In patients with normal ejection fraction the prevalence is by far more common in females, the reason being unknown (97, 119).

However, despite a rapid increase in the technique improvement, echocardiography is still limited in demonstrating clearly the events of relaxation. Brutsaert et al (120), have extensively described the aspects of ventricular relaxation.

Relaxation is part of pre-contracted properties and essentially four (contractile) proteins are involved in the contraction-relaxation cycle, i.e. myosin, actin, troponin and tropomyosin. Furthermore, essential for relaxation is the re-uptake of calcium by sarcoplasmic reticulum. Relaxation of the right ventricle as a muscle pump can be defined as the events after the pulmonary valve closure that lead to restoration of a pre-contractile state.

Torrent-Guasp and co-workers proposed that ejection and suction are derived from an apical loop contracting first in a descendent segment (ejection) with opposite rotations at base and apex causing a torsion of the ventricle (10). Studies using MRI have shown that the untwisting of the heart takes place during isovolumic relaxation with counter clockwise rotation at base and clockwise at apex (121).

Prolongation of IVRt has been observed in patients with aortic stenosis and hypertrophy and hibernating myocardium (122, 123). We used the definition of the cardiac cycle in its different phases as proposed by Wiggers in 1921 (124), and stated that the phases of isovolumic contraction being part of systole and isovolumic relaxation as part of diastole. Two phases, during pressure rise and fall at closed valves that prepares for both ejection and filling of the ventricle. However, diastolic function is a complex interplay of numerous components, including not only relaxation but also viscoelastic forces, pericardial re-strain, ventricular interaction and atrial contribution (125). The onset of isovolumic relaxation time (IVRt), as defined by Wiggers, is the aortic valve closure.
which can readily be determined by echocardiography from the artefact of aortic valve closure. However, this approach is not applicable for the assessment of global right ventricular filling for obvious reasons. Therefore, the use of detecting valve closure from the pulmonary component of the second heart sound is preferable. In the normal left ventricle IVRt increases with age, both globally and regionally (126). In Paper II we found a weak prolongation in IVRt measured from tricuspid flow as a measure of global function but no change in the regional (DTI) IVRt.

The difference between the left and right ventricular relaxation properties that occurs with increasing age may be explained by the difference in loading during relaxation and amount of muscle tissue that may undergo fibrosis, as both are known to occur in the elderly heart (120).

As IVRt is sensitive to heart rate a simplified correction to the R-R time interval may limit this error. In healthy subjects IVRt indexed for the R-R time interval was approximately 6% (5.8±3% for base and 6.3±4 % for the mid segment of the RV). In patients with SSc we found IVRt/RR to be 9.6±4.4% using DTI at basal segment and 7.5±2.8 using pulsed Doppler trans-tricuspid flow.

From the results of Study IV we showed the relationship between DTI derived IVRt/RR% and PASP. From these linear regression equations an IVRt/RR of more than 10% at the base or 12% at the mid segment of the RV free wall could be proposed to correspond to a PASP above 30 mm Hg or slightly elevated.

This relationship was previously reported in 1967 by Luis Burstin who suggested that by measuring the time interval between pulmonary valve closure and the onset of tricuspid flow (IVRt), from phonocardiogram and external pulse curves, closely correlated to the PASP and presented a nomogram that included a correction for heart rate (127). Fourteen years later, Hatle et al, using phonocardiogram and pulsed Doppler flow velocities confirmed this observation (128). Prolonged IVRt leads not only to a reduced total RV filling time and early diastolic velocity, but also to increased late diastolic velocity. This has been shown in hypertrophic cardiomyopathy (106, 129), systemic arterial hypertension (130), RV infarction (108), restrictive LV filling pattern (49), chronic obstructive lung disease and PHT (131). Recently, pulsed DTI was used to distinguish subsets of patients affected by lung disease with or without echocardiographic evidence of PHT (109).
The duration of IVRt is determined by: (i) right atrial pressure which, in the absence of tricuspid stenosis or insufficiency or right heart failure, remains normal; (ii) the systolic pulmonary artery pressure which when raised, delays the opening of tricuspid valves and proportionately prolongs IVRt; and (iii) heart rate which is inversely related to the duration of IVRt (132). Increased right atrial pressures lead to premature opening of the tricuspid valve and thereby shortens the IVRt (128). We considered this in a sub group of patients in study IV by excluding those with elevated right atrial pressures and by performing a simple correction for actual R-R time intervals. Previous studies have shown that the measurement of RV IVRt may not be appropriate in patients with arrhythmias (45). It is known that bundle branch block influences IVRt (133), therefore patients with complete right bundle branch block were excluded. In PHT, the rate of pressure fall is reduced and onset of RV filling may occur more than 100 ms after closure of pulmonary valves. Therefore, PHT causes a decline in RV tension (134). This decline can be observed with several echocardiographic techniques, such as increased time between pulmonary valve closure to tricuspid valve opening and prolongation of the tricuspid regurgitation time. Protracted early relaxation can be assessed by M-mode, pulsed Doppler from tricuspid flow and with pulsed DTI, where the onset of relaxation is dependent on the pressure gradient across the tricuspid valve (Figure 13).
Figure 13. Simultaneous superimposed pulsed Doppler tissue imaging, tricuspid regurgitation and RV long axis motion from M-mode echocardiography. The onset of relaxation is dependent on the pressure gradient. In this figure the gradient between RV and RA was 65 mm Hg and the onset of relaxation was found at the time for atrial contraction. Note the impaired filling time.
As prolonged IVRt seems to be a sensitive marker for early diastolic disturbance, which might be caused by an in-coordinated relaxation and contraction, the wall motion during isovolumic contraction (IVC) might indicate pre-systolic disturbance. Studies of the left ventricle have shown that the longitudinal motion precedes the short axis motion during IVC phase leading to the ventricle becoming spherical. This coordination may be altered in disease (135). By using tagged cine MRI, studies have also shown that during IVC, overall ventricular rotation is counter-clockwise. Later in systole, the basal segments change direction and rotate in a clockwise direction, whereas the apical segments continues counter-clockwise (136). Thus, rotation or twisting occurs within the IVC phase whereas most of the untwisting take places during IVR (137).

Pre-ejection period (PEP) indexed to the ejection time (PEP/ET) as measured by pulsed Doppler technique is a sensitive marker for LV dysfunction (138). As part of the myocardial performance index (MPI) or Tei index, it has been shown to increase in RV dysfunction (139), pulmonary hypertension (46) chronic heart failure and also correlates with +dP/dt max. Furthermore, the index increases in infiltrative diseases (107), and coronary artery disease (108).

The time interval IVC is also relatively insensitive to heart rate (140), and does not alter with increasing age. By the use of Doppler tissue imaging, both isovolumic timings as well as peak velocities during IVC are easily detectable and may be used to measure the intrinsic systolic myocardial behaviour. In Study V we were able to demonstrate that IVCv, measured by pulsed DTI of the RV free wall, can estimate the RV filling pressures. Not only that, but it can also determine the state of RV contractility. IVCv may reflect changes in the intrinsic systolic work of the RV myocardium due to changes in the pre-ejection pressure.

It is known that RV end diastolic pressures in health modestly increase with age, particularly over 60 years (141). However, if the RV end diastolic pressure further rises, it leads to elevation of RA pressure, more severe tricuspid regurgitation and increased stiffness of the ventricle. This may cause impairment of RV systolic function, a physiological phenomenon which is in agreement with the Frank-Starling law (84, 98).

Contraction of the right ventricle
From Study V, IVCv less than 6 cm/s may indicate elevated RAMP in patients with different cardiac diseases with high sensitivity and specificity.

+dP/dt\text{max} has been considered a measurement of myocardial contractility because its maximum rate of pressure rise occurs before aortic and pulmonary valve opening. The main limitation of +dP/dt\text{max} is its pre-load dependency as well as being influenced by cavity size and thickness index (142). Therefore, dP/dt/P\text{max} is considered less sensitive to preload and a more reliable index for RV contractility (142, 143).

In an animal study Vogel et al showed that IVC acceleration is a reliable measurement of RV contractility and is relatively load independent (77). For technical reasons, we found that the acceleration for IVC was not easy to measure by pulsed DTI and we therefore decided to measure the peak velocity. Thus, in Study V we found that peak IVCv was influenced by the contractile function, measured at the base and mid cavity segments of the RV free wall. This relationship was even stronger, when RA pressure was normal. Once again, this emphasizes that atrial pressure is essential when assessing ventricular function. Finally, we could not observe any correlation between IVCv to indices of pre- or afterload conditions.

*Right ventricular long axis amplitude and right heart function.*

Kaul et al demonstrated that the RV systolic ring motion towards apex, measured by means of using 2D echocardiography, correlated to ejection fraction obtained from radionuclide angiography (48). This relationship was recently confirmed by measuring systolic velocities by DTI technique (50). The same study reported a weak but significant relationship between the systolic velocity and mean pulmonary artery pressure. From our invasive data we could confirm this weak relationship. The systolic long axis motion has been shown to determine the prognosis in patients with heart failure (144) and can therefore be proposed to be a late finding related with an adverse outcome.
The use of phonocardiogram

Today, it is well established that early disturbances in the myocardium occur predominantly during the isovolumic phases, relaxation and/or contraction, and therefore are sensitive markers of ventricular dysfunction (105). One complicating factor in analysing these events is the great variation of velocities and profiles in normal cardiac function (55, 73), which may be more difficult to measure in different cardiac diseases (54, 71, 105, 145, 146). Therefore, it is important to standardize the measurements (125). Phonocardiogram is a very important tool that helps in determining cardiac cycle timing as it displays the time of the second heart sound. Superimposed on M-mode and Doppler tracings it allows accurate assessment of different phases during the cardiac cycle. A major disadvantage in using the phonocardiogram is the limitation of availability. Importantly, none of the ultrasound systems used in the present studies have been reported to have any error due to time delays. (147).

Doppler Tissue versus conventional Doppler technique

The most common echocardiographic method for the assessment of the LV diastolic function is by using mitral and pulmonary vein tracings from pulsed Doppler technique (148). The diagnostic value of such Doppler derived indices is limited by the strong influence of heart rate and loading conditions (125). Recently, regional myocardial wall motion assessed by pulsed or colour Doppler tissue imaging (DTI) have been used to assess ventricular function. Doppler tissue imaging analysis has the potential to determine the primary event of the myocardial velocity dynamics of ventricular structural function (125). Unlike the conventional pulsed Doppler technique, DTI is proposed relatively preload independent and the analysis can be done regionally (57,149).
Comparing the two methods in healthy individuals shows a direct relationship between the mitral flow and myocardial velocities (126, 150). However, this relation may vary in different cardiac diseases (151).
CONCLUSIONS

I. Right ventricular outflow tract fractional shortening is an easy, non-invasive and directly applicable measurement of right ventricular function. It provides a measure that can be used for assessment and follow up of patients who are prone to right ventricular dysfunction. Although it only assesses systolic performance of the outflow tract, its combination with long axis measurements and Doppler tissue imaging analysis should provide a comprehensive evaluation of the RV function.

II. Age does not affect systolic RV function except for the free wall motion velocities during the isovolumic contraction. The changes in RV function due to age are related to the diastolic filling velocities, which mirror those of the left ventricle. Basal and mid cavity segment RV systolic and diastolic functions are the main determinants of the longitudinal behaviour of the inflow tract, again in parallel with the respective segments of the left ventricle. Knowledge of these changes in regional RV ventricular function and its change with increasing age is mandatory when assessing patients.

III. In patients with SSc we found altered right ventricular diastolic function, together with an increase in RV wall thickness and right atrial area. A primary myocardial defect such as fibrosis or ischemia is a less likely explanation to the findings since both are supposed to be more generalized phenomena and should therefore also influence the LV function. Neither is pulmonary fibrosis a probable cause as no relationship between degree of pulmonary fibrosis and RV diastolic disturbances was found. The most probable cause is therefore mild or early intermittent pulmonary hypertension. Assessment of RV diastolic function might, early in the disease, identify patients at risk for developing progressive heart failure which can be important in the clinical management and improve the prognosis.
IV. Isovolumic relaxation time, derived from RV myocardial free wall by using DTI, is a new and easy method proposed being a additional measurement for estimating the PASP. The advantage of the DTI method, compared to the peak tricuspid regurgitation velocity measurement, is that DTI is more easily obtained.

V. Doppler tissue imaging in measuring the myocardial velocity during isovolumic contraction phase is a reproducible and easily obtainable non-invasive parameter that can estimate the state of RV contractility. Furthermore, IVCv can be useful in detecting patients with elevated RV filling pressures.
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