Echocardiographic measurements of the heart
To my family
Hubert, Lovisa and Natasha
Echocardiographic measurements of the heart
With focus on the right ventricle
Abstract


Echocardiography is a well established technique when evaluating the size and function of the heart. One of the most common ways to measure the size of the right ventricle (RV) is to measure the RV outflow tract 1 (RVOT1). Several ways to measure RVOT1 are described in the literature. These ways were compared with echocardiography on 27 healthy subjects. The result showed significant differences in RVOT1, depending on the way it was measured, concluding that the same site, method and body position should be used when comparing RVOT1 in the same subject over time.

One parameter to evaluate the RV diastolic function (RVDF) is to measure the RV isovolumetric relaxation time (RV-IVRT), a sensitive marker of RV dysfunction. There are different ways to measure this. In this thesis two ways of measuring RV-IVRT and their time intervals were compared in 20 patients examined with echocardiography. There was a significant difference between the two methods indicating that they are not measuring the same interval.

Another way to assess the RVDF is to measure the maximal early diastolic velocity (MDV) in the long-axis direction. MDV can be measured by different methods, hence 29 patients were examined and MDV was measured according to two methods. There was a good correlation but a poor agreement between the two methods meaning that reference values cannot be used interchangeably.

Takotsubo cardiomyopathy is characterized by apical wall motion abnormalities without coronary stenosis. The pathology of this condition remains unclear. To evaluate biventricular changes in systolic long-axis function and diastolic parameters in the acute phase and after recovery, 13 patients were included and examined with echocardiography at admission and after recovery. The results showed significant biventricular improvement of systolic long-axis function while most diastolic parameters remained unchanged.

Keywords: Echocardiography, heart, right ventricle, right ventricular outflow tract 1, isovolumetric relaxation time, maximal early diastolic relaxation velocity, takotsubo cardiomyopathy, long-axis function
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ABBREVIATIONS

RV  Right ventricle
LV  Left ventricle
EF  Ejection fraction
DF  Diastolic function
IVRT Isovolumetric relaxation time
PW  Pulsed wave
DTI Doppler tissue imaging
TDI Tissue Doppler imaging
2D color DTI Two-dimensional color Doppler tissue imaging
MAM Mitral annulus motion
TAM Tricuspid annulus motion
MDV Maximal early diastolic velocity
S  Peak systolic velocity
E  Peak velocity during early diastole
A  Peak velocity during atrial systole (late diastole)
E/A Ratio of the E and A velocity
e Myocardial peak velocity during early diastole
á Myocardial peak velocity during atrial systole (late diastole)
RVOT1 Right ventricular outflow tract 1
RVIT3 Right ventricular inflow tract 3
INTRODUCTION

The heart is an amazing muscle. The heart muscle cell is striated and shares the same contractile unit as the skeletal muscle, the sarcomere. The sarcomere contains myosin thick filaments and thin filaments of actin, tropinin and tropomyosin. In the presence of calcium the myosin interacts with actin, which produces a cross-bridge between the filaments enabling contraction (systole) to occur. The relaxed state (diastole) is brought about by a decrease in intracellular calcium and the tropomyosin inhibitory subunit prevents myosin from interacting with actin (1). What makes the heart muscle cells unique are the intercalated discs that connect the cells together at specialized junctional sites. The intercalated discs serve at least three important functions:

1. They bind the heart muscle cells together with desmosomes, which helps to stabilize and maintain the structure of the tissue.
2. They connect the actin filament of the myofibrils in two interlocking heart cells so the two cells can "pull" together with maximum efficiency.
3. They contain gap junctions, which allows a direct electrical connection between two cells, an action potential can spread rapidly from one heart muscle cell to another.

This means the heart muscle cells are unique in their kind since they are mechanically, chemically and electrically linked together. The heart tissue functions like a single, enormous muscle cell and the contraction of one cell will trigger the contraction of several others making the contraction spread throughout the myocardium (2,3).

The heart is located slightly left of the midline of the thorax in the body. The base is at the level of the third costal cartilage, posterior to the sternum. The inferior, pointed tip, called the apex, reaches the fifth intercostal space about 7.5 cm to the left of the midline. A normal adult heart measures approximately 12.5 cm from base to apex. The anatomical differences between left and right ventricles are quite substantial. The right ventricle (RV) wall is thin and it resembles a crescent shaped moon attached to a full moon, the massive wall of the left ventricle (LV). The ventricles share the inter-ventricular septum, which separates the RV from the LV. The RV contraction resembles a bellows pump, squeezing the blood against the mass of the LV, an efficient way to move blood with minimal effort. This develops a relatively low pressure, approximately 1/6 of the pressure of the
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LV, which is important to protect the delicate pulmonary vessels. The LV has a thick wall and it is almost round in cross section. When the LV contracts, two things happen; the long-axis distance between the base and the apex decreases and the short-axis diameter of the ventricular chambers decreases, making the pressure high enough to push the blood around the systemic circuit. When the LV contraction occurs, the inter-ventricular septum bulges into the RV cavity (2).

**Echocardiography and right ventricular size**

Echocardiography is a well established technique used worldwide. The size of the heart, especially its ventricles, is important to establish during the clinical echocardiographic examination, since larger ventricles often indicate an underlying disease such as dilated cardiomyopathy, valvular disorder or shunt.

The size of the LV is associated with the prognosis of the patient. It has important therapeutic implications and can provide data that is necessary to determine the optimal time for cardiac surgery, for instance, in patients with aortic- or mitral regurgitation (4). A large RV may be seen in patients with different kinds of conditions such as arrhythmogenic right ventricular dysplasia (ARVD) (5) and primary pulmonary disease, but it could also be a result of elevated LV filling pressure through the pulmonary circulation, thus augmenting RV afterload (6). Large ventricles and ventricular hypertrophy, however, is not always an indication of pathology but could also be seen in apparently healthy individuals such as athletes (7).

The RV has a complex anatomy. It has a separate outflow and inflow portion and a main body, which is crescent shaped and truncated. The RV free wall consists of a variable trabecular pattern. These factors make evaluation of the structure of the RV including the measurement of cavity size and wall thickness difficult. The position of the RV, close to the sternum and an anterior relation to the left heart, also complicates the accessibility (8). Several ways to measure the RV have been suggested in the literature (8-18). To measure the RV inflow tract 3 (RVIT3) and RV outflow tract 1 (RVOT1) are the most commonly used ways, probably due to the high reproducibility (8). RVIT3 is measured in the apical four-chamber view 1/3 from the base of the RV (14), but when it comes to the RVOT1, different ways to measure it are described (8,9,13,14,16-18).

Anatomically the RVOT extends cephalic and in a leftward direction from the anteromedial portion of the tricuspid valve annulus to the pulmonary annulus. The anterior border is the anterior RV free wall. The posterior border is the anteromedial portion of the aortic root. In normal hearts,
the crista supraventricularis is an anatomically identifiable structure to RVOT (18).

The myocardial fiber architecture of the RV is fundamentally different from the fiber architecture of the LV. The dominant muscle layer of the LV is circumferential fibers. In the RV the inflow tract mainly consists of circumferential fibers in the subepicardium and partially longitudinal fibers in the subendocardium. At the outflow tract the fibers run longitudinally overlain by fibers running at right angles to the outflow long-axis, which can be traced to the crista supraventricularis and to the anterior sulcus. Some of these fibers continue across the sulcus, crossing the infundibulum, serving to bind the two ventricles together. Because the inflow and outflow long-axis are approximately at right angles to each other, the fibers perpendicular to the inflow long-axis are running parallel to the outflow long-axis with little change in orientation (19).

Since several ways have been described to measure RVOT1, both at different locations and with different methods, echocardiographers do not use a uniform way to implement the measurement.

When performing an echocardiographic examination the patient is usually lying in the left lateral decubitus position simply because the quality of images improves. However, seriously ill patients or patients that for other reasons are unable to lie in the left position, have to be examined in the supine decubitus position. This does not only impair the quality of image but there are indications that the RV dimension increases when the patient move from supine to left lateral decubitus position (9).

**Right ventricular function**

The LV function has earned a lot of interest in the past; whereas the RV function has played a more inconspicuous part. More focus has recently been dedicated, however, to the RV function since it plays a very important role as it has shown to be a sensitive predictor in a number of cardiac syndromes. The RV, for example, is involved in approximately 40-50% of patients with acute inferior infarction and may result in a hemodynamic compromised situation with a poor clinical outcome. Pulmonary diseases affect the RV function as a result of pulmonary hypertension and of course a lot of LV pathology such as severe aortic or mitral valve disease give pulmonary hypertension and commonly affects the RV function. The consequence of this is that early detection of RV dysfunction is important to optimize patient management (15,20,21).

For early diagnosis of RV dysfunction the commonly used technique has been two-dimensional echocardiography. This is not ideal because of the complex anatomy of the RV and its position close to the sternum. Meth-
ods, such as Simpson’s formula, are based on mathematical assumptions of RV anatomy, which result in inaccuracies and are not useful in clinical practice (15,22). Several authors instead recommend M-mode and Doppler tissue imaging (DTI, in the text also referred to as tissue Doppler imaging (TDI)), as useful methods in clinical practice (15,20,21,23). M-mode measurement of the systolic long-axis motion of the RV free wall, also called tricuspid annulus motion (TAM), is a popular method, simple to implement and it has shown a good correlation with the RV ejection fraction (EF) obtained by radionuclide angiography (24). Using TAM, however, in assessing the RV function only gives an estimate over the function of the inflow free wall segments, thus missing the function of the outflow tract and the septal segments. A method, measuring the RVOT fractional shortening, adds great value (11). Conventional Doppler can be used to estimate pulmonary artery systolic and mean diastolic pressure. Tei index, is used to assess the overall RV function and is calculated as the ratio between several RV Doppler parameters (15).

DTI is a relatively new echocardiographic technique, available in most modern ultrasound systems, and it allows characterisation of myocardial movement and time intervals throughout the cardiac cycle. Pulsed wave (PW) Doppler detects high velocity with low amplitudes while DTI detects low velocity with high amplitudes. Pulsed DTI is simple to use, has a high temporal resolution but a poor spatial resolution (because of movements of the heart since the sample volume is fixed). Two-dimensional color DTI (2D color DTI) is another way to measure myocardial movement and can be used off-line, giving the echocardiographer multiple choice for simultaneous wall motion analysis, although it provides mean values compared to pulsed DTI that provides peak velocities (15).

Other ways to assess the right heart function are radionuclide techniques, computed tomography (CT), cardiac catheterisation and magnetic resonance imaging. These methods give accurate and good evaluation of the RV function although availability, cost and sometimes a risk of side effects makes echocardiography an attractive alternative due to its simplicity.

**Right ventricular isovolumetric relaxation time**

For the early detection of an incipient RV dysfunction, the RV diastolic function (RVDF) has to be evaluated since a decrease in RVDF precedes a RV systolic dysfunction. One of the most sensitive functional markers of RV dysfunction is to measure the RV isovolumetric relaxation time (RV-IVRT) (23). The RV-IVRT is a parameter of RVDF and has been shown to correlate well to elevated pulmonary artery pressure where RV-IVRT is prolonged (23,25). RV-IVRT is defined as the interval from the pulmonic valve closure to the start of the tricuspid valve opening (26). Since there is no good echocardiographic view from which both the pulmonic valve and the tricuspid valve can be seen at the same time, RV-IVRT is investigated, however, in patients whether the interval measured with the both techniques and is available on all ultrasound systems while TDI is a relatively new technique that might not be available on older echocardiographic systems, such as Simpson’s formula, are based on mathematical assumptions of RV anatomy, which result in inaccuracies and are not useful in clinical practice (15,22). Several authors instead recommend M-mode and Doppler tissue imaging (DTI, in the text also referred to as tissue Doppler imaging (TDI)), as useful methods in clinical practice (15,20,21,23). M-mode measurement of the systolic long-axis motion of the RV free wall, also called tricuspid annulus motion (TAM), is a popular method, simple to implement and it has shown a good correlation with the RV ejection fraction (EF) obtained by radionuclide angiography (24). Using TAM, however, in assessing the RV function only gives an estimate over the function of the inflow free wall segments, thus missing the function of the outflow tract and the septal segments. A method, measuring the RVOT fractional shortening, adds great value (11). Conventional Doppler can be used to estimate pulmonary artery systolic and mean diastolic pressure. Tei index, is used to assess the overall RV function and is calculated as the ratio between several RV Doppler parameters (15).

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During recent years some authors have used PW-DTI when measuring RV-IVRT (20,21,23,25), a method that is easier and faster than the method based on ECG and PW Doppler. It has not been sufficiently investigated, however, in patients whether the interval measured with the both methods are in fact the same.

Maximal early diastolic velocity in right ventricular long-axis direction
During recent years recordings of the maximal early diastolic relaxation velocity in the LV long-axis direction obtained by echocardiographic M-mode (MDV MAM) (28-30) or tissue Doppler imaging (31-33) have been used in the assessment of LVDF. At the right side of the heart the maximal early diastolic relaxation velocity in the RV long-axis direction obtained by tissue Doppler imaging (MDV TDI) has been found to have a fairly good correlation with other diastolic parameters of the RV such as transtricuspid E wave and transtricuspid E/A waves ratios (34). In accordance with the findings on the left side of the heart MDV TDI has been found to decrease with age and it has been suggested that this is due to deterioration in the diastolic properties of the myocardium of the ventricles with age (34,35).

As mentioned earlier it is of great importance to have simple tools to evaluate RVDF. In the same way as MDV MAM has been used in the assessment of LVDF, it has been suggested that the maximal early diastolic relaxation velocity in the long-axis direction of the RV obtained by M-mode echocardiography (MDV TAM) can be an index of RVDF (36). This method is based on M-mode, which is one of the oldest echocardiographic techniques and is available on all ultrasound systems while TDI is a relatively new technique that might not be available on older echocardiographs. Since both indices are measuring the MDV there are reasons to believe that there could be a good correlation and a good agreement between them. If that is the case, either technique could be used in clinical evaluation of the RVDF.

Takotsubo cardiomyopathy
Takotsubo cardiomyopathy is a clinical syndrome, typically characterized by acute reversible apical LV dysfunction with acute reduced EF that suc-
cessively normalises (Fig. 1) (37,38). There are reports of atypical takotsubo cardiomyopathy, for instance with inferior wall akinesia, although it is not common. The name takotsubo cardiomyopathy has its origin in Japan, where the first cases were described in the early 1990. Takotsubo means octopus trap. It was given this name because of the typical shape of the LV during ventriculogram, with a round bottom and a thin neck, resembling the trap in which Japanese fisherman catch octopuses (Fig. 2).

A typical characteristic for this syndrome is that the area of myocardium involved does not correspond to any specific coronary artery territory. Clinically at the onset of the disease the symptom is acute chest pain with ECG changes. The characteristic ECG changes associated with takotsubo cardiomyopathy are transient Q-waves, ST-segment elevation during the acute phase, which evolves into deep negative T-waves and QT interval prolongation. Cardiac enzymes are often slightly elevated. The onset of this cardiomyopathy is therefore very similar to acute myocardial infarction with the significant difference that coronary angiography shows no signifi-

Figure 1. Echocardiographic apical four-chamber view in end-systole in a 77 year-old woman during the acute phase of takotsubo cardiomyopathy. Note the apical ballooning of the left ventricle (LV).
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![Figure 2. Left ventriculogram in 30 degrees right anterior oblique view of the same patient as in figure 1.](image)

Earlier echocardiographic studies have mainly focused on the LV function, although RV apical involvement can also occur (39,41). There are very few reports of systolic long-axis function of the LV and the RV, to our knowledge there is only one study dealing with takotsubo cardiomyopathy and mitral annulus motion (MAM) (38) and no study dealing with TAM.
AIMS OF THE THESIS

 To investigate if there is a significant difference in size of RVOT using different methods, described in literature, to measure it. A second objective is to evaluate if there actually is a significant difference in size of RVOT due to body position.

 To compare RV-IVRT measured with the method based on ECG and PW Doppler with RV-IVRT measured with PW-DTI and to try to explain any eventual difference.

 To compare RV MDV TDI with MDV TAM.

 To investigate biventricular changes in systolic long-axis and diastolic function between the acute phase and the recovery phase of a specific disease, takotsubo cardiomyopathy.
AIMS OF THE THESIS

- To investigate if there is a significant difference in size of RVOT1 using different methods, described in literature, to measure it. A second objective is to evaluate if there actually is a significant difference in size of RVOT1 due to body position.

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SUBJECTS AND METHODS

SUBJECTS

Study I
27 healthy subjects, mean age 25±4 years, were included. They had a normal ECG and no history of cardiac disease.

Studies II and III
In study II, 20 consecutive patients, mean age 63±13 years, referred to echocardiography, were included. Since earlier studies have shown prolonged RV-IVRT in patients with hypertrophic cardiomyopathy (42), patients with LV wall thickness >14 mm were not included nor patients with atrial fibrillation, bundle branch block, pacemaker treatment or a history of cardiac surgery since the effect of RV-IVRT has not been sufficiently investigated in these cases.

In study III, 29 consecutive patients, mean age 56±15 years, referred to echocardiography, were included. Patients with atrial fibrillation, bundle branch block, pacemaker treatment or a history of cardiac surgery were not included. The number of patients, in studies II and III, with diseases that might influence the heart, is presented in Table 1.

Study IV
In this prospective study all consecutive patients between January 2008 and March 2010 admitted to acute coronary angiography, suspected of having ST-elevation myocardial infarction, were screened for takotsubo cardiomyopathy if no angiographically significant stenosis was seen in the coronary angiogram. The definition of takotsubo cardiomyopathy was chest pain discomfort, ECG changes (ST-elevation, ST-depression, negative T-waves or Q-waves), no significant angiographic stenosis (≥50% visual estimate) on coronary angiogram and apical dysfunction on contrast left ventriculogram in 30 degrees right anterior oblique view. In the screening period 16 patients fulfilled inclusion criteria and 13 patients (all women), mean age 68±10 years, were willing to participate in the study. Echocardiography was performed within 24 hours after admission (acute phase) and repeated after about three months (recovery phase).

No patient had a history of cardiac disease except for one who had previously suffered from arrhythmia and had received a pacemaker.
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### Table 1. Number of patients with diseases, in studies II (n=20) and III (n=29), which might influence the heart.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients study II</th>
<th>Number of patients study III</th>
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</thead>
<tbody>
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METHODS

ECHOCARDIOGRAPHIC EXAMINATION

Study I. Echocardiography was performed using a Vivid 7 system (GE Vingmed Ultrasound A/S Horten, Norway) equipped with a multifrequency phased array transducer (M3S, 1.5-4.0 MHz). Measurements were made after the examination using stored images in an Echopac (GE Vingmed Ultrasound A/S) Compaq DeskPro Workstation 300 (Compaq Computer Corporation, Houston, Tx, USA).

Studies II and III. Echocardiography was performed using an Acuson Aspen system (Siemens-Acuson Co., Mountain View, CA, USA) equipped with PW-DTI technology and variable frequency phased array transducers (4V2c and 3V2c). All measurements were made on screen during the examination.

Study IV. Echocardiography was performed using a Vivid 7 system (GE Vingmed Ultrasound A/S, Horten, Norway) equipped with a multifrequency phased array transducer (M3S 1.5-4.0 MHz) and PW-DTI technology. Measurements were made after the examination using stored images in an Echopac (GE Vingmed Ultrasound A/S) Compaq DeskPro Workstation 300 (Compaq Computer Corporation, Houston, Tx, USA). The average time between the echocardiographic examination at the acute and recovery phase was 12.9±1.0 weeks.

In all the studies the measurements were made at the end of expiration in the left lateral decubitus position except for study I in which, in addition, measurements were also performed in the supine decubitus position. All patients or subjects were in sinus rhythm.
**2D/M-mode echocardiography**

Echocardiographic techniques and calculations of different cardiac dimensions in study I-IV were performed in accordance with the recommendations of The American Society of Echocardiography Committee (16,43,44).

LV EF was measured using the Teichholz method (study I) and the bi-plane Simpson’s method (45) (study II-IV).

As a measure of RV systolic function TAM was measured from the RV atrioventricular plane at the basal lateral site in the apical four-chamber view from M-mode recordings (46,47) (study I-IV). The size of the RV was measured one-third from the base of the RV, RVIT3 (14,47) (study II-IV). In study IV RVOT1 was measured according to Foale et al. (8).

In study I the measurements of RVOT1 were performed from the parasternal long-axis view. The different ways of measuring RVOT1 from this view were at site “b” from the 2D-image (Fig 3.) and from the M-mode image (8,9) (Fig. 4), at site “a” from the 2D-image (13,18) (Fig. 5) and from the M-mode image (16,17) (Fig. 6). RVOT1 in the short-axis projection has in earlier studies, to the best of our knowledge, been measured only by using 2D-images, except for Lindqvist et al. (11), who focused on the RV function (RVOT fractional shortening) and not the size of the RV, which is why it was only measured with this method in the present study (14) (Fig. 7).
Echocardiographic measurements of the heart

2D/M-mode echocardiography

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Figure 3. RVOT1 measured in the parasternal long-axis view from the 2D-image according to site b (8,9).

Figure 4. RVOT1 measured in the parasternal long-axis view in the M-mode image according to site b (8,9).

Figure 5. RVOT1 measured in the parasternal long-axis view from the 2D-image according to site a (13,18).

Figure 6. RVOT1 measured in the parasternal long-axis view from the M-mode image according to site a (16,17).

Figure 7. RVOT1 measured in the parasternal short-axis view from the 2D-image (14).
In studies III and IV MDV TAM was measured from the basal lateral corner of the RV in the apical four-chamber view. The steepest portion of the M-mode curve in early diastole was identified and measured. The inclination of the dotted line represents MDV TAM (mm s\(^{-1}\)) (36) (Fig. 8). In study IV MDV MAM was measured in the same way but from the lateral corner of the LV (29).

Figure 8. The maximal early diastolic velocity in the long-axis direction of the right ventricle (RV) obtained by M-mode echocardiography (MDV TAM) was measured from the basal lateral corner of the RV in the apical four-chamber view. The steepest portion of the M-mode curve in early diastole was identified and measured. The inclination of the dotted line represents MDV TAM (mm s\(^{-1}\)).

In study IV M-mode measurements of the amplitude of MAM were performed from four sites situated about 90 degrees apart according to Höglund et al. (48). Recordings from the septal and lateral part of the mitral annulus were obtained from the apical four-chamber view (Fig. 1) and recordings from the inferior and anterior parts from the apical two-chamber view. MAM was calculated as the average of four sites. The leading edge technique was used.

In the same study the length of the LV was measured in end-diastole from the epicardial apex to the septal and lateral site of the mitral annulus. The end-diastolic and end-systolic diameter of the LV basal part was measured. The widest part of the LV in end-diastole was also measured.

The length of the RV was measured in end-diastole from the epicardial apex to the septal and lateral site of the tricuspid annulus.
**Doppler echocardiography**

The PW-Doppler examinations were performed at a transducer frequency of 2 MHz and the PW gate was set at 3 mm. PW-Doppler mitral and tricuspid diastolic flow velocities were recorded from the apical four-chamber view by placing the sample volume between the leaflet tips in the center of the flow stream. The transmitral and transtricuspid peak rapid filling velocity (E), peak atrial filling velocity (A), E-wave deceleration time and E/A ratio were measured (study IV).

The LV-IVRT using PW-Doppler was recorded from the apical four-chamber view by simultaneous recording of the aortic and mitral flows (study IV).

The RV-IVRT using PW-Doppler was measured as described by Larrazet et al. (27) (Figs. 9 and 10): the time from the R wave on the ECG to the end of the pulmonic flow (R-P) was measured from the parasternal short-axis view at the level of the aortic orifice for pulmonic flow velocity recording. The apical four-chamber view was used for measuring the time from the R wave on the ECG to the onset of tricuspid flow (R-T). The sample volume was located at the central part of the tricuspid annulus at the tips of the tricuspid leaflets. RV-IVRT was calculated as [(R-T)-(R-P)]. The measurements were performed almost at the same heart rate (R-R-interval) for each patient (study II and IV).

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**Figure 9.** PW-Doppler was used to measure the time (R-P) from the R wave on the ECG to the end of the pulmonic flow (PV) from the parasternal short-axis view.

**Figure 10.** PW-Doppler was used to measure the time (R-T) from the R wave on the ECG to the onset of the early diastolic wave (E) of the tricuspid flow from an apical four-chamber view. A=atrial contraction.
Doppler tissue imaging

The PW-DTI examinations were performed at a transducer frequency of 2 MHz and the PW gate was set at 3 mm.

In study IV the velocities at the mitral annulus were measured using PW-DTI from four sites about 90 degrees apart. Recordings from the septal and lateral part of the mitral annulus were obtained from the four-chamber view (Fig. 1) and the recordings from the inferior and anterior parts from the apical two-chamber view. The parameters measured were the velocities of the myocardial systolic wave (S), the early diastolic wave (é), the atrial wave (á), the é/á ratio and the ratio between E by PW-Doppler and é by PW-DTI (E/é). The velocities were calculated as the average of the values at the four sites. Velocities at the tricuspid annulus were measured at the basal lateral part of the RV in the apical four-chamber view, the same parameters measured as from the mitral annulus, except for E/é. The PW-DTI measurements of both the mitral and the tricuspid annuli were made according to Alam et al. (34). The different components of the PW DTI pattern are shown in Fig. 11.

The MDV TDI in study III was measured from the outer edge of the dense part of the spectral curve in accordance with the recommendations of the American Society of Echocardiography Committee (49) (Fig. 11).

The IVRT at the both annuli was also measured using PW-DTI as described by Caso et al. (23) (study II and IV). The different components of the PW-DTI pattern from the RV are shown in Fig. 12, RV-IVRT (PVDTI) was measured as the duration in milliseconds (ms) between the end of the systolic wave and the onset of the early diastolic wave. In study II the time from the R wave on the ECG to the end of the S wave (R-S) was also measured. The time from the R wave on the ECG to the onset of the early diastolic wave (R-E) was calculated as [(R-S)+(RV-IVRT(PWDTI))]]. The angle to the beam was kept as small as possible because the measured velocities in the tissue depend on the angle between the Doppler beam and the measured tissue.
The PW-DTI examinations were performed at a transducer frequency of 2 MHz and the PW gate was set at 3 mm. In study IV the velocities at the mitral annulus were measured using PW-DTI from four sites about 90 degrees apart. Recordings from the septal and lateral part of the mitral annulus were obtained from the four-chamber view (Fig. 1) and the recordings from the inferior and anterior parts from the apical two-chamber view. The parameters measured were the velocities of the myocardial systolic wave (S), the early diastolic wave (E), the atrial wave (A), the E/A ratio and the ratio between E by PW-Doppler and E by PW-DTI (E/E). The velocities were calculated as the average of the values at the four sites. Velocities at the tricuspid annulus were measured at the basal lateral part of the RV in the apical four-chamber view, the parameters measured as from the mitral annulus, except for E/E. The PW-DTI measurements of both the mitral and the tricuspid annuli were made according to Alam et al. (34). The different components of the PW-DTI pattern are shown in Fig. 11.

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Figure 11. The maximal early diastolic velocity in long-axis direction of the right ventricle obtained by tissue Doppler imaging (MDV TDI) was measured from the apical four-chamber view at the basal lateral corner of the tricuspid annulus. The components of the DTI patterns are: S=myocardial systolic wave, E=early diastolic wave and A=atrial wave. MDV TDI was measured from the outer edge of the dense part of the early diastolic wave (horizontal white line).

Figure 12. The pattern obtained using pulsed wave Doppler tissue imaging (PW-DTI) at the basal lateral corner of the tricuspid annulus in the apical four-chamber view. S corresponds to the systolic myocardial wave, E is the early diastolic wave and A is the atrial contraction. R-S is the time in milliseconds from the R wave on the ECG to the end of the S wave and R-E is the time from the R wave on the ECG to the onset of the E wave. The interval between the two vertical lines, marked with an x represents the isovolumetric relaxation time of the right ventricle (RV-IVRT(PW-DTI)) measured with PW-DTI.
In study IV the velocities at the mitral and tricuspid annuli were also measured with 2D color TDI in the same way as described with PW-DTI. The measurements were made from the peak point of the systolic curve and from the lowest point of the early diastolic and late diastolic curves, respectively, in accordance with Nikitin et al. (35). When measuring the peak systolic velocities, the initial peak, which is observed during the isometric ventricular contraction, was ignored. The IVRT at the both annuli was also measured using 2D color TDI as described by Lind et al. (50).

**Reproducibility of the measurements**

Reproducibility of measurements was investigated by repeating measurements by the same investigator (A), intraobserver, and independently by a second investigator (B), interobserver. Investigator A first implemented the measurements on screen during the examination and then investigator B (blinded from the measurements of investigator A) measured the same parameters in the same way. Investigator A then performed the same procedure again. The intra- and interobserver reproducibilities were examined in:

- 10 of the subjects in study I in which RVOT according to Figs. 3-7 were measured with the subject in the left lateral decubitus position and in the supine decubitus position.
- 12 new subjects in study II in which R-T and R-P (R-T–R-P=RV-IVRT) and RV-IVRT(PWDTI) were measured.
- 11 of the patients in study III in which MDVTAM and MDVTDI were measured.

**Statistics**

All data was analyzed using SPSS statistical software (versions 10.0, 12.0.1, 16.0 and 17.0 respectively, SPSS Inc., Chicago, IL, USA). All values are given as mean ± SD. A difference at the 5% level was regarded as significant.

The paired sampled t-test was used to compare the difference between the parameters in papers II-III. This test was also used to compare the difference between body positions in paper I.

Bland-Altman diagrams were used in papers II and III to evaluate the agreement (51).

The Pearson’s correlation coefficient was used for analyses of linear correlation between different variables in study III. The two-tailed t-test was used to determine whether correlations were statistically significant.
ANOVA for repeated measurements, General Linear Model (GLM), was used to compare the difference between several groups in study I. Post hoc test was performed using the Bonferroni correction.

The Wilcoxon signed-rank test was used to test for differences between the acute and recovery phases in study IV as some of the parameters were found not to be normally distributed.

The reproducibility of measurements, an estimate of agreement, was obtained by using Pearson’s intraclass correlation coefficient, r (52), in studies I-III. The coefficient has a range from -1.0 to +1.0 with high positive values indicating high agreement, negative values indicating disagreement.

Ethics
All studies were approved by the regional ethical committee. Informed consent was obtained from each participant. In study IV the patients also gave written consent.
Echocardiographic measurements of the right ventricle: RVOT1

The diameters of RVOT1 measured at site a and b were compared with each other, both from 2D-images, when using M-mode and from the two body positions. There was found to be an overall significant difference \((p < 0.001)\) between the diameters of RVOT1 measured at site a and b, with the diameters measured at site b being higher than those measured at site a \((30.9 \pm 5.7 \text{ mm vs. } 24.2 \pm 5.4 \text{ mm})\).

Comparing the diameters of RVOT1 at sites a and b measured with 2D and M-mode, respectively, also shows an overall significant difference \((p < 0.001)\) between both methods (Table 2). There was also an overall significant difference when comparing the different body positions, \((p = 0.001)\) (Table 2).

The two-way interaction between the different sites and methods was also statistically significant \((p < 0.001)\), as was the interaction between the sites and body positions \((p = 0.022)\). There was no significant difference between the methods and body positions \((p = 0.290)\). Three-way interaction between the different sites, methods and body positions did not show any significant difference \((p = 0.270)\) (Table 2).

Table 2. ANOVA for repeated measurements of RVOT1 at two different sites, a and b, measured with different methods, 2D and M-mode, in different body positions. Left=left lateral decubitus position, supine=supine decubitus position.

<table>
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<th>Site (a/b)</th>
<th>Method (2D/M-mode)</th>
<th>Body position (left/supine)</th>
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<td>Site/method/position</td>
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RESULTS

Echocardiographic measurements of the right ventricle: RVOT1

The diameters of RVOT1 measured at site a and b were compared with each other, both from 2D-images, when using M-mode and from the two body positions. There was found to be an overall significant difference ($p<0.001$) between the diameters of RVOT1 measured at site a and b, with the diameters measured at site b being higher than those measured at site a (30.9±5.7 mm vs. 24.2±5.4 mm).

A comparing of the diameters of RVOT1 at sites a and b measured with 2D and M-mode, respectively, also shows an overall significant difference ($p<0.001$) between both methods (Table 2). There was also an overall significant difference when comparing the different body positions, ($p=0.001$) (Table 2).

The two-way interaction between the different sites and methods was also statistically significant ($p<0.001$), as was the interaction between the sites and body positions ($p=0.022$). There was no significant difference between the methods and body positions ($p=0.290$). Three-way interaction between the different sites, methods and body positions did not show any significant difference ($p=0.270$) (Table 2).

Table 2. ANOVA for repeated measurements of RVOT1 at two different sites, a and b, measured with different methods, 2D and M-mode, in different body positions. Left=left lateral decubitus position, supine=supine decubitus position.

<table>
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<td>Method (2D/M-mode)</td>
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<td>Body position (left/supine)</td>
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<tr>
<td>Site/method/position</td>
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Comparing RVOT1 measured in the parasternal long-axis view at site a, site b and short-axis using 2D-images shows an overall significant difference \((p<0.001)\) with the highest mean at site b (31.4±5.8 mm vs. short-axis 29.5±5.6 mm and site a 27.4±4.6 mm) (Table 3). There was also an overall significant difference \((p=0.013)\) between RVOT1 measured using 2D at the three different sites and the body positions (Table 3).

The two-way interaction between the sites and the body positions was also shown to be statistically significant \((p=0.042)\) (Table 3).

Table 3. ANOVA for repeated measurements of RVOT1, using 2D at three different sites (a, b and short-axis) and in different body positions. Left=left lateral decubitus position, supine=supine decubitus position.

<table>
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<td>Position (left versus supine)</td>
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<table>
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<th>Two-way interaction</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site/position</td>
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Pair wise comparisons using post hoc test (Bonferroni correction) of ANOVA between the three different sites also showed significant differences (a vs. b \(p<0.001\), a vs. short-axis \(p=0.009\) and b vs. short-axis \(p<0.001\)).

**Comparing RVOT1 at the three different sites with the two body positions**

There was no significant difference in RVOT1 measured from the parasternal long-axis view from 2D-image or with M-mode according to site b in the left lateral decubitus position versus the supine decubitus position \((p=0.28\) and \(p=0.27\)). Nor was there any significant difference in RVOT1 measured from the parasternal short-axis view from the 2D-image in the left lateral decubitus position versus the supine decubitus position \((p=0.43)\).

There was, however, a significant difference between the left lateral decubitus position and the supine decubitus position in RVOT1 measured from the parasternal long-axis view according to site a, from the 2D-image \((p=0.01)\) and with M-mode \((p=0.01)\).
Comparing RVOT1 measured in the parasternal long-axis view at site a, site b and short-axis using 2D-images shows an overall significant difference ($p<0.001$) with the highest mean at site b (31.4±5.8 mm vs. short-axis 29.5±5.6 mm and site a 27.4±4.6 mm) (Table 3). There was also an overall significant difference ($p=0.013$) between RVOT1 measured using 2D at the three different sites and the body positions (Table 3). The two-way interaction between the sites and the body positions was also shown to be statistically significant ($p=0.042$) (Table 3).

Table 3. ANOVA for repeated measurements of RVOT1, using 2D at three different sites (a, b and short-axis) and in different body positions. Left=left lateral decubitus position, supine=supine decubitus position.

1. Main effects
   - Site (a, b and short-axis) $p<0.001$
   - Position (left versus supine) $p=0.013$

2. Two-way interaction
   - Site/position $p=0.042$

Pair wise comparisons using post hoc test (Bonferroni correction) of ANOVA between the three different sites also showed significant differences (a vs. b $p<0.001$, a vs. short-axis $p=0.009$ and b vs. short-axis $p<0.001$).

Comparing RVOT1 at the three different sites with the two body positions there was no significant difference in RVOT1 measured from the parasternal long-axis view from 2D-image or with M-mode according to site b in the left lateral decubitus position versus the supine decubitus position ($p=0.28$ and $p=0.27$). Nor was there any significant difference in RVOT1 measured from the parasternal short-axis view from the 2D-image in the left lateral decubitus position versus the supine decubitus position ($p=0.43$).

There was, however, a significant difference between the left lateral decubitus position and the supine decubitus position in RVOT1 measured from the parasternal long-axis view according to site a, from the 2D-image ($p=0.01$) and with M-mode ($p=0.01$).

Two parameters to evaluate right ventricular diastolic function

Right ventricular isovolumetric relaxation time
There was a significant difference ($p<0.001$) between RV-IVRT (measured with the method based on ECG and PW-Doppler) and RV-IVRT(PWDTI) (15.0±10.1 ms vs. 48.5±30.2 ms). The agreement between RV-IVRT and RV-IVRT(PWDTI) is shown in Fig. 13.

A significant difference ($p<0.001$) was found between the time from the R wave to the end of the pulmonic flow (R-P) with PW-Doppler (387.3±40.7 ms) and the time from the R wave on the ECG to the end of the S wave (R-S) with PW-DTI (348.0±41.0 ms). There was no significant difference between the time from the R wave on the ECG to the onset of the tricuspid flow (R-T) with PW-Doppler (402.3±37.1 ms) and the time from the R wave on the ECG to the onset of the early diastolic wave (R-E) with PW-DTI (396.5±44.9 ms).

![Figure 13. Bland-Altman diagram showing the agreement, or rather disagreement, between the right ventricular isovolumetric relaxation time (IVRT) measured in milliseconds (ms) obtained by the method based on ECG and pulsed wave Doppler (PW) and the method based on pulsed wave Doppler tissue imaging (PWDTI) (n=20).](image-url)
Maximal early diastolic velocity in right ventricular long-axis direction

There was a good correlation ($r=0.76; p<0.001$) between MDV TAM and MDV TDI (Fig. 14).

The agreement between MDV TDI and MDV TAM is shown in Fig. 15. MDV TDI ($126.7\pm38.9$ mm s$^{-1}$) was significantly ($p<0.001$) higher than MDV TAM ($78.3\pm27.8$ mm s$^{-1}$).

**Figure 14.** Correlation between the maximal early diastolic velocity in the long-axis direction of the right ventricle obtained by M-mode echocardiography (MDV TAM) and tissue Doppler imaging (MDV TDI).

**Figure 15.** Bland-Altman diagram showing the agreement between the maximal early diastolic velocity in the long-axis direction of the right ventricle obtained by M-mode echocardiography (MDV TAM) and tissue Doppler imaging (MDV TDI) ($n=29$).
**Reproducibility studies**

The intra- and interobserver reproducibilities were measured using Pearson’s intraclass correlation coefficient and the results are presented in Table 4 for study I and Table 5 for study II and III respectively.

<table>
<thead>
<tr>
<th>Agreement, single measurements, investigator A and B</th>
<th>Agreement, double measurements, investigator A</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVOT1 measured from 2D-image, site b, left</td>
<td>0.94</td>
</tr>
<tr>
<td>RVOT1 measured from 2D-image, site b, supine</td>
<td>0.94</td>
</tr>
<tr>
<td>RVOT1 measured from M-mode, site b, left</td>
<td>0.91</td>
</tr>
<tr>
<td>RVOT1 measured from M-mode, site b, supine</td>
<td>0.92</td>
</tr>
<tr>
<td>RVOT1 measured from 2D-image, site a, left</td>
<td>0.88</td>
</tr>
<tr>
<td>RVOT1 measured from 2D-image, site a, supine</td>
<td>0.84</td>
</tr>
<tr>
<td>RVOT1 measured from M-mode, site a, left</td>
<td>0.35</td>
</tr>
<tr>
<td>RVOT1 measured from M-mode, site a, supine</td>
<td>0.48</td>
</tr>
<tr>
<td>RVOT1 measured from 2D-image, short-axis, left</td>
<td>0.95</td>
</tr>
<tr>
<td>RVOT1 measured from 2D-image, short-axis, supine</td>
<td>0.78</td>
</tr>
</tbody>
</table>
Table 5. The intra- and interobserver reproducibility of measuring: 1. the isovolumetric relaxation time of the right ventricle using a method based on ECG and pulsed wave Doppler (RV-IVRT) and a method using pulsed wave Doppler tissue imaging (RV-IVRT(PWDTI)) (n=12). 2. The maximal early diastolic velocity in right ventricular long-axis direction obtained by M-mode echocardiography (MDV TAM) and the maximal early diastolic velocity obtained by tissue Doppler imaging (MDV TDI) (n=11). The agreement was measured using Pearsons’s intraclass correlation coefficient (which has a range -1.0 to +1.0, high positive values indicating high agreement, negative values indicating disagreement).

<table>
<thead>
<tr>
<th></th>
<th>Agreement, single measurements, investigators A and B</th>
<th>Agreement, double measurements, investigator A</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV-IVRT</td>
<td>0.77</td>
<td>0.83</td>
</tr>
<tr>
<td>RV-IVRT(PWDTI)</td>
<td>0.88</td>
<td>0.84</td>
</tr>
<tr>
<td>MDV TAM</td>
<td>0.60</td>
<td>0.96</td>
</tr>
<tr>
<td>MDV TDI</td>
<td>0.80</td>
<td>0.94</td>
</tr>
</tbody>
</table>
Table 5. The intra- and interobserver reproducibility of measuring: 1. the isovolumetric relaxation time of the right ventricle using a method based on ECG and pulsed wave Doppler (RV-IVRT) and a method using pulsed wave Doppler tissue imaging (RV-IVRT(PWDTI)) (n=12). 2. The maximal early diastolic velocity in right ventricular long-axis direct ion obtained by M-mode echocardiography (MDV TAM) and the maximal early diastolic velocity obtained by tissue Doppler imaging (MDV TDI) (n=11). The agreement was measured using Pearson’s intra-class correlation coefficient (which has a range -1.0 to +1.0, high positive values indicating high agreement, negative values indicating disagreement).

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<tr>
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</tr>
<tr>
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<td>0.88</td>
<td>0.84</td>
</tr>
<tr>
<td>MDV TAM</td>
<td>0.60</td>
<td>0.96</td>
</tr>
<tr>
<td>MDV TDI</td>
<td>0.80</td>
<td>0.94</td>
</tr>
</tbody>
</table>

40

KARIN LOISKE

Echocardiographic measurements of the heart

Takotsubo cardiomyopathy

Left ventricle
There was a significant difference between the amplitudes of MAM (the total of four sites) between the acute (9.6±1.0 mm) and recovery phase (11.2±1.9 mm) (p=0.02) (Table 6). There was a significant difference between the different sites except for the septal site (Table 6). There was a significant difference (p<0.01) between LVEF obtained by the biplane Simpson’s method in the acute phase (53.4±9.5%) compared to the recovery phase (63.3±4.4%).

Both the é and á diastolic velocities as well as the S velocity measured by PW-DTI increased significantly from the acute to the recovery phase but there were no significant differences when they were measured using 2D color DTI. The S, é and á diastolic velocities were all significantly higher when measured at the acute and recovery phase using PW-DTI compared to using 2D color DTI. There was no statistically significant difference between the other measured diastolic parameters (Table 6).

There was no significant difference in the length of the LV in end-diastole from the epicardial apex to the septal or lateral sites of the mitral annulus between the acute and the recovery phase. There was also no significant difference in end-diastolic diameter, not even at the widest part of the LV, or end-systolic diameter between the two phases.
Table 6. Significance of difference between the acute and recovery phase of some left ventricular variables (EF=ejection fraction, MAM=mitral annulus motion, PW=pulsed wave, PW DTI=pulsed wave Doppler tissue imaging, 2D color DTI=two-dimensional color Doppler tissue imaging, IVRT=Isovolumetric relaxation time, S=systolic velocity, E=early diastolic velocity by PW, A=late diastolic velocity by PW, é=early diastolic velocity by PW DTI, á=late diastolic velocity by PW DTI) (n=13).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute phase</th>
<th>Recovery phase</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (biplane Simpson’s method, %)</td>
<td>53.4±9.5</td>
<td>63.3±4.4</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>MAM, septal site (mm)</td>
<td>9.4±2.1</td>
<td>10.1±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MAM, lateral site (mm)</td>
<td>10.1±2.3</td>
<td>12.1±2.6</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>MAM, inferior site (mm)</td>
<td>9.9±2.8</td>
<td>11.6±2.0</td>
<td>p=0.03</td>
</tr>
<tr>
<td>MAM, anterior site (mm)</td>
<td>9.0±2.6</td>
<td>10.8±1.9</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Total MAM (all sites, mm)</td>
<td>9.6±2.2</td>
<td>11.2±1.9</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2±0.7</td>
<td>0.9±0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>206.2±91.5</td>
<td>249.6±69.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW (ms)</td>
<td>91.5±19.3</td>
<td>90.6±17.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW-DTI (ms)*</td>
<td>89.4±20.0</td>
<td>87.1±23.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by 2D color DTI (ms)</td>
<td>65.2±17.9</td>
<td>66.3±16.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by PW-DTI (cm/s)</td>
<td>5.9±1.5</td>
<td>7.2±1.9</td>
<td>p=0.02</td>
</tr>
<tr>
<td>é (cm/s)</td>
<td>6.5±2.6</td>
<td>8.2±3.3</td>
<td>p=0.04</td>
</tr>
<tr>
<td>á (cm/s)</td>
<td>7.0±2.0</td>
<td>8.6±2.9</td>
<td>p=0.04</td>
</tr>
<tr>
<td>é/á</td>
<td>1.1±0.8</td>
<td>1.1±0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by 2D color DTI (cm/s)</td>
<td>5.3±3.2</td>
<td>5.3±1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>é by 2D color DTI (cm/s)</td>
<td>4.4±2.1</td>
<td>6.1±3.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>á by 2D color DTI (cm/s)</td>
<td>5.4±1.8</td>
<td>6.2±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>é/á by 2D color DTI</td>
<td>0.9±0.6</td>
<td>1.2±1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relaxation velocity (cm/s)</td>
<td>51.0±32.7</td>
<td>52.9±28.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-septal site, mm)</td>
<td>82.2±8.5</td>
<td>79.1±7.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-lateral site, mm)</td>
<td>86.7±8.8</td>
<td>83.7±8.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-diastolic diameter (basal, mm)</td>
<td>43.7±4.6</td>
<td>43.1±3.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-diastolic diameter (widest place, mm)</td>
<td>47.8±5.0</td>
<td>46.4±4.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-systolic diameter (basal, mm)</td>
<td>27.9±6.1</td>
<td>26.9±3.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>E/é</td>
<td>12.6±6.5</td>
<td>11.9±9.6</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*one missing patient due to difficulties measuring IVRT by PW-DTI
Table 6. Significance of difference between the acute and recovery phase of some left ventricular variables (EF=ejection fraction, MAM=mitral annulus motion, PW=pulsed wave, PW DTI=pulsed wave Doppler tissue imaging, 2D color DTI=two-dimensional color Doppler tissue imaging, IVRT=isovolumetric relaxation time, S=systolic velocity, E=early diastolic velocity by PW, A=late diastolic velocity by PW, é=early diastolic velocity by PW-DTI, á=late diastolic velocity by PW-DTI) (n=13).

<table>
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<tr>
<th>Variable</th>
<th>Acute phase</th>
<th>Recovery phase</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (biplane Simpson’s method, %)</td>
<td>53.4±9.5</td>
<td>63.3±4.4</td>
<td><em>p</em>&lt;0.01</td>
</tr>
<tr>
<td>MAM, septal site (mm)</td>
<td>9.4±2.1</td>
<td>10.1±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MAM, lateral site (mm)</td>
<td>10.1±2.3</td>
<td>12.1±2.6</td>
<td><em>p</em>&lt;0.02</td>
</tr>
<tr>
<td>MAM, inferior site (mm)</td>
<td>9.9±2.8</td>
<td>11.6±2.0</td>
<td><em>p</em>=0.03</td>
</tr>
<tr>
<td>MAM, anterior site (mm)</td>
<td>9.0±2.6</td>
<td>10.8±1.9</td>
<td><em>p</em>&lt;0.02</td>
</tr>
<tr>
<td>Total MAM (all sites, mm)</td>
<td>9.6±2.2</td>
<td>11.2±1.9</td>
<td><em>p</em>&lt;0.02</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2±0.7</td>
<td>0.9±0.3</td>
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</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>206.2±91.5</td>
<td>249.6±69.4</td>
<td>n.s.</td>
</tr>
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<td>IVRT by PW (ms)</td>
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<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW-DTI (ms)*</td>
<td>89.4±20.0</td>
<td>87.1±23.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by 2D color DTI (ms)</td>
<td>65.2±17.9</td>
<td>66.3±16.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by PW-DTI (cm/s)</td>
<td>5.9±1.5</td>
<td>7.2±1.9</td>
<td><em>p</em>=0.02</td>
</tr>
<tr>
<td>é (cm/s)</td>
<td>6.5±2.6</td>
<td>8.2±3.3</td>
<td><em>p</em>=0.04</td>
</tr>
<tr>
<td>á (cm/s)</td>
<td>7.0±2.0</td>
<td>8.6±2.9</td>
<td><em>p</em>=0.04</td>
</tr>
<tr>
<td>é/á</td>
<td>1.1±0.8</td>
<td>1.1±0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by 2D color DTI (cm/s)</td>
<td>5.3±3.2</td>
<td>5.3±1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>é by 2D color DTI (cm/s)</td>
<td>4.4±2.1</td>
<td>6.1±3.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>á by 2D color DTI (cm/s)</td>
<td>5.4±1.8</td>
<td>6.2±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>é/á by 2D color DTI</td>
<td>0.9±0.6</td>
<td>1.2±1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relaxation velocity (cm/s)</td>
<td>51.0±32.7</td>
<td>52.9±28.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-septal site, mm)</td>
<td>82.2±8.5</td>
<td>79.1±7.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-lateral site, mm)</td>
<td>86.7±8.8</td>
<td>83.7±8.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-diastolic diameter (basal, mm)</td>
<td>43.7±4.6</td>
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<td>n.s.</td>
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<td>n.s.</td>
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<td>27.9±6.1</td>
<td>26.9±3.0</td>
<td>n.s.</td>
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<td>n.s.</td>
</tr>
</tbody>
</table>

*one missing patient due to difficulties measuring IVRT by PW-DTI

Right ventricle
There was a statistically significant difference (*p*=0.02) between the total amplitude of TAM in the acute phase (21.3±3.6mm) and the recovery phase (24.1±2.8mm) but no significant differences were found between the size or the length of the RV. Nor were there any significant differences of the diastolic parameters between the two phases (table 7).

Table 7. Significance of difference between the acute phase and the recovery phase of some right ventricular variables (TAM=tricuspid annulus motion, PW=pulsed wave, PW DTI=pulsed wave Doppler tissue imaging, 2D color DTI=two-dimensional color Doppler tissue imaging, IVRT=ivsovolumetric relaxation time; S=systolic velocity, E=early diastolic velocity by PW, A=late diastolic velocity by PW, é=early diastolic velocity by PW-DTI, á=late diastolic velocity by PW-DTI, RVOT1=right ventricular outflow tract 1, RVIT3=right ventricular inflow tract 3) (n=13).

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Recovery phase</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAM (mm)</td>
<td>21.3±3.6</td>
<td>24.1±2.8</td>
<td><em>p</em>=0.02</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3±0.5</td>
<td>1.1±0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>195.0±58.7</td>
<td>201.3±42.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW (ms)</td>
<td>84.8±27.5</td>
<td>63.4±25.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW-DTI (ms)</td>
<td>70.4±21.9</td>
<td>60.6±23.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by 2D color DTI (ms)</td>
<td>53.1±35.2</td>
<td>44.9±16.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by PW-DTI (cm/s)</td>
<td>12.2±2.2</td>
<td>12.5±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>é (cm/s)</td>
<td>11.3±3.6</td>
<td>11.8±2.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>á (cm/s)</td>
<td>16.2±3.9</td>
<td>15.7±3.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>é/á</td>
<td>0.7±0.2</td>
<td>0.8±0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by 2D color DTI (cm/s)</td>
<td>10.3±2.4</td>
<td>10.8±2.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>é by 2D color DTI (cm/s)</td>
<td>9.5±3.6</td>
<td>8.6±2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>á by 2D color DTI (cm/s)</td>
<td>11.7±3.1</td>
<td>12.3±2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>é/á by 2D color DTI</td>
<td>0.9±0.4</td>
<td>0.8±0.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relaxation velocity (cm/s)</td>
<td>87.2±37.5</td>
<td>78.8±23.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-septal site, mm)</td>
<td>72.3±11.6</td>
<td>71.7±8.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-lateral site, mm)</td>
<td>83.9±14.4</td>
<td>82.4±9.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>RVOT1 (mm)</td>
<td>27.0±4.2</td>
<td>28.0±4.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>RVIT3 (mm)</td>
<td>29.7±5.2</td>
<td>30.0±2.9</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
DISCUSSION

Methodological considerations

Reproducibility of RVOT1
There was a good intraindividual reproducibility for most of the investigated parameters (table 4) except when measuring RVOT1 at site a with M-mode, which was somewhat lower. Even interindividual reproducibility was good for most of the measured parameters. The lowest interindividual reproducibility was found when measuring RVOT1 at site a with M-mode. This indicates that site a should be avoided.

One cause of the lower reproducibility at this site compared to the other sites is probably due to the absence of a reference point from which to measure. At site b, the aortic root can be used as a reference point and at the short-axis it is easier to find a reference point at the aortic root level than when measuring from site a. When RVOT1 is measured according to site a, using M-mode, there is also a risk that the M-mode line cuts the RV more apically than at the RVOT1 region. It may also be difficult to determine the septal wall contour, especially in the M-mode image but also in the 2D-image, since the chordae tendinae and papillary muscles sometimes make it hard to determine the septal wall border which therefore makes it difficult to assess the border of the RV lumen.

In some cases, however, the lower interindividual reproducibility was probably due to investigator B being less experienced in measuring RVOT1 compared to investigator A.

Reproducibility of RV-IVRT and RV-IVRT(PWDTI)

The reproducibility study (table 5), concerning RV-IVRT and RV-IVRT(PWDTI) indicate good intra- and interobserver reproducibility of the measurements.

Reproducibility of MDV TAM and MDV TDI

The reproducibility study (table 5) indicate good intraobserver reproducibility in the measurement of MDV TAM and MDV TDI. There was also good interobserver reproducibility in the measurement of MDV TDI. The interobserver reproducibility in the measurement of MDV TAM was somewhat poorer. This was probably due to investigator B being less experienced in measuring MDV TAM compared to investigator A. When measuring MDV TAM it is important to measure during the end of expiration.
DISCUSSION

Methodological considerations

Reproducibility of RVOT1
There was a good intraindividual reproducibility for most of the investigated parameters (table 4) except when measuring RVOT1 at site a with M-mode, which was somewhat lower. Even interindividual reproducibility was good for most of the measured parameters. The lowest interindividual reproducibility was found when measuring RVOT1 at site a with M-mode. This indicates that site a should be avoided.

One cause of the lower reproducibility at this site compared to the other sites is probably due to the absence of a reference point from which to measure. At site b, the aortic root can be used as a reference point and at the short-axis it is easier to find a reference point at the aortic root level than when measuring from site a. When RVOT1 is measured according to site a, using M-mode, there is also a risk that the M-mode line cuts the RV more apically than at the RVOT1 region. It may also be difficult to determine the septal wall contour, especially in the M-mode image but also in the 2D-image, since the chordae tendinae and papillary muscles sometimes make it hard to determine the septal wall border which therefore makes it difficult to assess the border of the RV lumen.

In some cases, however, the lower interindividual reproducibility was probably due to investigator B being less experienced in measuring RVOT1 compared to investigator A.

Reproducibility of RV-IVRT and RV-IVRT(PWDTI)
The reproducibility study (table 5), concerning RV-IVRT and RV-IVRT(PWDTI) indicate good intra- and interobserver reproducibility of the measurements.

Reproducibility of MDV TAM and MDV TDI
The reproducibility study (table 5) indicate good intraobserver reproducibility in the measurement of MDV TAM and MDV TDI. There was also good interobserver reproducibility in the measurement of MDV TDI. The interobserver reproducibility in the measurement of MDV TAM was somewhat poorer. This was probably due to investigator B being less experienced in measuring MDV TAM compared to investigator A. When measuring MDV TAM it is important to measure during the end of expira-
tion and to search for the steepest portion of the M-mode curve in early-
diastole.

**Correlation and agreement between MDV TDI and MDV TAM**

There was a good correlation between MDV TAM and MDV TDI (Fig. 14) indicating that MDV TAM might be used in the same way as MDV TDI in the assessment of RVDF. The agreement, however, was rather poor (Fig. 15), with MDV TDI ($126.7 \pm 38.9$ mm s$^{-1}$) being about 60% higher ($p<0.001$) than MDV TAM ($78.3 \pm 27.8$ mm s$^{-1}$). This finding is somewhat surprising as both MDV TAM and MDV TDI measure the maximal early diastolic relaxation velocity in the long-axis direction of the RV.

One reason for the difference between the MDV TDI and MDV TAM could be that the TDI technique reports instantaneous velocities, whereas the M-mode procedure implies some degree of averaging around the maximal value as a finite-length segment in the maximal slope tract must be chosen for practical reasons.

Another reason for the difference could have been that MDV TAM is measured endocardially whilst MDV TDI is measured in the myocardium more epicardially. As the spatial resolution when using MDV TDI is poor (15,53), however, the placement of the sample volume seems to be of minor importance. In addition, another study (54) has shown no significant difference between the diastolic velocities of TAM measured endocardially and the diastolic velocities at two sites of the right coronary artery, which is situated epicardially.

In a study by Fornander et al. (30) it was discussed whether the difference between the maximal diastolic velocities of the LV measured by M-mode echocardiography and TDI could be due to the point of the spectral curve from which the MDV TDI is measured. In accordance with guidelines (49) it was measured by Fornander et al. as well as in study III from the outer edge of the dense part of the spectral curve. As the cells in the myocardium move together and not separately from each other (in contrast to blood velocity measurements) there is seldom a scatter of velocities and the spectral curve is often very easy to define so it is not probable that this could explain the difference found. Furthermore, a phantom study has shown overestimation of velocities by PW-DTI (55).

**Limitations of the studies**

Study I was performed on healthy subjects aged 25-35 years, with generally good quality of image and examination technique. It would be of interest to perform a similar study on patients, in which the quality of the images and examination technique are not always optimal. Patients with different
heart conditions also sometimes present anatomically deviant ventricles, which could make it more challenging to implement the measurement of RVOT1 than on healthy subjects.

In study IV there were surprisingly few diastolic parameters that improved between the acute phase and the recovery phase of takotsubo cardiomyopathy. Considering that both the LV and RV functions improved significantly (Tables 6 and 7) we expected an increase in the diastolic parameters as well. In the LV there was only a significant difference for the early and late diastolic velocities measured by PW-DTI, both increasing from the acute to the recovery phase (Table 6). In the RV none of the diastolic parameters showed a significant difference (Table 7). Perhaps some of the diastolic measurements, that didn’t differ between the acute and recovery phase, would have become significant with a larger sample.

**Theoretical implications**

**RVOT1**

The size of RVOT1 was measured significantly higher from site a, with the subjects in the left lateral decubitus position compared to when the subjects were in the supine decubitus position (both 2D and M-mode indicate this). If this difference was not due to the measuring technique, one could wonder if there is a difference in RV volume depending on body position. This would also, however, have affected RVOT1 measured from site b and short-axis, so this theory seems less probable.

There is also a risk that the RV may appear abnormal, especially from the parasternal view, in some individuals due to the position of the RV relative to the image plane and where the RV may be imaged in an oblique orientation (56). It is therefore important that the size of the RV, in addition to measuring from the parasternal view, is also measured from other echocardiographic windows, such as apical four-chamber view or subcostal view.

*Isovolumetric relaxation time*

IVRT of the RV is usually defined as the time from the closure of the pulmonic valve to the opening of the tricuspid valve (26) that is, to the onset of the tricuspid flow. The time from the R wave on the ECG to the closure of the pulmonic valve (R-P) was found to be significantly longer than the time from the R wave on the ECG to the end of the S wave (R-S), meaning that the method using PW-DTI does not measure the time from the closure of the pulmonic valve.
That the myocardium stops its systolic movement, which is the end of the S-wave with PW-DTI, just before the closure of the pulmonic valve is not surprising. During systole the myocardium of the RV contracts causing the pressure in the RV to rise. When the pressure in the pulmonary artery is exceeded the pulmonic valve opens and blood can flow into the pulmonary artery. As the myocardium starts to relax the pressure in the RV falls and at the end of systole, that is, at the end of the S wave, when the pressure in the pulmonary artery exceeds that in the RV (57), the pulmonic valve closes, which explains why R-P has a longer duration than R-S.

The somewhat, but not significantly, shorter duration from the R wave on the ECG to the onset of the E wave (R-E), (that is, to the onset of the myocardium moving), compared to the duration to the onset of the tricuspid flow (R-T), may as has been suggested on the left side of the heart (31), be due to elastic recoil of the RV during diastole promoting the flow across the tricuspid orifice into the RV (58).

_Takotsubo cardiomyopathy and its effect on LV function_

The improvement of LV systolic long-axis shortening is in line with the improvement of LVEF obtained by the biplane Simpson’s method (table 6). The lower amplitudes of MAM in the acute phase indicate that the longitudinal fibers are affected in takotsubo cardiomyopathy. These fibers are mostly located subendocardially and this part of the myocardium has the highest risk of ischaemia (19,59). From this it’s easy to make the conclusion that atherosclerotic coronary disease-mediated myocardial ischemia could be a cause of the decrease in systolic long-axis shortening. This theory is not, however, supported by findings during, for instance, magnetic resonance imaging studies since there is no evidence of focal perfusion abnormalities corresponding to a specific coronary vessel territory (60). Also, the fact that all the patients had no significant coronary artery stenosis makes this theory less probable.

The non-significant difference of the amplitude of MAM at the septal site between the two phases could be explained by fewer longitudinal fibers at septum than at the other anatomical locations. Septum is composed of subendocardial fibers from the RV and LV together with at middle layer composed of circumferential fibers in continuity with those from the corresponding layer of LV free wall. Circumferential septal fibers are lacking towards the apex (19).

One conjecture of the pathogenesis of takotsubo is elevated catecholamine levels causing epicardial coronary arterial spasm, but multivessel epicardial spasms seem unlikely (61). Other studies have been unable to
confirm spasms as a cause of takotsubo, which is why it seems unlikely to be the cause of this disease (39).

Another theory is catecholamine mediated myocardial stunning caused by direct myocyte injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic AMP-mediated calcium overload (62). Interaction of the endocardial endothelium with circulating substances in the blood such as catecholamine may modify myocardial performance (39). The catecholamine hypothesis, which seems like the most plausible theory which could explain the findings in study IV, is supported by apical ballooning in some case reports with dobutamine stress echocardiography (41), in reports of patients with phaeochromocytoma (63,64) and in patients with subarachnoid haemorrhage (65). In the latter case a catecholamine surge has been proposed as the explanation for the cardiomyopathy.

When looking at the LVDF there were, as mentioned earlier, only two parameters that significantly improved from the acute to the recovery phase, namely the early and the late diastolic velocities measured by PW-DTI. This is not an unexpected improvement since the velocities are measured at the basal parts of the LV as are the amplitudes of MAM. The increase in the systolic long-axis shortening may therefore also explain the increase in those parameters. What is surprising, however, is that the same parameters measured by 2D color DTI did not change significantly although these velocities are also measured at the basal part of the LV. These velocities were significantly lower than the velocities measured by PW-DTI. One explanation for this could be that the velocities obtained with 2D color DTI are peak-mean velocities due to autocorrelation methodology, while PW-DTI measures peak velocities with a fast Fourier transformation technique (66). Where the sample volume is placed in the myocardium at the basal part of the LV may also cause the differences as well as the angle of the transducer.

Another reason for the lack of the expected increase of diastolic parameters could be that few patients had severely reduced LVEF and total amplitude of MAM during the acute phase. In another study (38), however, LVEF in the acute phase was lower than in the present study and higher in the recovery phase and despite this the authors found no significant changes in diastolic parameters.

There were no significant differences found in LV length or diameter between the two phases (Table 6), which also is somewhat surprising since it could have been expected that the apical ballooning contributes to a longer/wider LV in the acute phase. The angle of the transducer, however, might have influenced this result.
Takotsubo cardiomyopathy and its effect on RV function

There was, as with the total amplitude of MAM, a significant difference between the acute and recovery phase concerning the amplitude of TAM (table 7). The improvement of this systolic long-axis shortening of the RV at the lateral site indicates that also the longitudinal fibers of the RV are affected in this disease, probably most in the apical regions.

This suggests that the RV is involved in takotsubo cardiomyopathy, something that only has been shown in a few studies (37,67). When RV involvement occurs it follows a similar pattern of regional wall motion abnormalities as the LV, but RV involvement portends a longer and more critical hospitalization course compared to patients with isolated LV involvement (67). The mechanisms explaining the involvement of the RV in takotsubo are unclear but argue against LV outflow tract obstruction as a cause of takotsubo (37).

There were no significant differences found in the RV length between the two phases (table 7). The angle of the transducer, however, might have influenced this result.

Practical implications

RVOT1

From this thesis it seems obvious that echocardiographers should use the same site, method and body position when measuring RVOT1 in a single patient/subject that is followed over time. RVOT1 should preferably be measured from site b (Figs. 3 and 4) or short-axis (Fig. 7) since these sites showed good intra- and interindividual reproducibility and also did not show a significant difference when the subject was examined in the left lateral decubitus position or the supine decubitus position.

Isovolumetric relaxation time of the right ventricle

The RV-IVRT is one of the most sensitive markers on RV dysfunction (23). In study II two different methods for measuring the IVRT of the RV were compared, one method based on ECG and PW-Doppler (27), RV-IVRT, and the other based on PW-DTI (20,21,23), RV-IVRT(PWDTI). A significant difference was found between IVRT obtained by the two methods, RV-IVRT being shorter than RV-IVRT(PWDTI).

Since the two methods, RV-IVRT and RV-IVRT(PWDTI), have been shown not to measure the same time interval in patients it seems obvious that different reference values have to be used when using the method based on PW-DTI than when using the method based on ECG and PW-
Doppler. Since the method based on ECG and PW-Doppler is more time consuming to perform than the method based on PW-DTI this latter method seems to be the first choice to use if PW-DTI is available on the echocardiograph.

Maximal early diastolic velocity of the right ventricle
MDV TDI and MDV TAM showed a good correlation but a rather poor agreement indicating that reference values cannot be used interchangeably. Since there already are established reference values for MDV TDI it seems preferable to use this technique as most ultrasound systems today are equipped with PW-DTI technology. Furthermore, MDV TAM showed a somewhat poorer interindividual reproducibility.

Takotsubo cardiomyopathy
The significant improvement in RV systolic long-axis function between the acute and recovery phase in takotsubo cardiomyopathy indicates that takotsubo is not an isolated LV disorder. As earlier studies have shown a longer and more critical hospitalization for patients with RV dysfunction (67) it is important to, in addition to the LV function, also examine the RV function among patients with takotsubo cardiomyopathy. However, to fully understand the underlying pathophysiology behind this rare disease more large-scale studies need to be performed.
CONCLUSIONS

- There is an overall significant difference of the diameters of RVOT1 at different sites, when using different methods and in different body positions. Thus, the same site, method and body position should preferably be used when comparing RVOT1 over time in the same patient or subject. Site b or short-axis should preferably be used since there was a good reproducibility and no significant difference between body positions when RVOT1 is measured from these sites. Site a should be avoided due to the lower reproducibility and the significant difference of RVOT1 between the two body positions when using this site.

- The two methods measuring RV-IVRT are not measuring the same time interval. With PW-DTI the time interval measured is the time from the end of the systolic motion of the tissue at the tricuspid annulus to the onset of the diastolic motion of the tissue at the same annulus. This interval has a longer duration than the time interval measured with ECG and PW-Doppler, which measures the time from the closure of the pulmonic valve to the onset of the tricuspid flow, which is the usual definition of RV-IVRT. Thus, different reference values have to be used when measuring RV-IVRT with the two different methods.

- The RV MDV can be measured using two different methods, one based on M-mode and one based on PW-DTI. The methods showed a good correlation but a poor agreement. This means that reference values cannot be used interchangeably between the two methods. As most new ultrasound systems are equipped with PW-DTI technology it seems preferable to use this method, which already has established reference values (34).

- The systolic long-axis shortening of the LV and the RV improved significantly between the acute phase and the recovery phase in takotsubo cardiomyopathy. There were also improvements in LV early and late diastolic velocities measured by PW-DTI while other diastolic parameters of the LV and the diastolic parameters of the RV remained unchanged.
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Leif Bojö my "sparring partner", for your involvement and constructive critics.

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STUDY I
Echocardiographic measurements of the right ventricle:

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Abstract

Purpose

The size of the ventricles of the heart is important to establish during the clinical echocardiographic examination. Due to the complex anatomy of the right ventricle, it is difficult to measure its size at times. One of the most frequently used ways is to measure the right ventricular outflow tract (RVOT1), probably due to its good reproducibility. However, in the literature different ways are described to measure RVOT1, both at different sites and using different methods such as M-mode and 2D.

The first aim of the present study was to examine if there is a significant difference in the outcome of RVOT1 using different sites and methods to measure it. The second aim was to study if there is a significant difference between the usually preferred left lateral decubitus position during the echocardiographic examination and the supine decubitus position, which the echocardiographer sometimes can be compelled to use if the patient is unable to lie in the left lateral decubitus position.

Methods

Twenty-seven healthy subjects were included and examined by echocardiography. RVOT1 was measured at different sites using different methods; first with the subject in the left lateral decubitus position and then repeating the same measurements with the subject in the supine decubitus position.

Results

Comparing the RVOT1 measured at different sites and with different methods showed an overall significant difference ($p < 0.001$). Also when comparing the different body positions, there was an overall significant difference ($p = 0.001$).

Conclusions

When comparing RVOT1 of the same patient or subject over time, the results from the present study indicate that the same site, method and body position should be used.

Keywords

Heart / Right ventricular size / Echocardiography / Body position

Introduction

The size of the heart, especially its ventricles, is important to establish during the clinical echocardiographic examination, since larger ventricles often indicates an underlying disease such as dilated cardiomyopathy, valvular disorder or shunt.

The size of the left ventricle (LV) is associated with the prognosis of the patient. It has important therapeutic implications and can provide data that are necessary to define the optimal time for cardiac surgery, for instance, in patients with aortic- or mitral regurgitation [1]. A large right ventricle (RV) may be seen in patients with different kinds of heart diseases such as arrhythmogenic right ventricular dysplasia (ARVD) [2], primary pulmonary disease, but often it is a result of backward transmission of elevated LV filling pressure through the pulmonary circulation, thus augmenting RV afterload [3]. Large ventricles and ventricular hypertrophy could, however, also be seen in apparently healthy individuals such as athletes [4].

Different techniques such as two dimensional (2D)- or three dimensional (3D) echocardiography and magnetic resonance imaging, can be used to measure the size of the

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Echocardiographic measurements of the right ventricle: right ventricular outflow tract 1

K. Loiske · S. Hammar · K. Emilsson

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Abstract

Purpose The size of the ventricles of the heart is important to establish during the clinical echocardiographic examination. Due to the complex anatomy of the right ventricle, it is difficult to measure its size at times. One of the most frequently used ways is to measure the right ventricular outflow tract (RVOT1), probably due to its good reproducibility. However, in the literature different ways are described to measure RVOT1, both at different sites and using different methods such as M-mode and 2D. The first aim of the present study was to exam if there is a significant difference in the outcome of RVOT1 using different sites and methods to measure it. The second aim was to study if there is a significant difference between the usually preferred left lateral decubitus position during the echocardiographic examination and the supine decubitus position, which the echocardiographer sometimes can be compelled to use if the patient is unable to lie in the left lateral decubitus position.

Methods Twenty-seven healthy subjects were included and examined by echocardiography. RVOT1 was measured at different sites using different methods; first with the subject in the left lateral decubitus position and then repeating the same measurements with the subject in the supine decubitus position.

Results Comparing the RVOT1 measured at different sites and with different methods showed an overall significant difference (p < 0.001). Also when comparing the different body positions, there was an overall significant difference (p = 0.001).

Conclusions When comparing RVOT1 of the same patient or subject over time, the results from the present study indicate that the same site, method and body position should be used.

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Different techniques such as two dimensional (2D)- or three dimensional (3D) echocardiography and magnetic resonance imaging, can be used to measure the size of the
ventricles. Even though 3D echocardiography nowadays has increased popularity, most echocardiographic examinations still are performed using 2D echocardiography.

Due to the complex anatomy of RV, it is at times difficult to measure its size. Several ways to measure the RV have been suggested in the literature [5–15]. However, probably because earlier studies [14] have shown the best reproducibility measuring the RV inflow tract (RVIT3) and RV outflow tract (RVOT1), those are the most frequently used parameters.

RVOT3 is measured in the apical four chamber view one-third from the base of the RV [10] but when it comes to RVOT1, different ways are described in the literature on how to measure it [5, 9, 10, 12–15].

Anatomically the RVOT extends cephalic and in a leftward direction from the anteromedial portion of the tricuspid valve annulus to the pulmonary annulus. The anterior border is the anterior RV free wall. The posterior boundary is the anteromedial portions of the aortic root. In normal hearts, the crista supraventricularis is an anatomically identifiable structure to RVOT [15].

Considering that in the literature different ways have been described to measure RVOT1 at different sites and using different methods such as M-mode and 2D, the main aim of the present study was to examine if there is a significant difference in outcome of RVOT1 using the different ways to measure it.

The left lateral decubitus position is often preferred to obtain the best quality of images during the echocardiographic examination. However, when echocardiography is performed on seriously ill patients, for instance, patients admitted to the intensive care unit or patients, for other reasons, unable to lie in the left lateral decubitus position, echocardiographers are sometimes compelled to examine patients in a supine decubitus position. Earlier studies have shown an increase in RV dimensions from supine to left lateral decubitus position [5], why our second aim with this study was to examine if there actually is a significant difference in RVOT1 due to the body position. If this is the case, this should be taken into account when RVOT1 is measured in the supine decubitus position.

**Patients and methods**

**Patients**

Twenty-seven healthy subjects, 15 men and 12 women aged 21–35 years with average age 25.5 years, were included and examined by echocardiography at the Department of Clinical Physiology, Örebro University Hospital. They had a normal ECG and no history of cardiac diseases. The investigations on the subjects were approved by the regional ethical committee and informed consent was obtained from each subject. Some basic characteristics and measured and calculated variables are shown in Table 1.

**Echocardiographic examination**

A Vivid 7 echocardiograph (GE Vingmed Ultrasound A/S, Horten, Norway) equipped with a multifrequency phased array transducer (M35, 1.5–4.0 MHz) was used for the echocardiographic examinations and measurements were made after the examination using stored images in an Echopac (GE Vingmed Ultrasound A/S) Compaq DeskPro Workstation 300 (Compaq Computer Corporation, Houston, TX, USA).

The measurements of RVOT1 were performed from the parasternal long-axis view, first with the subject in the left lateral decubitus position and then in the supine decubitus position. The different ways of measuring RVOT1 from this view was at site “b” from the 2D-image (Fig. 1) [5, 14] and from the M-mode image (Fig. 2) [5, 14], at site “a” from the 2D-image (Fig. 3) [9, 15] and from the M-mode image (Fig. 4) [12, 13].

As in the literature, RVOT1 in the short-axis projection has been measured only using 2D-images, except for Lindqvist et al. [7] who focused on the RV function (RVOT fractional shortening) and not on the size of the RV, it was only measured with this method in the present study, first with the subject in the left lateral decubitus position and then in the supine decubitus position (Fig. 5) [10].

To minimize the influence of respiration on RVOT1, the measurements were done at the end of expiration and the measurements and results were calculated as the average of three beats. All subjects were in sinus rhythm.

**Reproducibility of the measurements**

The intra- and interindividual reproducibility (reproducibility study) was examined in ten of the subjects.

**Table 1** Some basic characteristics and measured and calculated variables (n = 27)

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<thead>
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<th>Mean ± SD</th>
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<tr>
<td>Age (years)</td>
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<td>Height (m)</td>
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<tr>
<td>Weight (kg)</td>
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<td>Left ventricular end-diastolic diameter (mm)</td>
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<td>Left ventricular end-systolic diameter (mm)</td>
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<td>Left ventricular septal wall thickness (mm)</td>
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<tr>
<td>Left ventricular posterior wall thickness (mm)</td>
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<td>Tricuspid annulus motion (mm)</td>
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<td>Left ventricular ejection fraction (Teichholz)</td>
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</tbody>
</table>
RV have been suggested in the literature [5–15]. However, investigations still are performed using 2D echocardiography. As in the literature, RVOT1 in the short-axis projection has increased popularity, most echocardiographic examinations have been described to measure RVOT1 at different sites and normally the crista supraventricularis is an anatomically identifiable structure to RVOT [15]. The measurements of RVOT1 were performed from the parasternal long-axis view, first with the subject in the left lateral decubitus position and then in the supine decubitus position. Thereafter investigator B (Sofia Hammar) (blinded from the measurements of investigator A) measured the same parameters in the same way. Investigator A then again performed the same procedure.

Statistics

ANOVA for repeated measurements, General Linear Model (GLM), was used to exam if the overall obtained differences and interactions of RVOT1 at the different sites, different body positions and with different methods were statistically significant. Post hoc test was done using Bonferroni correction. The paired sampled t test was used to compare the difference between body positions (left lateral decubitus position versus supine decubitus position) at each site.

StUDY I

Fig. 1 RVOT1 measured in the parasternal long-axis view from the 2D-image according to site b [5, 14]

Investigator A (Karin Loiske) first measured RVOT1 according to Figs. 1, 2, 3, 4 and 5 in the left lateral decubitus position and in the supine decubitus position. Thereafter investigator B (Sofia Hammar) (blinded from the measurements of investigator A) measured the same parameters in the same way. Investigator A then again performed the same procedure.

Results

First, the diameters of RVOT1 measured at site “a” and “b” in the parasternal long-axis view were compared with each other, both from 2D-images and when using M-mode, and from the two different body positions. There was found to be an overall significant difference (p < 0.001) between the diameters of RVOT1 measured at sites “a” and “b”, with the diameters measured at “b” being higher than that.

In the intra- and interindividual reproducibility study, an estimate of agreement was obtained by using Pearson’s intraclass correlation coefficient, r [16]. The coefficient has a range −1.0 to +1.0 with high positive values indicating high agreement, negative values indicating disagreement. A difference at the 5% level was regarded as significant. Data were analysed using the SPSS 16.0 statistical software (SPSS, Chicago, IL, USA).

Fig. 2 RVOT1 measured in the parasternal long-axis view in the M-mode image according to site b [5, 14]

ANOVA for repeated measurements, General Linear Model (GLM), was used to exam if the overall obtained differences and interactions of RVOT1 at the different sites, different body positions and with different methods were statistically significant. Post hoc test was done using Bonferroni correction. The paired sampled t test was used to compare the difference between body positions (left lateral decubitus position versus supine decubitus position) at each site.

Fig. 3 RVOT1 measured in the parasternal long-axis view from the 2D-image according to site a [9, 15]
Comparing the diameters of RVOT1 at “a” and “b” measured with 2D and M-mode, respectively, also shows an overall significant difference ($p = 0.001$) with the highest mean at site “b” ($31.4 \pm 5.8$ mm vs. short-axis $29.5 \pm 5.6$ mm and site “a” $27.4 \pm 4.6$ mm) (Fig. 7). There was also an overall significant difference ($p = 0.013$) between RVOT1 measured using 2D at the three different sites and the body positions.

The two-way interaction between the sites and the body positions was also shown to be statistically significant ($p = 0.042$) (Table 3). Pair wise comparisons using post hoc test (Bonferroni correction) of ANOVA between the three different sites also showed significant differences: “a” versus “b” $p < 0.001$; “a” versus “short-axis” $p = 0.009$; “b” versus “short-axis” $p < 0.001$.

Using paired sampled $t$ test comparing RVOT1 at the three different sites and the two body positions there was found to be no significant difference in RVOT1 measured from the parasternal long-axis view from 2D-image according to site “b” in the left lateral decubitus position versus the supine decubitus position ($p = 0.28$). Nor was it found to be any significant difference between RVOT1 measured from the parasternal long-axis view with M-mode according to site “b” in the left lateral decubitus position versus the supine decubitus position ($p = 0.27$).

RVOT1 measured from the parasternal short-axis view from the 2D-image did not show any significant difference in the left lateral decubitus position versus the supine decubitus position either ($p = 0.43$). There was, however, a significant difference between the left lateral decubitus position and the supine decubitus position in RVOT1 measured from the parasternal long-axis view from the 2D-image according to site “a” ($p = 0.01$) and from the parasternal long-axis view with M-mode according to site “a” ($p = 0.01$). The intra- and interindividual reproducibility using the intraclass correlation coefficient is presented in Table 4.

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**Fig. 4** RVOT1 measured from the parasternal long-axis view in the M-mode image according to site a [12, 13]

**Fig. 5** RVOT1 measured from the parasternal short-axis view from the 2D-image [10]
Fig. 6 RVOT1, in mm, measured at site “a” and “b” in the parasternal long-axis view, from 2D-images and when using M-mode, and from the two different body positions (left lateral decubitus position and supine decubitus position)

Table 2 ANOVA for repeated measurements of RVOT1 at two different sites, “a” and “b”, measured with different methods, 2D and M-mode, in different body positions

1. Main effects
   - Site (“a”/”b”)
   - Method (2D/M-mode)
   - Body position (left/supine)
   - p < 0.001
   - p < 0.001
   - p = 0.001

2. Two-way interaction
   - Site/method
   - Site/position
   - Method/position
   - p < 0.001
   - p = 0.022
   - p = 0.290

3. Three-way interaction
   - Site/method/position
   - p = 0.270

Discussion

In the present study, a significant difference between RVOT1 has been shown when it is measured at the different proposed sites and also considering sites “a” and “b” there is a significant difference between when RVOT1 is measured using M-mode or from 2D-images. An overall significant difference between RVOT1 at the different sites and the body positions has also been shown.

How should then RVOT1 be measured? First of all it seems obvious that one should use the same site, method and body position when a single patient/subject is followed over time. However, due to the low interindividual reproducibility, especially using M-mode, and also rather low intra-individual reproducibility (Table 4), site “a” should be avoided.

The cause of the lower reproducibility at this site compared to the other sites is probably due to the absence of a reference point to measure from. When measuring at site “b” the aortic root can be used as a reference point giving higher inter- and intraindividual reproducibility. Also when measuring in short-axis it is easier to find a reference point at the aortic root level than when measuring according to site “a”. When RVOT1 is measured using M-mode according to site “a” it is also a risk that the M-mode line cuts the RV more apical than at the RVOT1 region.

The subjects RV are configured differently, some are more round in their shape while others are long. This could contribute to the significant differences between methods and body positions when using site “a” since it can make it difficult to examine the RV with a good image quality. It may, as was noted in some of the subjects, be difficult to determine the septal wall contour, especially in the M-mode image but also in the 2D image, due to that the chordae tendineae and papillary muscles sometimes disturb the determination of the septal wall border, and therefore making it difficult to assess the borders of the RV lumen.

When measuring at the different sites, thus preferably site “b” and short-axis, one should use the same method, M-mode or 2D, at different occasions if one should be able to compare if the diameter of RVOT1 has changed over time in the same patient or subject.

When it comes to the body position, this also preferably should be the same between different occasions of investigations. However, sometimes there are reasons to why the patient not can be in the same position as at the last examination, for instance unconscious patients at the intensive care unit that not can be laid in the left lateral decubitus position. In such cases, one should use site “b” or short-axis, since the present study have not shown...
significant difference in RVOT1 measured at those sites at different body positions. Site “a” should be avoided since there was found to be a significant difference at this site between RVOT1 measured in supine versus left lateral decubitus position.

The size of RVOT1 was significantly measured higher from site “a” with the subjects in the left lateral decubitus position compared when subjects were in the supine decubitus position (both 2D and M-mode indicated this). If this difference was not due to the measuring technique, one could wonder if there is a difference in the RV volume depending on body position. This would, however, also have affected RVOT1 measured from site “b” and from short-axis, why this theory seems less probable.

This study was performed on healthy subjects, aged 21–35 years, with generally good quality of image and examination technique. It would be of interest to perform a similar study on patients, in which the quality of images and examination technique are not always optimal.

Reproducibility study

There was a good intraindividual reproducibility for most of the investigated parameters except when measuring RVOT1 at site “a” with M-mode, which was somewhat lower. Even the interindivdual reproducibility was good for most of the measured parameters. However, in some cases lower intraindividual reproducibility was probably because investigator B was not an experienced echocardiographer as investigator A.

The lowest interindividual reproducibility was found for measuring RVOT1 at site “a” with M-mode, which to some extent may be due to investigator B not being an experienced echocardiographer as investigator A. Also probably due to the absence of reference point when measuring at site “a” compared to measuring at site “b” and at short-axis as has been mentioned earlier.

Conclusions

The RV has a complex anatomy and therefore it is often difficult to measure its size. A parameter that many times has been used to measure its size, probably due to that it has been found to have good reproducibility, is RVOT1. However, as has been shown in the present study, the diameters of RVOT1 are different at different sites, when using different methods and in different body positions. When comparing RVOT1 over time in the same patient or subject the results from the present study therefore indicate that the same site, method and body position should be used. Due to the lower reproducibility at site “a” than at site “b” and short-axis, probably due to the absence of reference point when measuring at site “a”, the two latter sites should be preferred before site “a” when measuring RVOT1.

Limitations of the study

It would have been of interest to compare the obtained values of RVOT1 in the present study with measurements of the same parameters with 3D echocardiography and to compare the obtained values with a reference method such as real-time 3D echo or magnetic resonance imaging to establish which of the measurements is the best estimate for true RV size. However, there was no equipment
available to do 3D echocardiography at our laboratory when the study was performed and a magnetic resonance imaging study in close connection to the echocardiographic examination could not be arranged.

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References

STUDY II
Isovolumetric relaxation time of the right ventricle assessed by tissue Doppler imaging

K. Emilsson and K. Loiske

Objectives—The isovolumetric relaxation time of the right ventricle (RV-IVRT) can be assessed using a method based on ECG and pulsed wave Doppler (PW). Recently pulsed wave Doppler tissue imaging (PW-DTI) has been introduced in the assessment.

Design—RV-IVRT obtained by the two methods was compared in 20 consecutive patients as was the time from the R wave on the ECG to the onset of tricuspid flow (R-T), to the closure of the pulmonic valve (R-P), to the onset of early diastolic motion of the tricuspid annulus tissue (R-E) and to the end of the systolic motion (R-S).

Results—RV-IVRT obtained by the PW method was significantly (p < 0.001) shorter than RV-IVRT obtained by PW-DTI. R-S had significantly (p < 0.001) shorter duration than R-P, while there was no significant difference between R-E and R-T.

Conclusions—The methods are not measuring the same interval. Only the PW method measures RV-IVRT according to the usual definition. Different reference values have to be used if the methods are used in the assessment of RV diastolic function.

INTRODUCTION

Left ventricular relaxation time (LV-IVRT), defined as the time from aortic valve closure to the start of mitral flow (1), is used in the assessment of LV diastolic function and is relatively easy to measure by echocardiography from an apical transducer position using the pulsed wave (PW) or continuous wave (CW) Doppler technique as described by Appleton et al. (1) or with ECG and PW Doppler as described by Larrazet et al. (2).

The right ventricular isovolumetric relaxation time (RV-IVRT), that is the interval from pulmonic valve closure to the start of tricuspid valve opening (3), may in the same way as the LV-IVRT is used as an index of LV diastolic function, be used as an index of RV diastolic function (4). RV-IVRT has been shown to have a shorter duration than LV-IVRT (2).

The RV-IVRT is more difficult to obtain than LV-IVRT since there is no good echocardiographic view from which both the pulmonic valve and the tricuspid inflow can be measured simultaneously. However, even in this case the method described by Larrazet et al. (2) can be used.

During recent years some authors, for instance Severino et al. (5), Caso et al. (6) and Özdemir et al. (7), have used pulsed wave Doppler tissue imaging (PW-DTI) when measuring RV-IVRT, from now on called RV-IVRT(PW-DTI). However, it has not been sufficiently investigated in patients whether the duration of the interval measured with PW-DTI is the same as the duration of the interval measured with the method based on ECG and PW Doppler. The aim of the present study was therefore to compare RV-IVRT and RV-IVRT(PW-DTI) and to try to explain an eventual difference.

PATIENTS AND METHODS

Patients

Twenty consecutive patients referred to echocardiography were included. Since earlier studies have shown prolonged RV-IVRT in patients with hypertrophic cardiomyopathy (8), patients with LV wall thickness >14 mm were not included as were not patients with atrial fibrillation, left and right bundle branch block, pacemaker treatment or a history of cardiac surgery since the effect on RV-IVRT has not been sufficiently investigated in those cases.

The investigations on the patients were approved by the local ethical committee and informed consent was obtained from each patient.

Some basic characteristics and measurements are shown in Tables I and II.

METHODS

Echocardiographic examination

Acuson Aspen or Sequoia echocardiographs equipped with PW-DTI technology and variable frequency phased-array transducers (4V2c and 3V2c, respectively) (Siemens-Acuson Co., Mountainview, CA, USA) were used for the echocardiographic examinations. The patients were studied in the lateral recumbent position. Echocardiographic techniques and calculations of different cardiac dimensions were performed in accordance with the recommendations of the American Society of
Echocardiography Committee (9–11). As a measure of RV systolic function (12) the amplitude of tricuspid annulus motion (TAM) was measured from the RV atrioventricular plane at the basal lateral site in the apical four-chamber view (13) from M-mode recordings. The size of the RV was measured in the apical four-chamber view one-third from the base of the RV (RVIT3) (13).

Both the PW Doppler and PW-DTI examinations were performed at a transducer frequency of 2 MHz and the PW gate was set at 3 mm. For optimal definition of the onset and of the end of the Doppler recordings, filter 1 (about 100 Hz) was used, which, according to the user manuals of the echocardiographs, allows the display of all velocities. The minimal optimal gain setting was used. A Doppler velocity range of −20 to 20 cm/s was used during the PW-DTI measurements. The examinations were recorded on magneto-optical disks and high-fidelity paper strips (velocity 50 mm/s). All measurements were made on screen during the examinations.

RV-IVRT was measured as described by Larrazet et al. (2) (Figs 1 and 2): the time from the R wave on the ECG to the end of the pulmonic flow (R-P) was measured from the parasternal short-axis view at the level of the aortic orifice for pulmonic flow velocity recording. The apical four-chamber view was used for measuring the time from the R wave on the ECG to the onset of tricuspid flow (R-T). The 3-mm sample volume was located at the central part of the tricuspid annulus at the tips of the tricuspid leaflets. RV-IVRT was calculated as [(R-T) − (R-P)]

RV-IVRT(PW-DTI), that is RV-IVRT obtained by PW-DTI, was measured as has been described by for instance Caso et al. (6) (Fig. 3): the apical view was chosen to obtain quantitative assessment of regional myocardial wall motion almost simultaneously with Doppler RV inflow and to minimize the angle between the Doppler beam and the RV longitudinal motion. The 3-mm sample volume was placed at the basal lateral corner of the tricuspid annulus. The different components of the PW-DTI pattern are shown in Fig. 3. S being the myocardial systolic wave, E the early diastolic wave and A the atrial wave. RV-IVRT(PW-DTI) was measured as the duration in milliseconds (ms) between the end of the systolic wave and the onset of the early diastolic wave. The time from the R wave on the ECG to the end of the S wave (R-S) was also measured. The time from the R wave on the ECG to the onset of the early diastolic wave (R-E) was calculated as [(R-S)+(RV-IVRT(PW-DTI))].

Although Larrazet et al. (2) did not find any correlation between RV-IVRT and heart rate the measurements with the two methods were done at almost the same heart rate (R-R) interval for each patient.
The main aim of the present study was to compare two different methods to calculate the IVRT of the RV, one method based on ECG and PW Doppler (2), RV-IVRT, and the other based on PW-DTI (5–7), RV-IVRT (PWDTI). A significant difference was found between IVRT obtained by both methods, RV-IVRT being shorter than RV-IVRT(PWDTI).

**DISCUSSION**

**Theoretical implications**

The main aim of the present study was to compare two different methods to calculate the IVRT of the RV, one method based on ECG and PW Doppler (2), RV-IVRT, and the other based on PW-DTI (5–7), RV-IVRT (PWDTI). A significant difference was found between IVRT obtained by both methods, RV-IVRT being shorter than RV-IVRT(PWDTI).
IVRT of the RV is usually defined as the time from the closure of the pulmonic valve to the tricuspid valve opening (3) that is, to the onset of tricuspid flow. The time to the closure of the pulmonic valve (R-P) was in the present study found to be significantly longer than the time to the end of the S wave, meaning that the method using PW-DTI doesn’t measure the time from the closure of the pulmonic valve.

The time to the onset of tricuspid flow (R-T) was somewhat, but not significantly, longer than the time to the onset of the early diastolic velocity (E) of the tricuspid annulus tissue (R-E).

From these findings it is obvious that PW-DTI is not measuring RV-IVRT according to the usual definition.

The found end of the tissue (myocardium) to move, that is the end of the S wave with PW-DTI, just before the closure of the pulmonic valve is not surprising: during systole the myocardium of the RV contracts causing the pressure in the RV to rise and when the pressure in the pulmonary artery is exceeded the pulmonic valve opens and blood can flow into the pulmonary artery. As the myocardium starts to relax the pressure in the RV falls and at the end of systole, that is, at the end of the S wave, when the pressure in the pulmonary artery exceeds that in the right ventricle (16) the pulmonic valve closes, which explains why R-P has a longer duration than R-S.

The somewhat, but not significantly, shorter duration from the R wave on the ECG to the onset of the early diastolic velocity (E) that is, to the onset of the tissue (myocardium) to move, than to the onset of tricuspid flow, may as has been suggested on the left side of the heart (17), be due to elastic recoil of the RV during diastole promoting the flow across the tricuspid orifice into the RV (18).

Reproducibility study

The findings concerning reproducibility of measuring RV-IVRT and RV-IVRT(PWDTI), which has been presented under “Results”, indicate good intra- and interobserver reproducibility of the measurements.

Practical implications

As both methods in the present study have been shown to not measure the same interval it seems obvious that different reference values have to be used when using the method based on PW-DTI than when using the method based on ECG and PW Doppler in the assessment of RV diastolic function.

CONCLUSIONS

PW-DTI measures the interval from the end of the systolic wave, that is, the end of the systolic motion of the tissue at the tricuspid annulus, to the onset of the early diastolic wave, that is, to the onset of the diastolic motion of the tissue at the tricuspid annulus. This interval is different from the interval measured with the method based on PW Doppler and ECG, which measures the time from the closure of the pulmonic wave to the onset of tricuspid flow, that is, the interval that usually is the definition of RV-IVRT. This means that different reference values have to be used when using the method based on PW-DTI than when using the method based on ECG and PW Doppler in the assessment of RV diastolic function.

REFERENCES


STUDY III
Comparison between maximal early diastolic velocity in long-axis direction obtained by M-mode echocardiography and by tissue Doppler in the assessment of right ventricular diastolic function

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Summary

Recently the maximal early diastolic velocity in long-axis direction of the right ventricle (RV) obtained by tissue Doppler imaging (MDV TDI) has been introduced in the assessment of RV diastolic function (RVDF). There are reasons to think that also the maximal early diastolic velocity in long-axis direction of the RV obtained using M-mode echocardiography (MDV TAM) could be used to assess RVDF. Therefore, 29 patients were examined with echocardiography and MDV TAM and MDV TDI were measured and compared. A good correlation ($r = 0.76$, $P < 0.001$) was found between MDV TAM and MDV TDI indicating that MDV TAM might be used in the assessment of RVDF. However, the velocities obtained by MDV TDI ($126.7 \pm 38.9$ mm $s^{-1}$) were significantly ($P < 0.001$) higher than the velocities obtained by MDV TAM ($78.3 \pm 27.8$ mm $s^{-1}$) and the agreement between MDV TAM and MDV TDI was rather poor probably mainly due to differences in the measuring technique. This means that reference values cannot be used interchangeably between MDV TAM and MDV TDI. If MDV TAM is going to be used in the assessment of RVDF new reference values have to be produced if today’s technique and recommendations to measure MDV TAM and MDV TDI are used. However, as most new echocardiographs are equipped with PW-TDI technology it seems preferable to use this technique and compare obtained values with already established reference values.

Introduction

During recent years recording of the maximal early diastolic relaxation velocity in the left ventricular (LV) long-axis direction obtained by echocardiographic M-mode (MDV MAM) (Bojo et al., 1998, 2000; Nilsson et al., 2002; Formander et al., 2004) or tissue Doppler imaging (TDI) (Garcia et al., 1996; Nagueh et al., 1997; Sohn et al., 1997) have been used in the assessment of LV diastolic function.

At the right side of the heart the maximal early diastolic relaxation velocity in the right ventricular (RV) long-axis direction obtained by tissue Doppler imaging (MDV TDI) has been found to be significantly lower in older healthy subjects than in younger subjects (Alam et al., 1999; Nikitin et al., 2003) and MDV TDI has been found to have a rather good correlation with other diastolic parameters of the RV such as tricuspid E wave and tricuspid E/A-waves ratio (Alam et al., 1999).

The decrease in MDV TDI with age is in accordance with the findings on the left side of the heart (Alam et al., 1999) and has been suggested to be due to deterioration in the diastolic properties of the myocardium of the ventricles with age (Nikitin et al., 2003).

In the same way as MDV MAM has been used in the assessment of LV diastolic function, Emilsson (2004a) has suggested the maximal early diastolic relaxation velocity in the long-axis direction of the RV obtained by M-mode echocardiography (MDV TAM) to be an index of RV diastolic function (RVDF).

In the present study the main aim was to compare MDV TAM with MDV TDI. As both indices are measuring the maximal early diastolic relaxation velocity in the RV long-axis direction there are reasons to think that there should be a good correlation and also a good agreement between them but is the agreement good and if not, why is it poor?
If the correlation between MDV TAM and MDV TDI is good MDV TAM might be used in the assessment of RVDF in the same way as MDV TDI.

Methods

Patients

Twenty-nine consecutive patients (18 women, 11 men) referred to echocardiography at the Department of Clinical Physiology at Karlskoga Hospital were included in the study.

Patients with atrial fibrillation, bundle branch block, pacemaker-treatment or an history of cardiac surgery were not included. The investigations on the patients were approved by the local ethical committee and informed consent was obtained from each patient.

Some basic characteristics and measurements are shown in Tables 1 and 2.

Echocardiographic examination

Acuson Aspen echocardiographs equipped with pulsed wave (PW) TDI technology and variable frequency phased-array transducers (4V2c) (Siemens-Acuson Co., Mountain View, CA, USA) were used for the echocardiographic examinations. The patients were studied in the left lateral recumbent position. Echocardiographic techniques and calculations of different cardiac dimensions were performed in accordance with the recommendations of The American Society of Echocardiography Committee (Sahn et al., 1978; Henry et al., 1980; Schiller et al., 1989). As a measure of RV systolic function (Kaul et al., 1984) the amplitude of tricuspid annulus motion (TAM) was measured from the RV atrioventricular plane at the basal lateral site in the apical four-chamber view from M-mode recordings (Feigenbaum, 1994). The size of the RV was measured in the apical four-chamber view one-third from the base of the RV (RVIT3) (Feigenbaum, 1994).

The PW TDI examinations were performed at a transducer frequency of 2 MHz and the PW gate was set at 3 mm. The minimal optimal gain setting was used. A Doppler velocity range of ~20 to 20 cm s⁻¹ was used during the PW TDI measurements. The examinations were recorded on magneto-optical discs and printed on high-fidelity paper strips (velocity 50 mm s⁻¹). All measurements were made on screen during the examinations at the end of expiration.

MDV TAM was measured during the end of expiration from the basal lateral corner of the RV in the apical four-chamber view. The steepest portion of the M-mode curve in early diastole was identified and measured on screen during the examination. The inclination of the dotted line represents MDV TAM (mm s⁻¹) (Fig. 1).

When measuring MDV TDI the apical four-chamber view was chosen to minimize the angle between the Doppler beam and the RV longitudinal motion. The 3 mm sample volume was placed at the basal lateral corner of the tricuspid annulus. The different components of the PW TDI pattern are shown in Fig. 2, 8 being the myocardial systolic wave, E the early diastolic wave and A the atrial wave. MDV TDI was measured from the outer edge of the dense part of the spectral curve in accordance with the recommendations of the American Society of Echocardiography Committee (Quinones et al., 2002). All patients were in sinus rhythm. The modified biplane Simpson’s rule was used for calculation of LV ejection fraction.

Reproducibility of the measurements

The intra- and interobserver reproducibility (reproducibility study) was examined in 11 consecutive patients, four women, seven men (mean age 55 ± 16 years). Investigator A (Karin Loiske) first measured MDVTAM and MDVTDI on screen during the examination and thereafter investigator B (Birgitta Ohlin) (blinded from the measurements of investigator A) measured the same parameters in the same way. Investigator A then again performed the same procedure.

Statistics

The Pearson’s correlation coefficient was used for analyses of linear correlation between different variables. The two-tailed
significant. The different components of the PW TDI pattern are: S being the myocardial systolic wave, E the early diastolic wave measured at the end of expiration using the echocardiographic apical four-chamber view with the 3 mm sample volume placed at the basal lateral corner of the tricuspid annulus. The maximal early diastolic velocity in long-axis direction of the right ventricle obtained by tissue Doppler imaging (MDV TDI) was measured from the basal lateral corner of the RV in the apical four-chamber view. The steepest portion of the M-mode curve in early diastole was identified and measured on screen during the examination at the end of expiration. The inclination of the dotted line represents MDV TAM (mm s⁻¹).

Figure 1. The maximal early diastolic velocity in the long-axis direction of the right ventricle (RV) obtained by M-mode echocardiography (MDV TAM) was measured at the basal lateral corner of the RV in the apical four-chamber view. The steepest portion of the M-mode curve in early diastole was identified and measured on screen during the examination at the end of expiration. The inclination of the dotted line represents MDV TAM (mm s⁻¹).

Figure 2. The maximal early diastolic velocity in long-axis direction of the right ventricle obtained by tissue Doppler imaging (MDV TDI) was measured at the end of expiration using the echocardiographic apical four-chamber view with the 3 mm sample volume placed at the basal lateral corner of the tricuspid annulus. The different components of the PW TDI pattern are: S being the myocardial systolic wave, E the early diastolic wave and A the atrial wave. MDV TDI was measured from the outer edge of the dense part of the early diastolic wave (horizontal white line).

t-test was used to determine whether correlations were statistically significant.

The paired samples t-test was used to compare the difference between MDV TAM and MDV TDI.

The Bland–Altman method (Bland & Altman, 1986) was used for a graphical assessment of agreement between MDV TAM and MDV TDI, respectively.
In the intra- and interobserver reproducibility study an estimate of agreement was obtained using Pearson’s intraclass correlation coefficient, \( r \) (Dunn, 1989). The coefficient has a range \(-1.0 \) to \(+1.0\) with high positive values indicating high agreement, negative values indicating disagreement.

A difference at the 5% level was regarded as significant. Data were analysed using the SPSS 12.0.1 statistical software (SPSS, Chicago, IL, USA).

Results

There was a good correlation \( (r = 0.76; \ P < 0.001) \) between MDV TAM and MDV TDI (Fig. 3).

The agreement between MDV TDI and MDV TAM is shown in Fig. 4.

MDV TDI \( (126.7 \pm 38.9 \text{ mm s}^{-1}) \) was significantly \( (P<0.001) \) higher than MDV TAM \( (78.3 \pm 27.8 \text{ mm s}^{-1}) \).

The intra- and interobserver reproducibility was measured using Pearson’s intraclass correlation coefficient and the results are presented in Table 3.

Discussion

As has been shown there was a good correlation between MDV TAM and MDV TDI (Fig. 3) indicating that MDV TAM in the same way as MDV TDI (Alam et al., 1999; Kukulski et al., 2000a; Nikitin et al., 2003) might be used in the assessment of RVDF.

However, the agreement was rather poor (Fig. 4), the maximal early diastolic velocities obtained by TDI being about 60% higher than MDV TAM. This finding is somewhat surprising as both MDV TAM and MDV TDI are measuring the maximal early diastolic relaxation velocity in the long-axis direction of the RV.

One reason to the difference between the maximal early diastolic velocities could be that the TDI technique reports instantaneous velocities, whereas the M-mode procedure implies some degree of averaging around the maximal value as a finite-length segment in the maximal slope tract must be chosen for practical reasons.

Another reason to the difference could have been that MDV TAM is measured endocardially whilst MDV TDI is measured in the myocardium more epicardially. However, as the spatial resolution when using MDV TDI is poor (Rambaldi et al., 1997) the placement of the sample volume is therefore of minor importance. In addition, a recent study (Emilsson et al., 2004b) has showed no significant differences between the diastolic velocities of TAM measured endocardially and the diastolic velocities at two sites of the right coronary artery, which is situated epicardially.

In a study by Fornander et al. (2004) it was discussed if the difference between the maximal diastolic velocities of the left ventricle measured by M-mode echocardiography and tissue Doppler imaging could be due to the point of the spectral curve from which the MDV TDI is measured: in accordance with recent guidelines (Quinones et al., 2002) it was measured by Fornander et al. (2004) as well as in the present
study from the outer edge of the dense part of the spectral curve. As the cells in the myocardium move together and not separately from each other (in contrast to blood velocity measurements) there is seldom a scatter of velocities and the spectral curve is often very easy to define so it seems obvious that this not explains the found difference.

A phantom study has shown overestimation of velocities by PW Doppler (Kukulski et al., 2000b).

**Reproducibility study**

The findings concerning reproducibility of measuring MDV TAM and MDV TDI, which has been presented under Results, indicate good intraobserver reproducibility of measuring both parameters and also good interobserver reproducibility of measuring MDV TAM. The interobserver reproducibility of measuring MDV TAM was somewhat poorer, probably mainly due to the MDV TAM was somewhat poorer, probably mainly due to that investigator B was not so experienced of measuring MDV TAM as was investigator A. When measuring MDV TAM it is important to do the measurements during the end of expiration and to search for the steepest portion of the M-mode curve in early diastole.

**Conclusions**

In the present study it has been shown that MDV TAM has a good correlation with MDV TDI and might as MDV TDI be used in the assessment of RVDF. However, the agreement between MDV TAM and MDV TDI was found to be rather poor probably mainly due to differences in the technique to measure the two indices.

This means that reference values cannot be used interchangeably between MDV TAM and MDV TDI.

If MDV TAM is going to be used in the assessment of RVDF, new reference values have to be produced if today’s technique and recommendations to measure MDV TAM and MDV TDI are used. However, as most new echocardiographs are equipped with PW TDI technology it seems preferable to use this technique and compare the obtained values with already established reference values (Alam et al., 1999).

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Left and right ventricular systolic long-axis function and diastolic function in patients with takotsubo cardiomyopathy

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Short title: Takotsubo cardiomyopathy and long-axis function

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**Summary**

*Aims:* Takotsubo cardiomyopathy is characterized by apical wall motion abnormalities without coronary stenosis. Limited information is available on the genesis of the underlying reversible contractile disorder.

Our objective in this prospective study was to investigate biventricular changes in systolic long-axis function and diastolic parameters in the acute phase and after recovery.

*Methods and results:* Thirteen consecutive patients were examined by echocardiography and coronary angiography at admission and again by echocardiography after three months. Amplitudes, systolic and diastolic velocities of the mitral and tricuspid annuli and conventional diastolic parameters were measured.

Systolic long-axis shortening of the left ventricle (LV) and right ventricle (RV) improved from 9.6±2.2 mm to 11.2±1.9 mm (p=0.02) and from 21.3±3.6 mm to 24.1±2.8 mm (p=0.02) respectively.

LV systolic, early and late diastolic velocities measured by pulsed wave tissue Doppler also improved while additional conventional diastolic parameters of the LV and RV diastolic function were unchanged.

*Conclusions:* Takotsubo cardiomyopathy temporarily affects systolic LV and RV function while most diastolic parameters remain unchanged.

**Key words:** Heart, Echocardiography, Annulus motion, Atrioventricular displacement, Doppler
Introduction
Takotsubo cardiomyopathy is a clinical syndrome characterized by acute reversible apical ventricular dysfunction. Patients typically complain of chest pain and experience of acute emotional stress in the days preceding their illness is common. The ECG is often abnormal showing ST segment changes or Q-waves, cardiac enzymes and troponins are elevated mimicking acute myocardial infarction and patients have no angiographic stenosis corresponding to the contractile dysfunction (Tsuchihashi et al., 2001). The main hypotheses regarding the cause of takotsubo cardiomyopathy are catecholamine cardiotoxicity and neurogenic stunned myocardium but the underlying pathophysiology remains unclear (Bielecka-Dabrowa et al., 2010).

To our knowledge, mitral annulus motion (MAM), has only been investigated in one previous study on takotsubo cardiomyopathy (Meimoun et al., 2009) and tricuspid annulus motion (TAM) has not been studied previously.

Our objective in this study was to investigate biventricular changes in systolic long-axis and diastolic function between the acute and the recovery phase in takotsubo cardiomyopathy.

Patients and methods
Patients
In this prospective study all consecutive patients between January 2008 and March 2010 admitted to acute coronary angiography in the department of Cardiology, Örebro University Hospital, suspected of having ST-elevation myocardial infarction were screened for takotsubo cardiomyopathy if no angiographically significant stenosis was seen in the coronary angiogram.

We defined takotsubo cardiomyopathy as chest pain discomfort, ECG changes (ST elevation, ST depression, negative T waves or Q waves), no significant angiographic stenosis (≥ 50%, visual estimate) on coronary angiogram and apical dysfunction on contrast left ventriculogram in 30 degrees right anterior oblique view. In the screening period, 16 patients fulfilled inclusion criteria and 13 patients (all women) with a mean age of 68.1±10.4 years were willing to participate in the study.

Echocardiography was performed within 24 hours after admission (acute phase) and repeated after about three months (recovery phase).

The study was approved by the regional ethical committee and all patients gave written informed consent to participate.
Echocardiographic examination
A Vivid 7 ultrasound machine (GE Vingmed Ultrasound A/S, Horten, Norway) equipped with a multi-frequency phased array transducer (M3S, 1.5-4.0 MHz) was used for the echocardiographic examinations and measurements were made after the examination using stored images on an EchoPac workstation (GE Vingmed). The subjects were examined in the left lateral recumbent position. Echocardiographic techniques and calculations of different cardiac dimensions were performed in accordance with the recommendations of The American Society of Echocardiography (Sahn et al., 1978; Henry et al., 1980; Schiller et al., 1989). The size of the RV was measured as right ventricular inflow tract 3 (RVIT3), which is measured in the apical four chamber view one third from the base of the RV (Lang et al., 2005) and as right ventricular outflow tract 1 (RVOT1) as described by Foale et al., (1986) from the parasternal long-axis view.

The amplitudes and velocities at the mitral annulus were measured using M-mode, pulsed wave tissue Doppler imaging (PW-DTI) and 2D color DTI (two-dimensional color Doppler tissue Imaging) from four sites about 90° apart. Recordings from the septal and lateral part of the mitral annulus were obtained from the apical four-chamber view and recordings from the inferior and anterior parts from the apical two-chamber view. Average amplitudes and velocities were calculated as the average of the values at the four sites.

The amplitudes and velocities at the tricuspid annulus were measured at the basal lateral part of the RV in the apical four-chamber view. Because the measured velocities of the tissues depend on the angle between the Doppler beam and the measured tissue, the angle to the beam was kept as small as possible.

M-mode measurements of the amplitudes of MAM were performed as described by Höglund et al., (1988) and the M-mode measurements of the amplitude of TAM as described by Feigenbaum, (2010a). The measurements of velocities using 2D color DTI from all the above mentioned sites were done from the peak point of the systolic curve and from the lowest point of the early diastolic and late diastolic curves, respectively, in accordance with Nikitin et al., (2003). When measuring the peak systolic velocities the initial peak that is observed during isometric ventricular contraction was ignored.

PW-DTI measurements of both the mitral and tricuspid annuli were done as described by Alam et al., (1999).

The maximal relaxation velocity of the mitral annulus was measured as the steepest part of the curve in early diastole (Nilsson et al, 2002) at the
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The maximal relaxation velocity of the mitral annulus was measured as the steepest part of the curve in early diastole (Nilsson et al., 2002) at the lateral site. The maximal relaxation velocity of the tricuspid annulus was measured in the same way (Emilsson, 2004).

PW-Doppler mitral and tricuspid diastolic flow velocities were recorded from the apical 4-chamber view by placing the sample volume between the leaflet tips in the center of the flow stream. The transmitral and transtricuspid peak rapid filling velocity (E), peak atrial filling velocity (A), E-wave deceleration time, and E/A ratio were measured.

The LV isovolumetric relaxation time (IVRT) using PW-Doppler was recorded from the apical 4-chamber view by simultaneous recording of the aortic and mitral flows. The IVRT of the RV by PW-Doppler was measured as described by Larrazet et al., (1997): the time from the R wave on ECG to the end of the pulmonic flow (R-P) was measured from the parasternal short-axis view at the level of the aortic orifice for pulmonic flow velocity recording. The apical four-chamber view was used for measuring the time from the R wave on ECG to the onset of tricuspid flow (R-T). The sample volume was located at the central part of the tricuspid annulus at the tips of the tricuspid leaflets. IVRT was calculated as [(R-T) - (R-P)]. Although Larrazet et al. did not find any correlation between IVRT and heart rate the measurements were done at almost the same heart rate (R-R-interval) for each patient.

The IVRT at the both annuli was also measured using PW-DTI as described by Caso et al., (2001) and by using 2D color DTI as described by Lind et al., (2004). LV ejection fraction (LVEF) was measured using the biplane Simpson’s method (Feigenbaum, 2010b).

The length of the LV was measured in end-diastole from the epicardial apex to the septal and lateral site of the mitral annulus.

The length of the RV was measured in end-diastole from the epicardial apex to the septal and lateral site of the tricuspid annulus.

All measurements were done at the end of expiration.

The average of three beats was calculated for each cardiac measurement.

Statistics

As some of the parameters were found not to be normally distributed Wilcoxon signed-rank test was used to test differences between acute and recovery phase parameters.

p<0.05 was considered statistically significant.

Data were analyzed using SPSS version 17 statistical software (SPSS Inc., Chicago, IL, USA).
Results
Baseline patient characteristics are shown in Table 1. No patient had a history of cardiac disease except for one who previously suffered from arrhythmia and had received a pacemaker.

The average time between the echocardiographic examination at the acute and recovery phase was 12.9±1.0 weeks (range 12-15 weeks).

Left ventricle
There was a significant difference between the amplitudes of MAM (the total of the four sites) between the acute (9.6±2.2 mm) and recovery phase (11.2±1.9 mm) (p=0.02) (Table 2). Regarding the different sites of measuring MAM there was a significant difference between the different sites (Table 2) except for the septal site.

There was a significant difference (p<0.01) between LVEF obtained by the biplane Simpson’s method in the acute (53.4±9.5%) compared with the recovery phase (63.3±4.4%).

There was no significant difference in length of the LV in end-diastole from the epicardial apex to the septal or lateral sites of the mitral annulus between the acute and the recovery phase.

There was also no significant difference in end-diastolic diameter, not even at the widest part of the LV, or end-systolic diameter between the two phases.

The area of the left atrium was significantly smaller (p=0.01) in the recovery phase (16.2±3.7 cm²) than in the acute phase (18.1±3.6 cm²).

Both the early and late diastolic velocities as well as the systolic velocity measured by PW-DTI increased significantly from the acute to the recovery phase but there was no significant differences when they were measured using 2D color DTI. The systolic, early and late diastolic velocities were all significantly higher when measured at the acute and recovery phase using PW-DTI than when using 2D color DTI. There was no statistically significant difference between the other measured diastolic parameters (Table 2).

Right ventricle
There was a statistically significant difference (p=0.02) between the total amplitude of TAM in the acute (21.3±3.6 mm) and the recovery phase (24.1±2.8 mm) but no significant differences were found between the size or the length of the RV or the diastolic parameters of the RV between the two phases (Table 3).
Discussion
The main findings of the present study of consecutive patients with takotsubo cardiomyopathy are that the systolic long axis shortening of both the LV and RV as well as the LV systolic, early and late diastolic velocities measured by PW-DTI improved from the acute to the recovery phase while conventional diastolic parameters of the LV and the diastolic parameters of the RV and the length of the ventricles remained unchanged between the two phases.

Left ventricle
Systolic function
The improvement in LV systolic long axis shortening is in line with the improvement of LVEF obtained by the biplane Simpson’s method.

Our findings of lower amplitudes of MAM in the acute phase indicate that the longitudinal fibers are affected in takotsubo. These fibers are mostly located subendocardially and this part of the myocardium has the highest risk of ischaemia (Greenbaum et al., 1981; Henein et al., 1993). One might therefore think that atherosclerotic coronary disease-mediated myocardial ischemia could be a cause to the decrease in systolic long-axis shortening. However, that theory is not supported by findings during for instance magnetic resonance imaging studies, since there is no evidence of focal perfusion abnormalities corresponding to a specific coronary vessel territory (Gerbaud et al., 2008).

One conjecture of the pathogenesis of takotsubo is rising catecholamine levels causing epicardial coronary arterial spasm, but multivessel epicardial spasm seems unlikely (Wittstein et al., 2005).

Another theory is catecholamine mediated myocardial stunning caused by direct myocyte injury. Elevated catecholamine levels decrease the viability of myocytes through cyclic AMP-mediated calcium overload (Mann et al., 1992). Interaction of the endocardial endothelium with circulating substances in the blood such as catecholamine may modify myocardial performance (Bielecka-Dabrowa et al., 2010).

The catecholamine hypothesis, which we think is the most plausible hypothesis and could explain our findings in the present study, is supported by findings of apical ballooning in some case reports with dobutamine stress-echocardiography (Margey et al., 2009), in reports of patients with phaeochromocytoma (Takizawa et al., 2007; Lassnig et al., 2009) and in patients with subarachnoid haemorrhage (Trio et al., 2010). In the latter case a catecholamine surge has been proposed as explanation to the cardiomyopathy.
The non-significant difference of the amplitude of MAM at the septal site between the two phases could perhaps be explained by fewer longitudinal fibers at septum than at the other anatomical locations. The septum is formed by subendocardial fibers from the RV and LV together with a middle layer composed of circumferential fibers in continuity with those from the corresponding layer of the LV free wall. Circumferential septal fibers are lacking towards the apex (Greenbaum et al., 1981).

Diastolic function
We found no significant change in any of the conventionally measured diastolic parameters between the acute and the recovery phase except for the early and late diastolic velocities measured by PW-DTI, both increasing from the acute to the recovery phase.

When using PW-DTI the velocities are measured at the basal parts of the LV as are the amplitudes of MAM. The increase in the systolic long-axis shortening may therefore also explain the increase in those parameters. However, the same velocities measured by 2D color DTI did not change significantly although these velocities are also measured at the basal parts of the LV. These velocities were significantly lower than the velocities obtained by PW-DTI. The lower velocities using 2D color DTI might be explained by autocorrelation methodology resulting in peak-mean velocity, while PW-DTI is computed with a fast Fourier transformation technique resulting in measured peak velocities (Hummel et al., 2010). Where the sample volume is placed in the myocardium at the basal part of the LV may also cause the differences as well as the transducer angulation.

Because of the increase in LVEF using the biplane Simpson’s method and in the total amplitude of MAM, we expected an increase in all the other conventional parameters of measuring diastolic function as well. One reason to the lack of increase could be that few patients had severely reduced LVEF and total amplitude of MAM during the acute phase. However, in a study by Meimoun (Meimoun et al., 2009) LVEF in the acute phase (43±7%) was lower than in the present study and recovery phase LVEF was higher (69±5%) and despite this, the authors found no significant changes in diastolic parameters.

We cannot exclude the possibility that statistical significance could have been reached in some of the diastolic measurements with a larger sample.

LV length
It could be expected that the apical ballooning often seen in takotsubo cardiomyopathy would contribute to a longer LV in the acute phase than
in the recovery phase, however, in the present study there was no significant difference in length in end-diastole from the epicardial apex to the septal and lateral sites of the LV. However, the transducer angulation might have influenced this result.

**Right ventricle**

**Systolic function**
There was also, as with the total amplitude of MAM, a significant difference between the acute and recovery phase concerning the total amplitude of TAM, that is, in the systolic shortening of the RV in long-axis direction measured at the lateral site. This means that also the RV is affected in takotsubo, something that has been shown in a few studies only (Elesber et al., 2006; Haghi et al., 2007). In the study by Elesber it was found that RV involvement, when present, follows a similar pattern of regional wall motion abnormalities, as does the LV in this syndrome and that RV involvement portends a longer and more critical hospitalization course as compared with patients with isolated LV involvement. The mechanisms explaining the involvement of RV in takotsubo are unclear and the involvement argues against LV outflow tract obstruction causing takotsubo (Haghi et al., 2007).

The improvement of systolic long axis shortening of the RV at the lateral site indicates that also the longitudinal fibers of the RV, are affected in this disease, probably most in the apical regions.

**RV diastolic function and length**
There was no significant change in RV diastolic parameters from the acute to the recovery phase, but trends in RV parameters might have been statistically significant with a larger sample. We have not been able to find previous accounts on RV diastolic function in takotsubo.

As with the LV there was no significant change in RV end-diastolic length between the two phases, but also in this case the transducer angulation might have influenced the result.
Conclusions
From the acute phase to the recovery phase in takotsubo cardiomyopathy we found not only a significant increase in LVEF obtained by the biplane Simpson’s method but also a significant increase in systolic long-axis shortening of both the LV and RV indicating that the longitudinal fibers are affected.

There was also an improvement in LV early and late diastolic velocities measured by PW-DTI while the other measured conventional diastolic parameters of the LV and the diastolic parameters of the RV as well as the length of the ventricles remained unchanged between the two phases.
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Table 1. Some basic characteristics of the patients and some measured and calculated variables at inclusion (n=13).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.1±10.4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.58±0.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.4±19.5</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>43.7±4.6</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (mm)</td>
<td>27.9±6.1</td>
</tr>
<tr>
<td>Septal wall (mm)</td>
<td>10.7±2.5</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>9.1±1.1</td>
</tr>
<tr>
<td>Right ventricular outflow tract 1 (mm)</td>
<td>27.0±4.2</td>
</tr>
<tr>
<td>Right ventricular inflow tract 3 (mm)</td>
<td>29.7±5.2</td>
</tr>
</tbody>
</table>

Table 2. Significance of difference between the acute and recovery phase of some left ventricular variables (EF=ejection fraction; MAM=amplitude of mitral annulus motion; PW=pulsed wave; PW DTI=pulsed wave Doppler tissue imaging; IVRT=isosvolumetric relaxation time; DT=deceleration time; S=systolic velocity; E=early diastolic velocity by PW; A=late diastolic velocity by PW; é=early diastolic velocity by PW-DTI; á=late diastolic velocity by PW-DTI; 2D color DTI=two-dimensional color Doppler tissue imaging; color coded é=early diastolic velocity by 2D color DTI; color coded á=late diastolic velocity by 2D color DTI) (n=13).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute phase</th>
<th>Recovery phase</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF obtained by biplane Simpson's method (%)</td>
<td>53.4±9.5</td>
<td>63.3±4.4</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>MAM at the septal site (mm)</td>
<td>9.4±2.1</td>
<td>10.1±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MAM at the lateral site (mm)</td>
<td>10.1±2.3</td>
<td>12.1±2.6</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>MAM at the inferior site (mm)</td>
<td>9.9±2.8</td>
<td>11.6±2.0</td>
<td>p=0.03</td>
</tr>
<tr>
<td>MAM at the anterior site (mm)</td>
<td>9.0±2.6</td>
<td>10.8±1.9</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Total MAM (all four sites, mm)</td>
<td>9.6±2.2</td>
<td>11.2±1.9</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2±0.7</td>
<td>0.9±0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>206.2±91.5</td>
<td>249.6±69.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW (ms)</td>
<td>91.5±19.3</td>
<td>90.6±17.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW-DTI (ms)*</td>
<td>89.4±20.0</td>
<td>87.1±23.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by 2D color DTI (ms)</td>
<td>65.2±17.9</td>
<td>66.3±16.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by PW-DTI (cm/s)</td>
<td>5.9±1.5</td>
<td>7.2±1.9</td>
<td>p=0.02</td>
</tr>
<tr>
<td>é (cm/s)</td>
<td>6.5±2.6</td>
<td>8.2±3.3</td>
<td>p=0.04</td>
</tr>
<tr>
<td>á (cm/s)</td>
<td>7.0±2.0</td>
<td>8.6±2.9</td>
<td>p=0.04</td>
</tr>
<tr>
<td>é/á</td>
<td>1.1±0.8</td>
<td>1.1±0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by 2D color DTI (cm/s)</td>
<td>5.3±3.2</td>
<td>5.3±1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded é (cm/s)</td>
<td>4.4±2.1</td>
<td>6.1±3.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded á by (cm/s)</td>
<td>5.4±1.8</td>
<td>6.2±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded é/á</td>
<td></td>
<td></td>
<td>n.s.</td>
</tr>
<tr>
<td>Relaxation velocity (cm/s)</td>
<td>51.0±32.7</td>
<td>52.9±28.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-septal site, mm)</td>
<td>82.2±8.5</td>
<td>79.1±7.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-lateral site, mm)</td>
<td>86.7±8.8</td>
<td>83.7±8.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-diastolic diameter (basal, mm)</td>
<td>43.7±4.6</td>
<td>43.1±3.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-diastolic diameter (widest place, mm)</td>
<td>47.8±5.0</td>
<td>46.4±4.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-systolic diameter (basal, mm)</td>
<td>27.9±6.1</td>
<td>26.9±3.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>E/é</td>
<td>12.6±6.5</td>
<td>11.9±9.6</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*one missing patient due to difficulties to measure IVRT by PW-DTI
Table 1. Some basic characteristics of the patients and some measured and calculated variables at inclusion (n=13).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.1±10.4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.58±0.09</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.4±19.5</td>
</tr>
<tr>
<td>Left ventricular end-diastolic diameter (mm)</td>
<td>43.7±4.6</td>
</tr>
<tr>
<td>Left ventricular end-systolic diameter (mm)</td>
<td>27.9±6.1</td>
</tr>
<tr>
<td>Septal wall (mm)</td>
<td>10.7±2.5</td>
</tr>
<tr>
<td>Posterior wall (mm)</td>
<td>9.1±1.1</td>
</tr>
<tr>
<td>Right ventricular outflow tract (mm)</td>
<td>27.0±4.2</td>
</tr>
<tr>
<td>Right ventricular inflow tract (mm)</td>
<td>29.7±5.2</td>
</tr>
</tbody>
</table>

Table 2. Significance of difference between the acute and recovery phase of some left ventricular variables (EF=ejection fraction; MAM=amplitude of mitral annulus motion; PW=pulsed wave; PW DTI=pulsed wave Doppler tissue imaging; IVRT=isovolumetric relaxation time; DT=deceleration time; S=systolic velocity; E=early diastolic velocity by PW; A=late diastolic velocity by PW; é=early diastolic velocity by PW-DTI; á=late diastolic velocity by PW-DTI; 2D color DTI=two-dimensional color Doppler tissue imaging; color coded é=early diastolic velocity by 2D color DTI; color coded á=late diastolic velocity by 2D color DTI) (n=13).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute phase</th>
<th>Recovery phase</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF obtained by biplane Simpson’s method (%)</td>
<td>53.4±9.5</td>
<td>63.3±4.4</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>MAM at the septal site (mm)</td>
<td>9.4±2.1</td>
<td>10.1±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MAM at the lateral site (mm)</td>
<td>10.1±2.3</td>
<td>12.1±2.6</td>
<td>p=0.02</td>
</tr>
<tr>
<td>MAM at the inferior site (mm)</td>
<td>9.9±2.8</td>
<td>11.6±2.0</td>
<td>p=0.03</td>
</tr>
<tr>
<td>MAM at the anterior site (mm)</td>
<td>9.0±2.6</td>
<td>10.8±1.9</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>Total MAM (all four sites, mm)</td>
<td>9.6±2.2</td>
<td>11.2±1.9</td>
<td>p&lt;0.02</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2±0.7</td>
<td>0.9±0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>206.2±91.5</td>
<td>249.6±69.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW (ms)</td>
<td>91.5±19.3</td>
<td>90.6±17.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW-DTI (ms)*</td>
<td>89.4±20.0</td>
<td>87.1±23.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by 2D color DTI (ms)</td>
<td>65.2±17.9</td>
<td>66.3±16.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by PW-DTI (cm/s)</td>
<td>5.9±1.5</td>
<td>7.2±1.9</td>
<td>p=0.02</td>
</tr>
<tr>
<td>é (cm/s)</td>
<td>6.5±2.6</td>
<td>8.2±3.3</td>
<td>p=0.04</td>
</tr>
<tr>
<td>á (cm/s)</td>
<td>7.0±2.0</td>
<td>8.6±2.9</td>
<td>p=0.04</td>
</tr>
<tr>
<td>é/á</td>
<td>1.1±0.8</td>
<td>1.1±0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by 2D color DTI (cm/s)</td>
<td>5.3±3.2</td>
<td>5.3±1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded é (cm/s)</td>
<td>4.4±2.1</td>
<td>6.1±3.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded á by (cm/s)</td>
<td>5.4±1.8</td>
<td>6.2±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded é/á</td>
<td>0.9±0.6</td>
<td>1.2±1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relaxation velocity (cm/s)</td>
<td>51.0±32.7</td>
<td>52.9±28.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-septal site, mm)</td>
<td>82.2±8.5</td>
<td>79.1±7.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-lateral site, mm)</td>
<td>86.7±8.8</td>
<td>83.7±8.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>End-diastolic diameter (basal, mm)</td>
<td>43.7±4.6</td>
<td>43.1±3.2</td>
<td>n.s.</td>
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<td>End-diastolic diameter (widest place, mm)</td>
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<td>12.6±6.5</td>
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</tr>
</tbody>
</table>

*one missing patient due to difficulties to measure IVRT by PW-DTI
Table 3. Significance of difference between the acute and recovery phase of some right ventricular variables (TAM=amplitude of tricuspid annulus motion; PW=pulsed wave; PW-DTI=pulsed wave Doppler tissue imaging; IVRT=ivovolumetric relaxation time; DT=deceleration time; S=systolic velocity; E=early diastolic velocity by PW; A=late diastolic velocity by PW; é=early diastolic velocity by PW-DTI; á=late diastolic velocity by PW-DTI; 2D color DTI=two-dimensional color Doppler tissue imaging; color coded é=early diastolic velocity by 2D color DTI; á=late diastolic velocity by 2D color DTI; RVOT1=right ventricular outflow tract 1; RVIT3=right ventricular inflow tract 3) (n=13).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute phase</th>
<th>Recovery phase</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAM (mm)</td>
<td>21.3±3.6</td>
<td>24.1±2.8</td>
<td>p=0.02</td>
</tr>
<tr>
<td>E/A</td>
<td>1.3±0.5</td>
<td>1.1±0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>195.0±58.7</td>
<td>201.3±42.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW (ms)</td>
<td>84.8±27.5</td>
<td>63.4±25.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by PW-DTI (ms)</td>
<td>70.4±21.9</td>
<td>60.6±23.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>IVRT by 2D color DTI (ms)</td>
<td>53.1±35.2</td>
<td>44.9±16.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by PW-DTI (cm/s)</td>
<td>12.2±2.2</td>
<td>12.5±2.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>é (cm/s)</td>
<td>11.3±3.6</td>
<td>11.8±2.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>á (cm/s)</td>
<td>16.2±3.9</td>
<td>15.7±3.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>é/á</td>
<td>0.7±0.2</td>
<td>0.8±0.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>S by 2D color DTI (cm/s)</td>
<td>10.3±2.4</td>
<td>10.8±2.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded é (cm/s)</td>
<td>9.5±3.6</td>
<td>8.6±2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded á (cm/s)</td>
<td>11.7±3.1</td>
<td>12.3±2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Color coded é/á</td>
<td>0.9±0.4</td>
<td>0.8±0.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relaxation velocity (cm/s)</td>
<td>87.2±37.5</td>
<td>78.8±23.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-septal site, mm)</td>
<td>72.3±11.6</td>
<td>71.7±8.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Length in end-diastole (apex-lateral site, mm)</td>
<td>83.9±14.4</td>
<td>82.4±9.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>RVOT1 (mm)</td>
<td>27.0±4.2</td>
<td>28.0±4.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>RVIT3 (mm)</td>
<td>29.7±5.2</td>
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Table 3. Significance of difference between the acute and recovery phase of some right ventricular variables (TAM=amplitude of tricuspid annulus motion; PW=pulsed wave; PW-DTI=pulsed wave Doppler tissue imaging; IVRT=ivsovolumetric relaxation time; DT=deceleration time; S=systolic velocity; E=early diastolic velocity by PW; A=late diastolic velocity by PW; é=early diastolic velocity by PW-DTI; á=late diastolic velocity by PW-DTI; 2D color DTI=two-dimensional color Doppler tissue imaging; color coded é=early diastolic velocity by 2D color DTI; á=late diastolic velocity by 2D color DTI; RVOT1=right ventricular outflow tract 1; RVIT3=right ventricular inflow tract 3) (n=13).

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<td>S by 2D color DTI (cm/s)</td>
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</table>

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