Assessment of Right Ventricular Systolic Function by Tissue Doppler Echocardiography

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PUBLICATIONS

The thesis is based on the following publications, referenced in the thesis by their roman numerals:

I. Kjaergaard J, Korinek J, Belohlavek M, Oh JK, Sogaard P, Hassager C. Accuracy, reproducibility, and comparability of Doppler tissue imaging by two high-end ultrasound systems. J Am Soc Echocardiogr 2006;19(3):322-8

II. Kjaergaard J, Sogaard P, Hassager C. Quantitative echocardiographic analysis of the right ventricle in healthy individuals. J Am Soc Echocardiogr 2006;19(11):1365-72

III. Kjaergaard J, Snyder EM, Hassager C, Oh JK, Johnson BD. Impact of preload and after-load on global and regional right ventricular function and pressure: A quantitative echocardiography study. J Am Soc Echocardiogr 2006;19(5):515-21

IV. Kjaergaard J, Schaadt BK, Lund JO, Hassager C. Quantitative measures of right ventricular dysfunction by echocardiography in the diagnosis of acute nonmassive pulmonary embolism. J Am Soc Echocardiogr 2006;19(10):1264-71

V. Kjaergaard J, Schaadt BK, Lund JO, Hassager C. Quantification of right ventricular function in acute pulmonary embolism: relation to extent of pulmonary perfusion defects. Eur J Echocardiogr 2008;9(5):641-5

VI. Kjaergaard J, Schaadt BK, Lund JO, Hassager C. Prognostic importance of quantitative echocardiographic evaluation in patients suspected of first non-massive pulmonary embolism. Eur J Echocardiogr 2009;10(1):89-95

VII. Kjaergaard J, Snyder EM, Hassager C, Olson TP, Oh JK, Johnson BD, Frantz RP. Right ventricular function with hypoxic exercise: effects of sildenafil. Eur J Appl Physiol 2007;102(1):87-95

VIII. Kjaergaard J, Svendsen JH, Sogaard P, Chen X, Bay NH, Kober L, Kjaer A, Hassager C. Advanced quantitative echocardiography in arrhythmogenic right ventricular cardiomyopathy. J Am Soc Echocardiogr 2007;20(1):27-35

IX. Kjaergaard J, Iversen KK, Vejlstrup NG, Smith J, Bonhoeffer P, Søndergaard L, Hassager C. Effects of acute severe pulmonary regurgitation on right ventricular geometry and contractility assessed by tissue Doppler echocardiography. Eur J Echocardiogr 2010;11(1):19-26

X. Kjaergaard J, Iversen KK, Vejlstrup NG, Smith J, Bonhoeffer P, Søndergaard L, Hassager C. Effects of chronic severe pulmonary regurgitation and percutaneus valve repair on right ventricular geometry and contractility assessed by tissue Doppler echocardiography. Echocardiography 2010;27(7):854-63

INTRODUCTION

Knowledge of the normal right ventricular (RV) physiology was lacking for some years after the mechanics of left ventricular (LV) was first described [1], not least owing to early reports of elegant animal models showing that cardiac output was maintained in electrically isolated RV in otherwise normal hearts [2] or when replacing the RV with a non-contracting material [3]. The concept of 'ventricular interdependence' was introduced as the LV contribution of the RV stroke work was estimated to 30% [3]. When the pressure-volume relationship of the RV was first determined in 1988 [4], the basis for improving our understanding of RV physiology improved and the significance of the RV in the circulatory system was increasingly being appreciated.

The RV significance in the normal circulation has been neglected for many years, indeed this part of the heart was referred to as 'the forgotten chamber' in the review of Rigolin et al in 1994 [5]. Even though the RV performance cannot be interpreted independently from the LV and vice versa, assessment of the RV and LV function in relation to diagnosing disease in humans as well as for acquiring prognostic information has been performed separately in most studies. And from findings in various diseases it seems that the dysfunction of the ventricles does have independent clinical or prognostic importance [6-10].

Assessment of the RV for clinical purposes, including diagnosis, prognosis and response to therapeutics has been challenging. Accurate and relatively load independent evaluation of RV hemodynamics can be accurately performed by invasive measurements, primarily by the use of conductance catheters that allow simultaneous volume and pressure measurements under manipulation of loading and contractility [11]. Non-invasively, and thus more appropriate for most clinical purposes magnetic resonance

imaging (MRI) can estimate RV volume with satisfactory accuracy [12,13]. Echocardiography has been challenged by the retrosternal position of the RV limiting the echocardiographic window, and the complex shape of the RV that makes calculation of volumes based on geometrical assumptions of shape impossible. 3D echocardiography has provided promising results, but is time-consuming and has limited feasibility [14-17]. Furthermore the load dependence of the thin-walled RV with its low afterload physiology, will influence measures of RV function based on volumes alone [1,11].
Assessment of RV function by echocardiography is challenging. The development of technology for measurement of regional myocardial velocities by means of tissue Doppler and software for calculation of regional deformation and deformation rate in the LV have offered researchers a promising new technology for non-invasive assessment of RV myocardial function [18]. Shortly thereafter studies reported on the applicability of tissue Doppler based deformation analysis in the RV as well [19,20]. These new parameters seemed clinically useful and potentially less load dependent than other echocardiographic markers of RV myocardial performance.

Purpose

The purpose of this thesis was to evaluate the clinical usefulness of application of tissue Doppler echocardiography of the RV. The thesis assesses 3 different applications of the technology with potential impact on the clinical utilization of this technology as an adjunct to existing echocardiographic and clinical knowledge: a) accuracy, reproducibility, normal values and load dependence in normal subjects, b) the diagnostic and prognostic importance in diseases associated with RV pressure overload, RV myocardial dysfunction or RV volume overload, and c) the response to therapy.
For this purpose the following in vitro models and in vivo populations were studied: 1) a gelatin phantom model for validation of tissue Doppler based measures of deformation; 2) three groups of normal subjects, n=54, 17 and 14; 3) patients suspected of acute pulmonary embolism, n=300; 4) 20 patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), and 5) an animal model of 52 farm pigs.

TISSUE DOPPLER ECHOCARDIOGRAPHY OF THE RIGHT VENTRICLE

The retrosternal position of the RV limits the number of views from which it can be imaged, in particular with regards to the anterior wall. Also the anatomical characteristics of the RV are associated with some challenges to the echocardiographer. The RV anatomy is often described by the trabeculated inlet or sinus portion and the outlet portion, the infundibulum, also referred to as the conus [1,21]. The middle myocardial layer of fibers is thin compared to the left ventricle [22] and the endocardial layer is relatively thick, in particular in the sinus portion of the ventricle [21]. The ejection of blood from the ventricle is therefore more dependent on the longitudinal shortening [22], and as the sinus part constitutes about 80% of the combined RV volume, most (>85%) of the combined stroke volume is ejected from this part of the RV [21]. Furthermore the pattern of RV contraction is distinctly different from that of the LV. The contraction starts in the sinus, and progresses via a peristalsis-like motion towards to infundibulum, where continuous shortening is seen even after pulmonary valve closure [23].
The RV hemodynamic physiology is also very different from the LV. As a given fact of homeostasis the stroke volume ejected from the two ventricles is the same in the absence of valvular insufficiency or shunts. The relatively high impedance of the pulmonary vascular bed makes the RV very dependent on its loading conditions and the RV functions in part as a conduit. The RV pressure-volume relationship was first defined in 1988 where Redington et al published the characteristic curve by simultaneous cine angiography and pressure recordings [4].
Estimation of RV volumes from echocardiography has been limited by the complex shape of the ventricle that cannot be sufficiently represented by any known geometrical shape. Volume estimation from 3D echocardiographic methods are promising [14,24], but still have limited feasibility due to the retrosternal position of the RV. Even though accurate volumetric data of the RV would be clinically helpful, more data on the myocardial function of the RV would be essential to non-invasively describe the RV physiology.

INTRODUCTION TO THE FUNDAMENTALS OF TISSUE DOPPLER ECHOCARDIOGRAPHY

Tissue Doppler echocardiography was introduced as an alternative to gray-scale imaging based assessment of myocardial deformation, in fact the technology was introduced as a quantitative measure of deformation of elastic organs, i.e. liver or breast by external forces [25]. The methods had several limitations when applicatied to cardiac deformation, in particular time and computational challenges although, in theory, the method had an appealingly great spatial and temporal resolution when based on M-mode imaging. Instead the velocity gradient method, based on instantaneous comparison of velocities measured in adjacent points along a scan line was introduced [26,27]. Analysis of myocardial motion by velocity imaging, however, had several drawbacks including the angle dependency in the measurements and that overall motion of the heart or tethering influences regional velocity estimates. But, by comparison of velocities recorded at adjacent myocardial regions, these limitations diminish, and the two parameters developed from this theory were named strain and strain rate (SR), corresponding to the terminology applied in mechanical engineering [28].
The mathematical basis for calculating deformation rate, i.e. SR, and deformation, i.e. strain can be shortly described as follows [28]. Deformation at a given time point, i.e. instantaneous strain, is defined as

$$Strain(t) = \frac{L(t) - L(t_0)}{L(t_0)} \quad (1)$$

which is referred to as *Lagrangian strain*, characterized by its relation to the initial length, L(t0) of the object. If the deformation instead is expressed relative to infinitesimally small time intervals:

$$dStrain_N = \frac{L(t+dt) - L(t)}{L(t)} \quad (2)$$

evaluation of deformation over time is possible. This is called the *Natural strain*, and is thus characterized by the reference value not being constant over time, which seems physiologically more correct.

The total amount of *Natural strain* is simply calculated by the adding all of measured instantaneous strain values:

$$Strain_N = \int_{t_0}^{t} dStrain_N(t) \quad (3)$$

and is a dimensionless number, often expressed as a percentage. *Lagrangian* and *natural strain* are mathematically related via a non-linear relation. By definition shortening is expressed as negative strain, lengthening as positive strain.

SR is defined as the speed at which the deformation occurs and it can be mathematically shown that instantaneous *natural* SR can be calculated as the difference between velocities recorded at two points (v_1 and v_2), divided by the distance between the points (L):

$$SR_{Natural} = \frac{v_1 - v_2}{L} \quad (4)$$

Color tissue Doppler echocardiography is based on the same principles as conventional spectral Doppler echocardiography, where the frequency of an emitted ultrasound wave is compared to the frequency of the signal received. The shift in frequency is related to the velocity of the object from which the ultrasound wave is reflected, and the principle is named after the Austrian scientist *Christian Doppler* who first described the phenomenon in 1842 based on his studies of colored light from binary stars.
In tissue Doppler echocardiography the filter settings and *Nyquist* limits are adjusted to maximize sensitivity to the strongly reflecting and slower moving myocardial tissue [29].

In tissue Doppler based deformation analysis the velocity gradients determine regional deformation rate, i.e. SR, and strain is calculated by temporal integration of the measured regional SR [29]:

$$Strain(t) = \int_{t_0}^{t} SR(t) \quad (5)$$

Several challenges in the application of this technique to clinical practice have been addressed. First: the angle dependency of the measurements. Velocities are measured only in the axial direction, and although the influence of motion in an angle to the axial measuring of SR can be calculated and thus adjusted for, the recommendation remains to carefully align the imaged regions [30]. Secondly: measurement of SR are susceptible to noise, and most software for SR analysis have several built-in features to increase the signal to noise ratio based on two concepts: velocities are averaged over a small region around the sample points and the SR curves are smoothed temporally, which reduces the spatial and temporal resolution of the technique, respectively [28]. High frame rate in the imaging is essential to avoid underestimation of peak values, and a lower limit of 100 frames per sec has been proposed for assessment of myocardial velocities [31], whereas requirements for accurate measurements of short lived velocities are higher [29]. Furthermore, the temporal integration of SR to Strain may result in a drift of the curves due to a bias in the SR estimates because heterogeneous velocities in the sampling region or change in insonation angle during the cardiac cycle will result in a small constant change in the net deformation at the end of each cardiac cycle. This is often dealt with by forcing the curve to zero at end-systole.

Tissue Doppler echocardiography

Tissue Doppler echocardiography of the RV has great theoretical potential in its ability to assess regional myocardial deformation rate (hereafter referred to as strain rate, SR) and deformation (hereafter referred to as strain) which has been shown to be closely correlated to invasive measures of contractility [20,23]. Several other parameters based on M-mode, 2D and spectral Doppler had been evaluated with regards to their relation to contractility, pressure or ejection fraction, but proved to have significant limitations due to the limited echocardiographic windows of the RV, complex geometry of the RV and inability to adjust for changes in geometry induced by progression of disease or changes in loading conditions [33].
Validations of tissue Doppler based parameters using invasive measures performed in animal models, such as dP/dtmax, showed a close direct correlation to SR value in the LV [32]. In the RV, it was suggested that although strain is also directly related to dP/dtmax, this parameter seemed to be more closely related to stroke volume [34]. Data from validation studies of the application of Tissue Doppler echocardiography on the right ventricle are limited, but one study investigated the accuracy of RV longitudinal deformation analysis using sonomicrometry crystals as a reference and found a good correlation even during preload reduction and afterload increase [20].
Based on tissue Doppler measurements, short-lived velocities can also be quantified if frame rate is sufficiently high. Special focus has been drawn towards the isovolumic contraction period, which often is seen as positive velocity peak during or immediately after mitral valve closure. The isovolumic acceleration (IVA) defined as the ratio of peak isovolumic velocity and time to peak isovolumic velocity has been proven to be directly related to dP/dtmax in an experimental model as well as in a small population with repaired transposition of the great arteries [35,36]. IVA has also been shown to be correlated to decreasing degree of pulmonary regurgitation in repaired Tetralogy of Fallot (ToF) [37]. The hemodynamic basis for the relation of IVA and contractility remains to be fully understood, and a recent animal study and mathematical modeling have shown that the LV IVA is likely to a be referred motion from mitral valve closure [38]. However, even though these short lived motions of the mitral annulus may not be related to distinct myocardial properties, this parameter could still in theory reflect global myocardial function, and further validation is being pursued.

Image acquisition and measurements from tissue Doppler Echocardiography of the right ventricle

In the studies on which the present thesis is based, the acquisition of tissue Doppler imaging and subsequent analysis has been carried out as described below. This approach is similar to most studies based on tissue Doppler imaging of the RV [39], enabling comparison to other studies.

Tricuspid annular velocity by pulsed tissue Doppler echocardiography

The pulsed wave analysis of the annular velocities are performed online using a pulsed wave Doppler with a ROI diameter of ≤ 8 mm [29]. The ROI is positioned in the annulus and measurements are performed at the upper border of the clear envelope of the signal [40], Figure 1.

Regional myocardial velocity by color coded tissue Doppler echocardiography

For regional myocardial velocity estimates, color Doppler coded images are recorded from the apical 4-chamber position, positioning the transducer at the RV apex to reduce angle error [30]. The sector angle is reduced to the minimal width possible to increase frame rate, and depth of the sector is reduced. The color coded region can also be reduced in size, but in practice this has little advantage over reducing the total sector width. A cine-loop of 3 or more consecutive loops is stored for off-line analysis. Off-line measurements are typically performed in three RV free wall segments: the basal, mid and apical [29]. Although no systematic evaluation exists of the bias due to difference within regions with regards to positioning of the sample volume or M-mode fragment or using the semi-automatic tracking algorithms available in some systems, the general consensus is: For velocity measurements sample regions of 3-5 mm in diameter (representing the better trade-off between accuracy and noise [28]) are placed in the basal part of the segment and on the endocardial side, if possible. The myocardial tracking algorithms are rarely used. To ensure recording of ventricular velocities only, the sample volume is positioned in end-systole, which yields smoother curves, and since the fibrous non-contracting annular plane is not pulled into the sampling area, the curves are more representable of ventricular velocities making the derived SR and strain less prone to artefacts.

Regional myocardial deformation (-rate) by color coded tissue Doppler echocardiography

For measurement of strain rate, regional velocities are compared, see equation 4 above, and the distance between these sites of comparison can be manipulated. In general greater distance produces less noise, but is increasingly less 'regional'. A frequently accepted trade-off is approximately 12 mm which was also applied in my studies. Samples volumes are often increased in size to 12*6 mm. (Natural) Strain is the simple temporal integration of the SR curve, equation 5. Different smoothing algorithms are available; I used 30 msec Gaussian smoothing where available, but again no data systematically comparing the effects of these algorithms exist.

Isovolumic acceleration by color coded tissue Doppler echocardiography

The IVA is measured directly using the velocity tracing from the tricuspid annulus, or as originally proposed and validated, from the velocity curve from the basal RV segment [35], Figure 1.

Pitt-falls in the image acquisition

Tissue Doppler Echocardiography is limited by several of the artefacts seen in 2D echocardiography, including reverberations, shadowing and mirroring artefacts. Reverberations are commonly seen, although less frequent with the introduction of 2nd harmonic imaging. The Doppler based velocities are often measured very low in the imaging artefacts, resulting is a high velocity gradient to nearby correctly imaged segments. Mirroring artefacts may also have extreme impact on the derived deformation calculations, and 2D imaging must therefore be optimized in order to avoid these artefacts. Shadowing will make Doppler interrogation of velocities impossible, and must therefore be minimized if possible, and near-field artefact also severely impacts velocity measurements, which is one of the reasons why RV radial motion cannot be interrogated with satisfactory precision [19]. The 'drop-outs' frequently seen due to the reduced lateral resolution is also a limitation, and may reduce spatial resolution of the tissue Doppler signal, in particular in the far field [28].

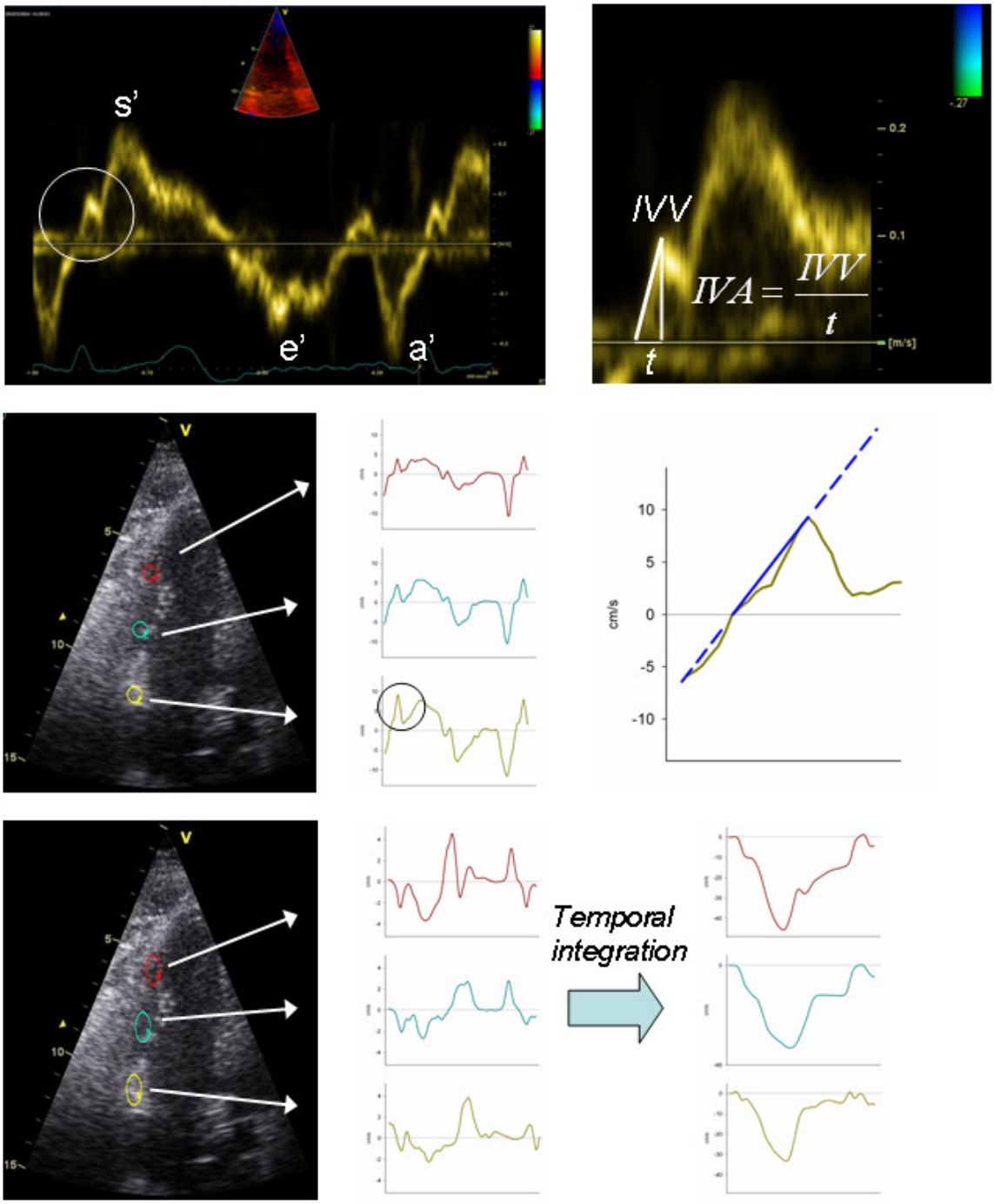

Figure 1
Tissue Doppler of the RV free wall performed in a normal subject.
In the top panels, pulsed wave tissue Doppler measurements of the tricuspid annular plane velocities are shown to the left. To the right, a magnified image of the part of the velocity curve marked by a white circle, illustrating the measurement of isovolumic acceleration, IVA.
In the middle panel, color tissue Doppler measurements of regional, i.e. basal (yellow), mid (cyan) and apical (red) velocities are shown to the left. To the right a magnified section of the basal velocity curve shown by a black circle on the velocity tracing, illustrating the measurement of isovolumic acceleration of the basal RV segment.
In the bottom panels, regional strain rate is calculated by comparing velocity measurements from adjacent segments within larger sample volumes to reduce noise as illustrated to the left. Regional strain is calculated by temporal integration and the resulting curve as shown to the right.

VALIDITY OF RIGHT VENTRICULAR TISSUE VELOCITY DATA AND DERIVED PARAMETERS

The clinical usefulness of parameters is among other factors, determined by the accuracy and reproducibility of the method. Accuracy is defined as the closeness of the measurements to the 'gold standard' or true value and reproducibility as repeatability of the measurements. In the following sections the current knowledge of accuracy and reproducibility of RV tissue Doppler imaging will be reviewed with special focus on existing data concerning the application of the technology in RV assessment.

Accuracy in vitro

In vitro validation studies have convincingly shown a high degree of accuracy in previous studies. The experiments conducted can be separated into two groups: test-phantoms in which velocities or deformation rate can be manipulated, and animal models where reference methods are alternative velocity or deformation measuring modalities, for example ultrasound emitting and receiving crystals, from which regional deformation can be calculated and used as 'gold standard'.

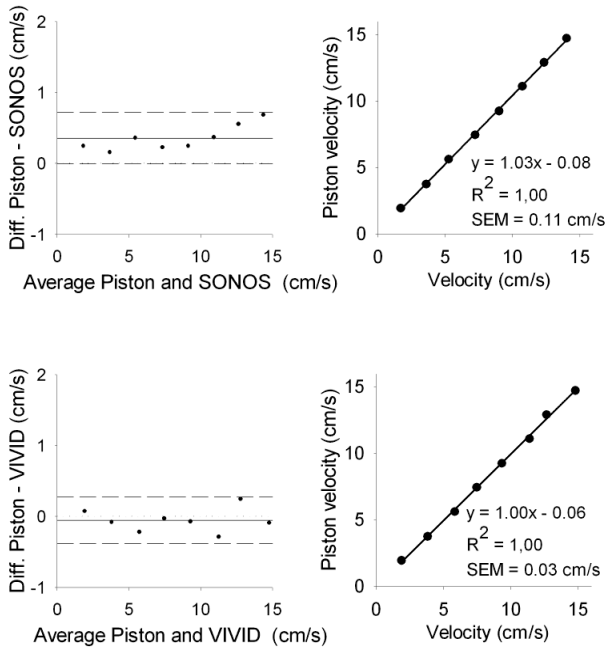

Figure 2

Comparison of velocities measured by Sonos or Vivid systems to velocities generated in a gelatin phantom. Left, Mean difference (solid line) plots with 95% limit of agreement (dashed line). Right, Correlation plot with regression line fitted.
SEE, Standard error of estimate. Diff, difference.
From Kjaergaard et al J Am Soc Echocardiogr 2006; 19:322-328.

Tissue mimicking phantoms assessing the accuracy of spectral Doppler and color Tissue Doppler velocities have been published concurrently with the introduction of the technology more than a decade ago. In general, very good agreement between tissue Doppler methods and the calculated reference velocities was found [40-45]. *Kukulski* et al, 2000 found that spectral tissue Doppler slightly overestimated true velocities, while color tissue Doppler consistently underestimated true velocity [40]. He also reported a very high agreement between the two modalities [40]. Some studies found that gain settings potentially could impact accuracy [41], while others found that accuracy differs among ultrasound systems [45]. However the data on the validity of strain and SR was sparse, and comparisons of these parameters measured by two different ultrasound systems were not available, which led me to perform the following validation study. Using a gelatine phantom model, I found excellent correlation and a high degree of accuracy in two commercially available high-end ultrasound systems in the full range of velocities seen in RV tissue Doppler echocardiography, Figure 2 [**I**]. Strain and SR have also been evaluated with regards to accuracy in phantom models, finding a very low error compared to expected values [43,46]. I found a low mean error overall, but a trend towards increasing error with increasing deformation rate, consistent with findings in previous studies [**I**,43]**.**

Accuracy in vivo

In humans, a validation study using mean velocity calculated from M-mode imaging showed no systematic error in spectral Doppler velocity measurements [42]. Also tricuspid annular systolic velocity has been shown to be correlated to RV ejection fraction in heart failure patients and in normal subjects [47,48]. Isovolumic acceleration was proposed and validated in an animal model by Vogel et al, 2002, using invasively measured dP/dt as reference [35], whereas no correlation to RV ejection fraction from MRI was found in another study [14]. Animal models using ultrasonic crystals for high frequency deformation analysis have also shown a high degree of accuracy of strain measurements [20,49]. Strain is accurately measured in humans using tagged Magnetic Resonance Imaging as reference [50], and studies have found only a modest correlation with variation in the range of what is found in tissue Doppler based measurement of strain and a slightly better correlation with 2D speckle tracking based methods [51]. Interestingly in the identification of dyskinetic segments, the 'gold standard' of tagged magnetic resonance imaging performed no better than tissue Doppler based measurements [51].

Reproducibility

image acquisition. If serial imaging is to be performed, as is frequently the case in echocardiography, this approach will likely underestimate the true variation with potential implications for treatments adjustment or risk of type II errors in trials. Assessment of reproducibility with repeated measurements of two sets of imaging acquired individually is often referred to as test-retest reproducibility [52]. This variation can directly be related to change in a given parameter needed for the method to be able to truly, i.e. with more than 95% confidence, state that a change has indeed occurred in the individual. The change necessary to be present for detection can therefore be calculated as:

$$2 \times \sqrt{2} \times CV\% \qquad (6)$$

where CV% is Coefficient of Variation defined as the ratio of the standard deviation to the mean in percent, corrected for repeated measurement as appropriate [53]. Data on the reproducibility of right ventricular tissue Doppler imaging is relatively sparse. Spectral tissue Doppler of the longitudinal motion was reported to have a high degree of reproducibility in a test-retest design, while radial motion of the anterior wall had a disappointingly low reproducibility [54]. For color Tissue Doppler measurement, error was reported to be < 10% both for intra- and interobserver variability [55]. I found a good reproducibility, CV%<10%, in a test-retest design in vitro and acceptable reproducibility, CV%=10-15%, in vivo with regard to color tissue Doppler velocity measurements, Table 1[**I**]. Mean difference in repeated measurements of IVA using the VIVID system was 0.02 (95% limits of agreement: -0.50-0.54), CV%=28% and 0.24(-1.68-2.17), CV%=28% for basal IVA by color tissue Doppler and annular IVA by pulsed wave tissue Doppler imaging, respectively.

Since the data in the literature on reproducibility in a test-retest design is sparse, reproducibility of SR, strain and isovolumic acceleration must be compared to data based on reanalyzing the same imaging. All of these studies found no systematic error between the two measurement on the same imaging [43,51,56]. As suggested by Bland and Altman, mean difference as well as 95% limits of agreement, defined as mean±1.96*SD, should be reported. I performed a test-retest assessment of variability in SR and strain, finding no systematic error, and limits of agreement of ±1 s-1 and ±10 % (percentage points), respectively, Table 1, [**I**]. This is consistent with later studies also finding wide limits of agreement for SR, strain as well as for IVA [51,56,57].

Summarizing the findings on the validity of tissue Doppler based measurements of regional velocities and deformation analysis, I found a high degree of accuracy of measurements of all of the parameters when tested in vitro as well as in vivo. The reproducibility of the technology in vivo may represent a limitation in the clinical application of deformation parameters as changes in serially evaluated individuals must be more than 28%, 40%, 35% and 78% for velocity, strain rate, strain and IVA, respectively. However the technology may still be useful for analysis of changes in groups and thus an interesting tool for improving our understanding of RV hemodynamics.

NORMAL VALUES OF RIGHT VENTRICULAR TISSUE DOPPLER ECHOCARDIOGRAPHIC PARAMETERS AND IMPACT OF CHANGE IN LOADING CONDITIONS

The following sections will review the current literature on data from normal subjects, and assess the impact of changes in loading conditions on these parameters. In general velocities measured in the RV annular and free wall are greater than velocities measured in the LV, likely due to the difference in afterload in the two parts of the circulation and the differences in myocardial fiber orientation [11,21]. Similar to the LV, a baso-apical gradient with higher velocities in the basal segment is found. Strain rate and strain values have interestingly been reported to exhibit an opposite baso-apical gradient with higher values (numerically) in the mid and apical segments [20,58,59] this may be due to differences in anatomy of the thin walled crescent shaped RV and an heterogeneous distribution of wall stress due to the complex RV shape. Later studies however, have suggested that this gradient may not be as clear as seen in the early studies [60].

Normal values

Normal values of regional longitudinal myocardial velocities from studies of the RV in healthy individuals have been reported in previous studies. The reported values range from 8-13 cm/s for peak systolic velocities of the basal segment [19,55,58,61,62], and higher annular velocities in the range of 12-15 cm/s [40,47,63].

Velocities decrease from annulus towards the basis, and are generally higher when measured by spectral tissue Doppler. Our study of 54 normal subjects represents one of the larger populations of healthy subjects reported to date and found a mean value of 9.1±2.5 cm/s in the basal by color tissue Doppler, Table 2 [**II**], consistent with the existing literature. Tricuspid annular velocity was measured as 14.5±3.9 cm/s by spectral tissue Doppler echocardiography. This difference is consistent with previous results, and can be explained in part by differences in how the velocities are computed in the two methodologies [40].

		Sonos			Vivid		
		Mean diff	95% LOA	CV%	Mean diff	95% LOA	CV%
In vitro	Velocity, cm/s	−0.01	−0.24, 0.21	1	0.10	−0.11, 0.31	1
	Strain rate, s^{-1}	0.06	−0.22, 0.35	6	−0.08	−0.31, 0.16	7
	Strain, %	0.65	−3.3, 4.6	6	−1.21	−3.7, 1.3	5
In vivo	Velocity s, cm/s	0.46	−2.6, 3.5	12	0.31	−2.3, 2.9	9
	Strain rate s, s^{-1}	0.04	−1.0, 1.1	13	0.09	−0.92, 1.1	16
	Strain, %	1.7	−9.9, 13	12	0.31	−9.7, 10	13

Table 1
Reproducibility of velocities, strain rates, and strains in vitro (gelatin phantom) and in vivo (10 healthy individuals; repeated measurements of the basal right ventricular free wall). LOA, Limits of Agreement; CV, Coefficient of variation
Adapted from Kjaergaard et al, J Am Soc Echocardiogr 2006; 19:322-328.

Segment	RV lateral wall	LV lateral wall
Peak s-wave velocity, cm/s		
Basal	9.1 ± 2.5	5.3 ± 1.8
Mid	7.3 ± 3.2	3.8 ± 2.1
Apical	4.4 ± 2.7	2.7 ± 2.0
Peak systolic strain, %		
Basal	31 ± 13	21 ± 8
Mid	28 ± 11	16 ± 6
Apical	34 ± 10	15 ± 5

Table 2
Peak regional myocardial velocity and peak systolic strain in 54 healthy individuals (derived from images acquired in the apical 4-chamber view). LV, left ventricular; RV, right ventricular; s-wave, systolic.
Adapted from Kjaergaard et al, J Am Soc Echocardiogr 2006; 19:1365-1372.

Normal values of isovolumic acceleration have been reported to be 1.8±0.5 m/s^2 in humans measured by color tissue Doppler echocardiography [37], and higher values have been reported when measured by spectral tissue Doppler Echocardiography [64]. Measurements of IVA from the two sites and by the two Doppler modalities cannot therefore be used interchangeably.
Normal values for Strain and SR have also been established. Previous studies found that longitudinal SR and strain increased from the basal to apical segment of the RV wall, in contrast to that which has been found for LV [19]. Our findings were to some extent consistent with these findings and confirmed that RV strain values are higher than for the LV, Table 2, although a less clear gradient was found.
The influence of different factors in normal values of tissue Doppler derived parameters have also been investigated including heart rate, age and sex. With regards to heart rate, no correlation was found with systolic velocities in normal subjects [19]. While some authors reported a slight reduction in systolic longitudinal velocities with increasing age [55,58,65], others did not find such a relation [19,66], including the study reported by our group, where systolic velocities also were shown to be unrelated to gender [**II**]. Possible explanation of the inverse relation of annular velocities and age include an increase in radial motion similar to the age related changes in the left ventricle and increase in RV afterload [58,67]. SR or strain are not related to heart rate [19], and I found no relation to gender or and only a weak relation to age, Figure 3 [**II**]. This would not be inconsistent with the data on annular and myocardial velocities mentioned above, and the physiological changes in afterload with increasing age is substantially less than the degrees of pulmonary hypertension causing RV failure in patients.

Impact of changes in loading conditions of the RV
Tissue Doppler based measures of myocardial velocities and contractility should ideally be fairly stable with small or physiological changes in preload, while sensitivity to changes in contractility should be relatively high. As per the Frank-Starling mechanism, reduction in preload is expected to reduce stroke volume, whereas increase in preload may not be consistently related to changes in cardiac output, depending on the degree of preload increase. As some of the indices measured by tissue Doppler echocardiography are more closely related to stroke volume than myocardial contractility, myocardial velocities and to some extent strain would be expected to be relatively sensitive to changes in preload [33].

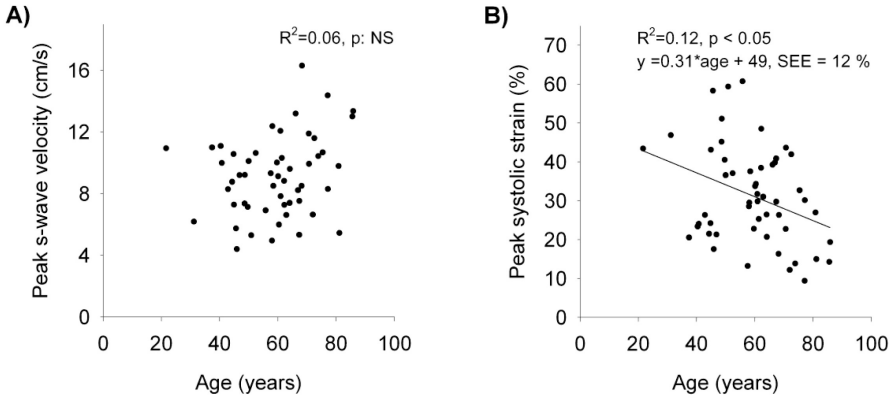

Figure 3
Regional measures in basal segment of right ventricular free wall of peak systolic velocity, s-wave, (A) and peak systolic strain, (B). Regression line (solid line), regression formula, and standard error of estimate (SEE) noted. NS, Not significant.
Adapted from Kjaergaard et al, J Am Soc Echocardiogr 2006; 19:1365-1372.

Previous studies in animals have consistently found that reduced RV preload is associated with decreasing RV contractility and cardiac output, changes that are well correlated with changes in SR [20,35]. In humans, non-invasive reductions in preload achieved by positive end-expiratory pressure breathing showed reduction in cardiac output [68,69]. Systolic RV myocardial and annular velocities are decreased with reduced RV preload in normal subjects [70,71] and in patients after hemodialysis with fluid removal [72,73]. I studied the effect of increasing preload by infusion of 30 ml/kg of isotonic saline in 17 healthy subjects and found that increased preload was associated with a small reduction in annular velocities, while no changes were seen in the basal segment longitudinal velocity of the RV free wall [**III**], consistent with observation from an animal study [74]. This would be consistent with the Frank Starling mechanism, where massive increases in loading would result in reduction of cardiac output or stroke volume. No changes in IVA, strain and SR were found with increasing preload, Figure 4 [**III**].

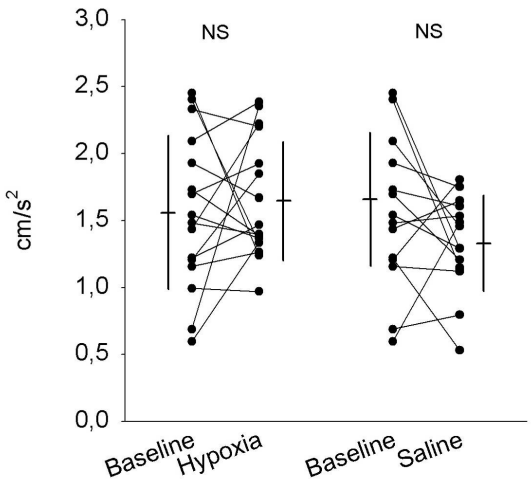

Figure 4
Changes in right ventricular isovolumic acceleration in basal free wall with increase in afterload (hypoxia) and preload (saline) compared with baseline. Differences assessed by paired t tests. Mean of observations at baseline, hypoxia, and saline as horizontal line ± 1 SD. NS, not significant.
Adapted from Kjaergaard et al, J Am Soc Echocardiogr 2006; 19:515-521.

The RV contractile performance is known to be considerably more dependent on afterload than the LV. Studies have shown that restoring preload by volume infusion in an animal model did not recover cardiac output during continuous positive end-expiratory pressure of 20 cm H_2O, indicating that the RV function is in fact sensitive to moderate increases in pulmonary vascular resistance or afterload [75]. Isolated increase in afterload in animal models is achieved by inflating a balloon in the pulmonary artery and thereby increasing pulmonary vascular resistance. In animal models this results in a significant increase in RV contractility as estimated by $dP/dt_{maximum}$, and these changes have been shown to be closely correlated to SR and IVA [20,35].
A method for non-invasively increasing afterload is exposure to controlled hypoxia inducing pulmonary vasoconstriction. This method has been utilized in studies of human adaptation to high altitude, finding no changes in myocardial systolic velocities with hypoxia [76], whereas a small reduction in annular velocities was found in our study [III]. Although great similarities in the two studies exist, some minor differences may still be important in explaining the discrepancies, including that the Huez et al study applied 1 hour of hypoxia, whereas our study exposed the subjects to 18 hours of hypoxia to allow some degree of acclimatization. A biphasic response to hypoxia cannot therefore be excluded. Also an inherent limitation in the hypoxia models is that a direct influence on myocardial contractility cannot be excluded. IVA seemed to be more robust with regards to changes in loading conditions, whereas this parameter was found to be sensitive to increases in contractility by dobutamine infusion in an animal model [35] and in human volunteers [76]. IVA was thus considered very promising as a load-independent non-invasive estimate of contractility [33,35]. In our study IVA was unchanged with hypoxia, Figure 4, but considerable variation in the measurements were seen [**III**], consistent with the variation reported in other studies of IVA [35,37,76]. Based on the reproducibility of IVA, CV%=28%, reported earlier in this thesis, a change of 80% from the baseline mean value would have been necessary to indicate a significant change in individual subjects, and of 22% to indicate a significant change in the 17 subject study group. Therefore, a minor effect on RV contractility from hypoxia cannot be excluded.

SR and Strain seem relatively stable with increase in afterload by hypoxia in normal subjects [76, **III**]. The results were therefore not concordant with the decrease in strain seen in the animal model study by Jamal et al, 2003 [20], and in patients with PAH and normal left ventricular function an inverse relation of strain and pulmonary vascular resistance has been demonstrated [77]. Further studies are needed to clarify the relation of RV afterload and RV deformation in normal subjects and in patients.

The impact of loading manipulation on myocardial velocities and IVA has been studied in the left ventricle, where no changes in LV systolic velocities was found with increased or decreased preload, while a direct impact in preload alteration was seen on the IVA [78], which was not seen in animal models [79]. No consistent changes in strain, SR or IVA is seen with either preload increase or with hypoxia in the LV [80,81].

VALIDITY, NORMAL VALUES AND LOAD DEPENDENCY OF TISSUE DOPPLER ECHOCARDIOGRAPHY OF THE RIGHT VENTRICLE – KEY FINDINGS

- Tissue Doppler derived measures of deformation are accurate and do not differ between newer ultrasound systems. Reproducibility is good for velocity measurements, and suboptimal for deformation imaging which limits the clinical application of tissue Doppler echocardiography for diagnostic purposes, especially in serial studies in individuals, whereas the technology is still valid for physiological studies in groups.
  Paper I. In vitro validation (phantom) & test-retest evaluation in vivo (N=10)
- Normal values for global and regional tissue Doppler echocardiographic analysis of the RV in adults analysis are well established in both sexes and in all age groups.
  Paper II. Normal subjects, N=54

- Tissue Doppler derived measures of myocardial deformation seem to be sensitive to changes in loading as well as RV myocardial function, and the technology therefore seems suitable for studies of physiologic and pathophysiologic changes in RV hemodynamics with simultaneous assessment of RV pressures and loading. IVA has been reported to be relatively load independent and thus of greater interest in studying diseases with a simultaneous impact of RV contractility and loading, but is limited by its poor reproducibility for serial studies in individual cases.
  Paper III. Normal subjects (N=17)

DIAGNOSTIC AND PROGNOSTIC POTENTIAL OF TISSUE DOPPLER ECHOCARDIOGRAPHY OF THE RIGHT VENTRICLE

Although diseases with an impact on RV hemodynamics can rarely be characterized as being associated with either RV pressure- or volume overload or by myocardial dysfunction exclusively, most diseases do have a predominant pathophysiological feature which allows some degree of categorization. This simplified approach was chosen in the present thesis in order to be able to study the mechanism of disease. In the following sections current knowledge of the clinical usefulness of Tissue Doppler echocardiography with regards to its diagnostic potential will be reviewed.

Diagnostic imaging is widely applied in the monitoring of treatments effects, and thus a highly relevant application of non-invasive technology such as tissue Doppler echocardiography could provide information for tailoring treatments, to identify complications of treatments or to obtain further prognostic information. There are however, further requirements for the imaging in particular with regards to reproducibility, which has direct implications for the ability to assess smaller changes in the RV function. Based on the reproducibility values presented earlier [**I**], tissue Doppler echocardiography does not seem to be particularly useful in this regard as changes ranging from 25%-79% are needed to measure effect of treatment, but the technology could still be useful for scientific purposes in monitoring treatment effects and prognostication in groups.

The prognostic importance of variables derived from tissue Doppler echocardiography can be seen individually, or, more appropriately, as the incremental prognostic effect of this modality, i.e. the prognostic information gained from the tissue Doppler echocardiography as an adjunct to evaluation of existing risk factors. Prognostic information is relevant not only in establishing new risk factors for improving risk stratification of patients, but is also important from a scientific standpoint as 'proof of concept' of the pathological mechanism shown by use of the modality.

In the following sections the current knowledge of the diagnostic and prognostic importance of RV tissue Doppler echocardiography is reviewed, dividing diseases in which it has been applied into groups determined by predominant mechanism as seen in the previous section in the present thesis, acknowledging that a considerable overlap in the end-stage of most diseases exists.

From the studies in normal populations in different age groups, it is known that age and gender differences in tissue velocity measurements and derived parameters are negligible. Although adjustments for these two confounding factors are usually performed, adjustments for potentially confounding co-existing diseases with a direct impact on mortality or RV deformation are more important. Therefore special emphasis will be placed on data from multivariable modelling of the risk factors

DISEASES ASSOCIATED WITH RIGHT VENTRICULAR PRESSURE OVERLOAD

The clinical manifestations of RV pressure overload can be separated into two groups: acute pressure overload in patients with previously normal pulmonary circulation and chronic pressure overload resulting in activation of several adaptive mechanisms. These two entities have distinct hemodynamic characteristics and will be discussed separately.

Acute RV pressure overload

The RV adapts poorly to abrupt increases in RV afterload as in pulmonary embolism, whereas significant remodeling occur with chronic progressive pulmonary hypertension. The clinical features of severe pulmonary embolism includes hypoxia which is thought to reflect ventilation-perfusion mismatch of the over-perfused non-obstructed segments and in some patients the increased RV pressure can cause a patent foramen ovale (estimated prevalence: 20-33 % [82,83]) to open resulting in right to left shunting [84]. It can be speculated that the hypoxia induced pulmonary vasoconstriction, known as the von Euler-Liljestrand mechanism [85], would to some extent improve the matching of flow and ventilation, but the obstruction occurs at a pre-capillary level and the widespread obstruction may exceed the capacity of this reflex. Vasoconstriction in pulmonary embolism has been widely studied and has been the target of therapeutic interventions, but its role in the hemodynamics of acute pulmonary embolism is still unclear, although some authors argue that vasoconstriction is a significant entity in acute RV failure in these patients [86]. Experimental studies have investigated the potential benefit of acute pulmonary vasodilatation, but it has yet to be implemented as a first line site of therapeutic intervention [87].

Another consequence of the increased RV pressures is rightward shift of the intraventicular septum causing LV filling to decrease. These changes initiate a circulus virtiosus of reduced cardiac output, myocardial ischemia and RV failure. Previous invasive studies have found that in patients with acute pulmonary embolism pulmonary arterial pressure was increased only when ≥ 30% of the vascular bed was obstructed and that mean RV pressure never exceeded 40 mmHg in these patients [88].

Echocardiographic findings in acute pulmonary embolism reflect these hemodynamic changes: RV dilatation and increase in tricuspid regurgitation due to RV dilation and increased systolic RV pressures [89,90]. The pulmonary flow pattern is frequently changed with shortening of pulmonary acceleration time of the RV outflow, defined as the time from onset of flow to peak flow velocity [91]. Another feature of pulmonary hypertension is mid-systolic deceleration of the flow resulting in partial pulmonary valve closure [92], sometimes referred to as a 'spike & dome' pattern. Retrospective data have shown that, compared to other types of pulmonary hypertension, this feature is more pronounced in patients with acute or chronic thromboembolic pulmonary hypertension, in particular where proximal emboli are present [93]. Hemodynamic explanations for this finding include changes in timing of the reflection of the pressure wave and in pulmonary vascular elastance [94].

RV systolic dysfunction is present in up to one third of the patients presenting with acute pulmonary embolism [95-99] and associated with adverse outcome [96-100]. Presence of RV dysfunction was one of the inclusion criteria in the landmark trial of trombolysis in non-massive pulmonary embolism [95] and may be considered as part of the indication for thrombolytic therapy of pulmonary embolism in these patients [87]. However presence of

RV dysfunction has been reported based on a variety of echocardiographic findings, including signs of RV dilatation, leftward septal shift, Doppler echocardiographic signs of increased RV systolic pressure and semi-quantitative wall motion scoring, yet there is still a lack of consensus on how RV dysfunction should be determined in acute pulmonary embolism [87].
A more quantitative approach was proposed by McConnell et al, 1986, who elegantly showed that mid wall RV dysfunction with preserved basal and apical wall radial motion was a specific feature of patients with pulmonary embolism [101]. 'The McConnell sign' as this finding was subsequently called, could theoretically be quantified by tissue Doppler based analysis of the RV free wall deformation. And indeed, I was able to demonstrate decreased mid wall strain, which resolved after thrombolysis in 3 patients with massive pulmonary emboli [102].
Echocardiography has only a limited role in the early diagnostic management of patients suspected of pulmonary embolism. The proposed features of acute RV overload have low negative predictive values in general, although shortened pulmonary acceleration time and presence of the McConnell's sign have been reported to be highly sensitive parameters [91,103].
All previous studies of the potential of acute echocardiography in the early management of patients with established or with clinical suspicion of pulmonary embolism have therefore been based on 2D and Doppler echocardiographic technologies only, and had yet to be proven to be suitable for clinical use in non-selected patients [91,104-108]. Therefore, tissue Doppler echocardiography of the RV and its potential for direct assessment of RV myocardial performance could increase the diagnostic potential in this setting.
In 300 consecutive patients suspected of first non-massive pulmonary embolism, I studied the diagnostic information from quantitative measures of RV systolic function, including other known Doppler and 2D echocardiographic measures of RV pressure load using planar ventilation/perfusion scintigraphy as diagnostic standard [**IV**]. Data were available for analysis in 283 patients after exclusion of patients predominantly for insufficient quality of the scintigraphy, N=13 (4%). Patients with pulmonary embolism were similar to patients without scintigraphic signs of thromboembolism with regards to symptoms and clinical presentation. Compared to patients with normal scintigraphies, patients with pulmonary embolism had RV dilatation, increased RV systolic pressure and shortened acceleration of the pulmonary outflow, as well as evidence of decreased global longitudinal function as estimated by tricuspid annular plane systolic excursion (TAPSE) [**IV**]. Regional RV function was assessed by strain in the basal and mid part of the RV, and mid wall longitudinal strain was significantly reduced in patients with pulmonary embolism compared to patients with no signs of pulmonary vascular obstruction, see Figure 5.

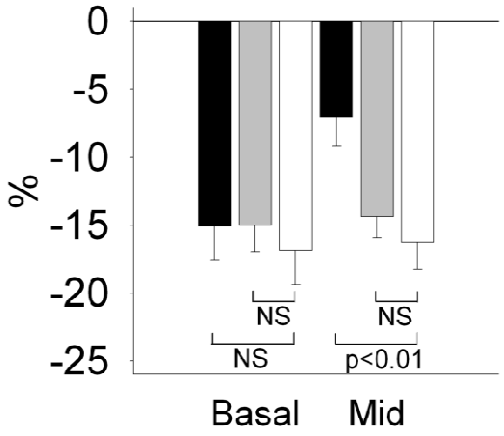

Figure 5
End-systolic strain of basal and midsegments of RV free wall by Doppler tissue imaging (TDI) data presented in categories of pulmonary embolism (black), indeterminate (gray), or normal (white) V/Q scintigraphies. Error bars, SE. NS, not significant. Adapted from Kjaergaard et al. J Am Soc Echocardiogr 2006; 19:1264-1271.

Mid wall RV strain was found to be a significant predictor of pulmonary embolism on univariate analysis, OR=1.03 per percentage point, (95% CI: 1.01-1.05) with an optimal cut-off of -14% on ROC analysis. In multivariate models D-dimer concentration, electrocardiographic signs of RV overload and acceleration time of the RV outflow were independent predictors of pulmonary embolism, while mid wall systolic strain, TAPSE or 2D echocardiographic measures of the RV did not add significantly to the model [**IV**]. These findings underline the use of echocardiography in the initial evaluation of patients suspected of pulmonary embolism, whereas the use of deformation imaging could be limited to patients in whom the diagnosis is confirmed.
Later studies have confirmed that a reduction of mid wall systolic strain does occur in patients with acute pulmonary embolism [109,110], and that similar findings although less pronounced can be seen in patients with pulmonary hypertension from various etiologies [111]. Global longitudinal systolic velocities are also reduced in patients with acute pulmonary embolism and in patients with pulmonary hypertension [112-116].

The invasive studies by McIntyre et al, 1971 showed that less than 30% obstruction of the pulmonary vascular bed does not consistently increase pulmonary pressure [88], and that a indirect relation between extent of perfusion defects and RV stroke volume exists [117]. A 20%-30% perfusion defect threshold for hemodynamic changes with pulmonary embolism was later confirmed [118,119], while others have disputed such a relation [120].
To further investigate the relation of mid wall systolic strain and acute RV pressure load, the population studied was stratified into the following groups: >25% (N=24), 25-49% (N=23) and ≥ 50% obstruction (N=11) of the pulmonary vascular bed by scintigraphy and compared to an age and gender matched group of patients with normal ventilation/perfusion scintigraphies (N=58).

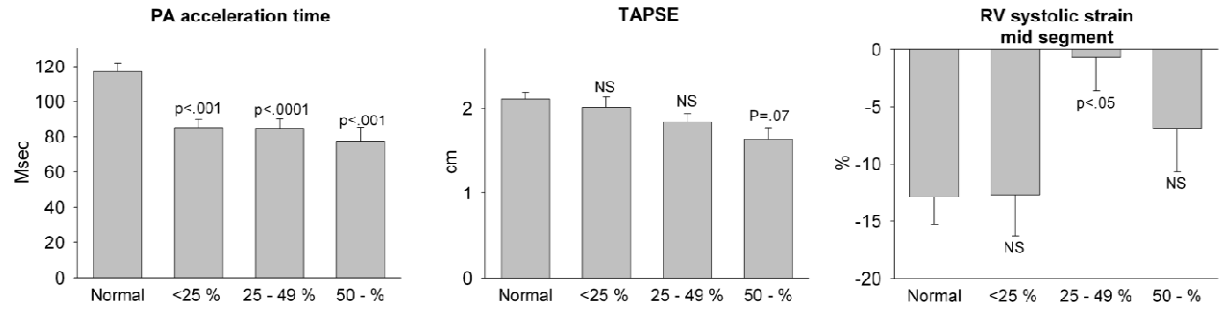

Figure 6
Mean values of acceleration time of the RV outflow (left panel; PA, pulmonary artery), global RV systolic function (middle panel, TAPSE; tricuspid annular pane systolic excursion) and mid wall systolic strain of the RV free wall (right panel) in patients with scintigraphically proven pulmonary embolism by degree of obstruction of the vascular tree, compared to patients with normal scintigrams. Error bars, SE. NS, not significant.
Adapted from Kjaergaard et al, Eur J Echocardiogr 2008; 9:641-645.

It can be appreciated from Figure 6 that the acceleration time of the RV outflow is shortened regardless of extent of perfusion defects in perfusion scintigraphies, whereas global RV longitudinal motion by TAPSE is reduced in patients with large emboli only. While not as sensitive as the acceleration time, the mid wall systolic strain of the RV is decreased with moderate extension of perfusion defects [**V**]. Therefore the study has shown that reduced mid-wall strain in patients with confirmed acute pulmonary embolism can be used as a marker of significant pulmonary embolism which may prove to have therapeutic implications. The study is also consistent with the 'McConnell-sign' of mid-wall failure in pulmonary embolism [101].

Monitoring treatment effects in diseases associated with right ventricular pressure overload

The natural history of patients with acute pulmonary embolism has been evaluated in a few studies. The obstruction of the pulmonary vascular bed resolves to a large extent in 1-2 months [121], and does not seem to be accelerated by the initiation of heparin at time of diagnosis [122]. The pulmonary pressure increase seen with RV outflow obstruction seems to resolve within the same time period [121,123], and improvement in measures of global RV ejection fraction are correlated with the relief of the outflow obstruction [121]. Interestingly, the apical segments seem to recover slower than the basal myocardial velocities, and in general parameters associated with global or regional RV function do not normalize until 6 months from the event [121]. My findings in the 1-year follow-up of 41 patients surviving the acute pulmonary embolism are in agreement with these findings [**VI**].

As a treatment option for pulmonary hypertension phospodiesterase-5 inhibition has become increasingly studied in the

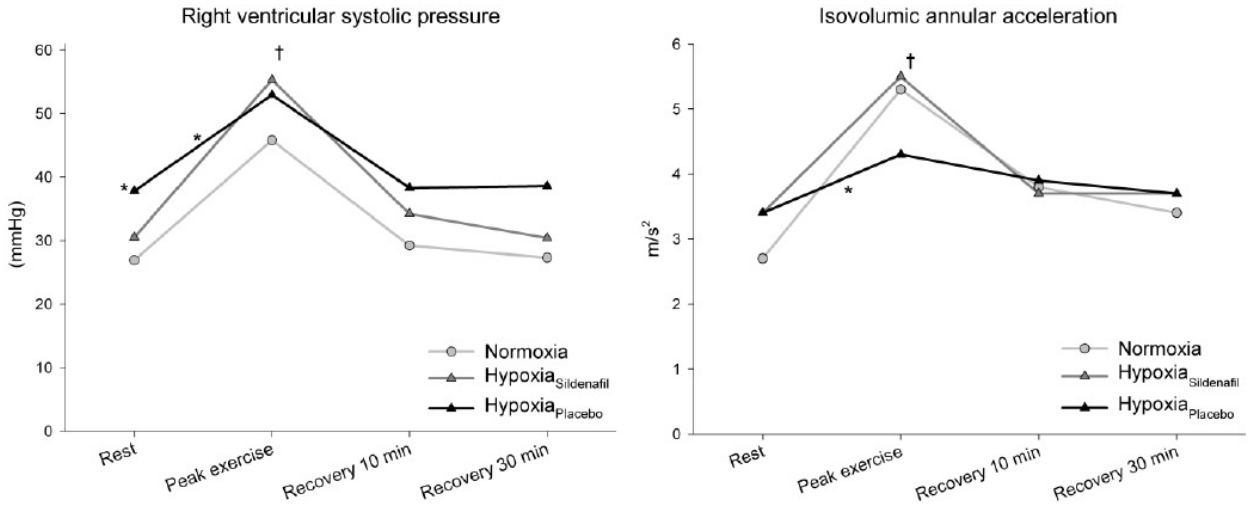

Figure 7
Mean values of estimated right ventricular systolic pressure (mmHg, right), and isovolumic acceleration (IVA, left), during the phases of rest, peak exercise, recovery at 10 min, and recovery at 30 min following the peak exercise in all three experimental conditions. Linear interpolation between these phases shown as lines; slopes of the lines were tested as the interaction term of the phase and experimental condition, see legend. * $p<0.05$ compared to values in normoxia in a given experimental phase, or slope of the line, † $p<0.05$ for the effect of peak exercise, as compared to other three phases.
Adapted from Kjaergaard et al. Eur J Appl Physiol 2007;102:87-95

setting of chronic pulmonary arterial hypertension [124], and thus a potential improvement of RV pressure overload could be anticipated. Phospodiesterase-5 inhibitors have also been shown to selectively reduce pulmonary vascular resistance in hypoxia induced pulmonary hypertension [125]. Sildenafil is the most studied phospodiesterase-5 inhibitor in this setting and has been shown to decrease pulmonary pressures in hypoxia and to increase exercise capacity [126-128], but the impact of hypoxia on RV function has not been fully established and the studies on RV deformation differ [76,**III**].
I studied the effects of hypoxia on RV function and symptom limited exercise in hypoxia in a double-blind placebo controlled experiment of 100 mg sildenafil vs. placebo in 14 healthy subjects. As expected, hypoxia was associated with an increased estimated pulmonary systolic pressure, which further increased with exercise. Consistent with earlier findings Sildenafil significantly reduced pulmonary pressure at rest [76,126,127,129], whereas no effect was seen at peak exercise, Figure 7 [**VII**].

IVA as measure of global RV contractility was increased at peak exercise in normoxia compared to rest, was unchanged with peak exercise in hypoxia and the response to exercise was normalized by Sildenafil, Figure 7. At rest in hypoxia, peak annular systolic velocity with sildenafil was increased compared to normoxia, whereas no differences between groups were seen at peak exercise. These results are not fully consistent, but it is hypothesized that sildenafil could have a direct effect on RV contractility at rest [VII]. A direct effect of sildenafil on RV contractility has also been suggested in a recent animal study [130].

Prognostic importance in diseases associated with right ventricular pressure overload

While several studies have confirmed the association of RV dysfunction and mortality or adverse events, very few studies have applied quantitative measures in the assessment of RV function. Different definitions of RV dysfunction in pulmonary embolism have been applied, including RV enlargement, hypokinesis of the free wall by semi-quantitative four-level scores (often reported dichotomized) , leftward septal shift or evidence of pulmonary hypertension [95,97,99,100,131-133]. Furthermore studies have shown that RV dysfunction as estimated by TAPSE or area change resolved gradually over a period of up to six months from the diagnosis [121]. In accordance with this, patients with large pulmonary embolism, defined as obstruction of ≥ 50% of the pulmonary vascular bed, more frequently have RV dysfunction and have an increased mortality in the first month. After that the mortality is similar to patients with smaller pulmonary embolism [134].
In the previously mentioned prospective study of 300 consecutive patients suspected of their first acute pulmonary embolism, I evaluated the incremental prognostic value of quantitative measures of the impact of PE on RV hemodynamics over a median follow-up time of 3.1 years [**VI**]. Overall the acceleration time of the pulmonary outflow, previously shown to be shortened in patients with pulmonary embolism [91] and related to mean and systolic pulmonary pressure [135], was found to be an independent predictor of mortality in the entire population studied [**VI**]. In the sub-group where pulmonary embolism was confirmed, longitudinal systolic motion, TAPSE as well as basal systolic strain were univariate predictors of the adverse events (death or heart-failure related hospitalization), while LVEF and acceleration time of the RV outflow were predictors in multivariable analysis, Table 3.
Peak RV systolic annular velocity measured by pulsed wave tissue Doppler was also predictive of events, HR=0.86 (0.76-0.98) per cm/s, p=0.02.
Echocardiographic markers of increased mortality in chronic pulmonary arterial hypertension include pericardial effusion and the myocardial performance index [136,137]. A recent study with a more quantitative approach in the analysis of RV systolic longitudinal motion found that TAPSE was an independent predictor of survival [138].

DISEASES ASSOCIATED WITH RIGHT VENTRICULAR MYOCARDIAL DYSFUNCTION

Diseases with an isolated effect on RV myocardial function include ischemic heart disease with RV infarction and some rarer types of primary or secondary cardiomyopathies, where the RV is predominantly involved.
In RV infarction, usually defined by presence of ST segment elevation in right precordial lead (V_{4R}) on ECG, the patient often presents with hypotension, clear lung fields and elevated jugular

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
RV end-diastolic diameter (cm)	1.09 (0.62–1.88)	NS		
RV to LV diameter ratio	3.61 (1.01–12.9)	<0.05		NS
TR maximum pressure gradient (per 10 mmHg)	1.24 (0.87–1.76)	NS		
PA acceleration time (per 10 ms)	0.84 (0.70–1.02)	0.08	0.78 (0.62–0.99)	0.04
RV fractional shortening (%)	1.00 (0.96–1.05)	NS		
RV outflow tract fractional shortening (%)	0.96 (0.93–1.00)	0.03		NS
TAPSE (cm)	0.39 (0.16–0.95)	0.03		NS
RV peak systolic strain, basal segment (per %)	1.03 (1.00–1.05)	0.03		NS
RV peak systolic strain, mid-segment (per %)	0.99 (0.97–1.01)	NS		
LV ejection fraction (per 10%)	0.55 (0.35–0.86)	0.008	0.42 (0.26–0.68)	0.0007
Presence of RV strain on ECG[a]	1.08 (0.45–2.58)	NS		

Table 3
Univariate analysis of baseline echocardiography and the relation to event-free survival (all-cause mortality or heart failure related hospitalization) in 58 patients with first non-massive pulmonary embolism. Multivariate model included parameters with a P-value <0.1 in the univariate analysis, and age and sex. RV, right ventricular; LV, left ventricular; TR, tricuspid regurgitation; PA, pulmonary artery; TAPSE, tricuspid annular plane systolic excursion. [a] Defined as presence of $S_IQ_{III}T_{III}$ pattern or negative T-wave in V_1–V_3.
From Kjaergaard et al, Eur J Echocardiogr 2009;10:89-95

pressure, and signs of RV dysfunction on echocardiography [139]. This type of myocardial infarction is associated with increased mortality [140] and calls for a different initial management strategy to maintain cardiac output until revascularization can be performed [141].
Proximal lesions of the right coronary artery in acute myocardial infarction are associated with decreased systolic RV annular motion and velocity [142], and annular motion and velocities are reduced in inferior myocardial infarctions with RV involvement [143-146]. Sevimli et al, 2007 showed that regional RV systolic strain and SR are reduced in patients with RV involvement in inferior myocardial infarction [147].
Impaired RV annular velocities and marginally decreased SR and strain has been reported in patients with diabetes independent of co-existing arterial hypertension and independent of degree of glycemic control [148]. Whether these findings can be attributed to the controversial existence of diabetic cardiomyopathy or are the result of sub-clinical ischemic heart disease remains to be determined.
Arrhythmogenic Right Ventricular Cardiomyopathy is an example of a primary cardiomyopathy, thought to affect the RV myocardium in particular, and is characterized by localized myocardial fibro-fatty replacements, causing the two predominant features of the disease: ventricular arrhythmias or sudden death and progressive RV failure [149-151]. About 50% of cases have a familial background with an autosomal dominant inheritance and several genetic substrates for the disease has been identified [152]. ARVC is a syndrome with diagnostic criteria proposed by McKenna et al, 1994 [153], allowing for some variation in the phenotype in these patients [154].
Several echocardiographic features of ARVC have been shown [155.156], but the diagnostic criteria include only signs of global or regional RV dilation, aneurysms or reduced RV systolic function. Since the disease is characterized by localized fibro-fatty replacements, regional myocardial dysfunction could potentially be an important modality in the diagnosis of sub-clinical disease or for the screening of a healthy family. Earlier reports had identified a modest reduction in systolic RV annular excursion and velocities [157], and two case reports in patients with advanced disease had shown decreased regional deformation [158,159]. As no studies of the diagnostic potential of echocardiographic deformation analysis had been reported, I performed a study in a population of 20 patients with confirmed ARVC, the majority of whom had no heart failure symptoms [**VIII**]. TAPSE and RV annular velocities were significantly reduced compared to an age and sex matched healthy control group, but the mean values in the ARVC patients were still within normal range. Tissue Doppler derived regional myocardial velocities and strain were significantly reduced, with considerable overlap between groups, see Figure 8.

The variation found, i.e. the large variation within the groups and the relatively small differences between the ARVC and in the control group, would seriously limit the applicability of the technology as a screening tool for ARVC in individual patients. Other modalities such as 3D echocardiography or analysis of biomarkers of heart failure (atrial and brain natriuretic peptides) did not prove to be an attractive alternative in our experience either [**VIII**].
Later in 2007 Prakasa et al published their data on the diagnostic value of tissue Doppler echocardiography and deformation analysis in the basal RV segment of 30 patients with ARVC, the majority of whom were symptomatic. In that study greater differences and less variation in measures of deformation between patients with ARVD and controls was reported. The authors concluded that Tissue Doppler Echocardiography and deformation analysis could have potential clinical value in the assessment of patients with suspected ARVD [160]. Teske et al also found a considerable overlap in measured strain values of RV free wall in patients with ARVC and normal controls, but suggested that an improved diagnostic performance if the lowest value of strain in the three RV segments was used [59]. These studies however, have not provided data that convincingly show that tissue Doppler derived measures of RV function can be of diagnostic value in these patients, particularly in screening for ARVC.
Monitoring treatment effects in diseases associated with right ventricular dysfunction
In patients with severe heart failure, relief of the RV afterload due

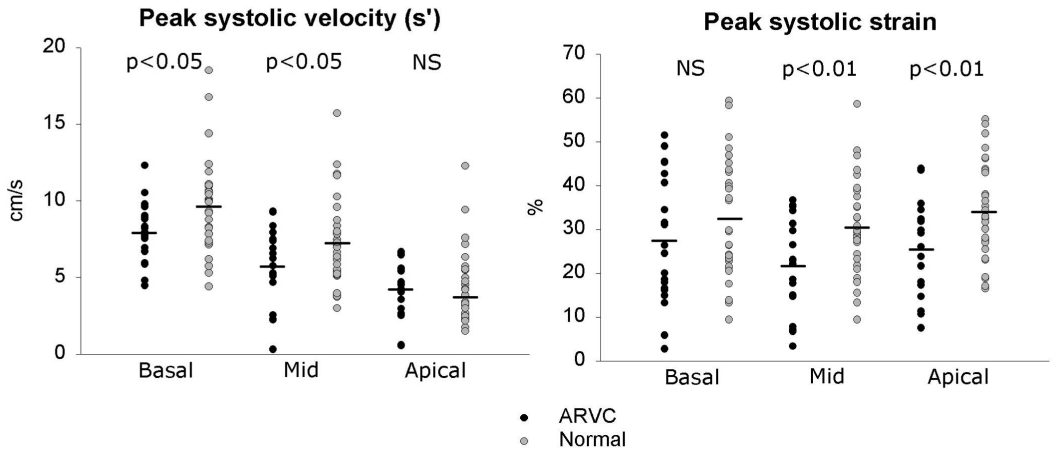

Figure 8
Peak systolic velocities (left) and numerical strain, ie, local deformation (right) of right ventricular (RV) free wall by Doppler tissue imaging in patients with arrhythmogenic RV cardiomyopathy (ARVC) (black dots) compared with healthy age- and sex-matched control subjects (gray dots). Horizontal bars, Mean values.
From Kjaergaard et al.J Am Soc Echocardiogr 2007;20:27-35.

to backward failure and increasing pulmonary artery pressures remains to be thoroughly investigated, although some encouraging results have been published. In 2007, Lewis et al reported that Sildenafil in patients with severe left heart failure was associated with improvements in cardiac output and a reduction in pulmonary artery pressures at rest and during exercise [161]. A post hoc analysis revealed that the beneficial effects including improvement in RV ejection fraction were greater in the subgroups with resting mean pulmonary artery pressure of >25 mmHg [161]. A subsequent randomized study in 34 patients confirmed the beneficial effects on exercise capacity in this subgroup and found fewer heart failure related hospitalizations [162]. Recent reports have shown a sustained response of sildenafil on exercise capacity [163,164]. No data on the impact on mortality are available, but several randomized clinical trials are ongoing.

Prognostic importance in diseases associated with right ventricular dysfunction

Pulmonary hypertension as a complication of LV, pulmonary or systemic diseases is well-known, and is usual associated with an adverse outcome. And although pulmonary hypertension will result in RV dysfunction in late stages, previous studies have illustrated an independent prognostic importance of RV dysfunction [165]. To the best of my knowledge, no studies have investigated the prognostic importance of tissue Doppler based assessment of RV dysfunction in heart failure or other diseases associated with RV dysfunction in adults without congenital heart disease.

The prognostic importance of TAPSE as a measure of global longitudinal displacement of the RV has been evaluated in a sub-study performed in the screenings database of a multi-centre randomized trial, the Echocardiography and Heart Outcome Study [166]. In 817 patients admitted and treated for heart failure reduced TAPSE, defined as TAPSE <14 mm, was associated with a significantly higher mortality than patients with TAPSE ≥ 14 mm [167]. Multivariable analysis demonstrated that TAPSE was an independent predictor of mortality, and, interestingly, that LV ejection fraction had no independent prognostic value when TAPSE was included in the model [167]. These results are thus in agreement with previous studies in heart failure patients [168,169] and the prognostic importance of RV systolic function assessment in heart failure is independent of the degree of pulmonary hypertension [165,170].

In patients with acute inferior myocardial infarction, the peak systolic RV annular plane velocity is a predictor of adverse events [145], likely due to the fact that it is marker of RV involvement. In heart failure patients with reduced LVEF, reduced longitudinal RV motion or velocity of the tricuspid annular plane is associated with an adverse prognosis [168,171,172], and a reduced RV ejection fraction has been shown to be independent of degree of pulmonary hypertension in symptomatic HF patients with reduced LV ejection fraction [165]. Analysis of tissue Doppler derived measures of contractility (IVA) have also been shown to have prognostic importance [172].

Diseases associated with right ventricular volume overload

Volume loading of the right ventricle is a feature of many congenital heart diseases, which are often associated with other cardiac abnormalities, making specific assessment of the consequences of volume loading in the normally structured heart difficult. Diseases associated with acute volume overload are rare, for example traumatic right heart valve ruptures or endocarditis, and thus not well suited for studies. Long-standing exposure to volume overload of the RV exists in congenital heart diseases, including ventricular and atrial septal defects or is an intended consequence in the repair of congenital heart diseases with pulmonary stenosis or pulmonary atresia [173]. The echocardiographic findings in these patients include progressive RV dilatation and RV dysfunction [174]. Another echocardiographic finding is visualization of the leftward septal shift which has been shown to be present predominantly in end-diastole in volume overload as intraventricular pressures normalize or at least equalize during systole. This distinctive feature of volume overload was first described and elegantly quantified by Ryan et al in 1985, also showing that in the pressure overloaded heart the septal shift is present in diastole as well as in systole [175].

After successfully implementing surgical correction of ToF in early childhood assuming that chronic pulmonary regurgitation would be well tolerated, several patients have needed repeated corrective surgery for the pulmonary incompetence. While percutaneus valve replacement seems to be an attractive alternative to conventional valve replacement [176], the issue of timing intervention before irreversible RV failure has occurred is still relevant. Recent studies have aimed at establishing ideal thresholds for pulmonary valve replacement in patients with repaired ToF [177], but reliable echocardiographic markers of imminent RV failure have yet to be identified.

Tissue Doppler based assessments of longitudinal RV function have been undertaken in previous studies all showing reduced peak systolic velocities in asymptomatic patients after ToF repair [178-185] and that the reduction in longitudinal motion or velocity is correlated to the degree of pulmonary regurgitation after ToF repair [37,185]. Since these patients have undergone open heart surgery, some of the reduction in longitudinal motion could be attributed to the effects of pericardiectomy [186], corresponding to patients having lower values of longitudinal motion after surgical closure than following percutaneus closure of atrial septal defect (ASD) [187]. Studies in patients with atrial septum defects have shown less consistent results, some have shown an increased RV annular velocity, likely to be related in part to the increased stroke volume [188,189]. Therefore differences in the background of volume overload and previous open heart surgery seem to be important factors in the assessment of RV function by longitudinal RV annular motion.

SR and strain have not been applied in the studies of these diseases, apart from one study finding that SR and strain are reduced in patients after surgical repair of ASD and only to a minor extent in patients following device closure [187]. 2D strain as an alternative method for deformation analysis showed significantly reduced strain values postoperatively while SR was unchanged, corresponding to previous observations that strain is not entirely preload independent, whereas SR may be more so [190]. IVA has been applied in a few studies, in which IVA seemed to be preserved in patients with ASD [188], whereas IVA was reduced in patients in patients with repaired ToF [180,191].

For the assessment of the isolated effects of volume loading, the majority of these studies are not ideal due to concomitant morphological abnormalities of the heart, and because the intervention occurs in a fully adapted or even failing heart. The ideal situation would be induction of volume overload in an otherwise normal heart to observe adaptive changes, as well as response to intervention after remodeling. For that purpose, animal models have been successfully applied. To assess the effect of acute volume load as with pulmonary regurgitation I used a porcine animal model, in which severe, 'free' pulmonary regurgitation

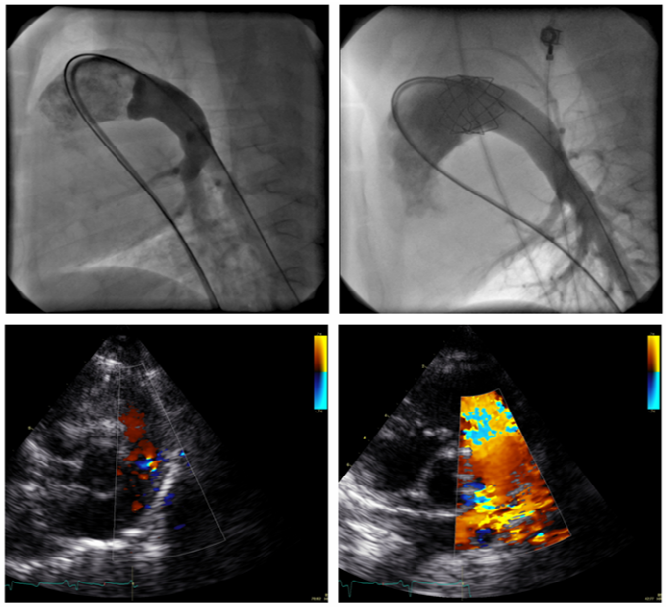

Figure 9
Representative examples of pulmonary angiography performed before (left) and after (right) induction of severe 'free' pulmonary regurgitation. Lower panels are corresponding color Doppler echocardiographic images of the pulmonary regurgitant flow.
From Kjaergaard et al. Eur J Echocardiogr 2010 Jan;11(1):19-26.

was induced by percutaneus insertion of a 22 mm stent in the pulmonary valve orifice in 32 piglets, Figure 9.

Volume overload of the right ventricle was associated with abrupt RV dilation and a small increase in heart rate indicating that the adaptation and maintenance of cardiac output is achieved mainly by an increase in stroke volume and to a small extent via an increase in heart rate [**IX**]. Interestingly no changes in global RV longitudinal motion or RV ejection fraction were seen implying that the end-systolic and end-diastolic volumes increased similarly and thereby significantly increased RV stroke volume, with no signs of global RV failure present. Regional RV systolic deformation parameters were reduced, but the reduction was not statistically significant, Figure 10.

No changes in peak systolic annular velocities or IVA were seen either, suggestive of relatively preserved contractility [**IX**].

The effects of chronic pulmonary regurgitation has previously been studied by Kuehne et al, 2003, showing that pigs had dilatation of RV the day after induction of PR by placement of a nitinol stent in the pulmonary valve orifice, and this dilatation further

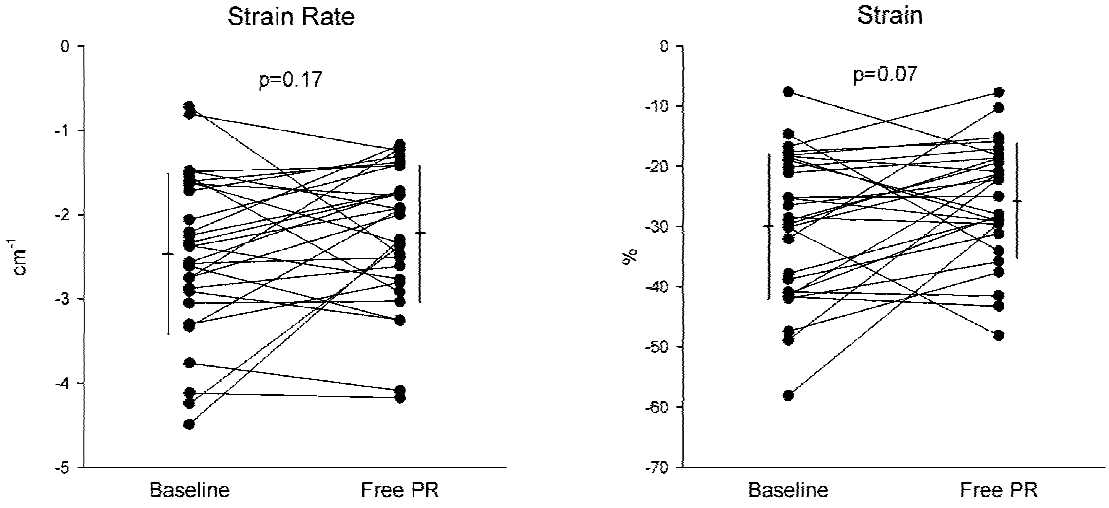

Figure 10
Longitudinal strain rate and strain as tissue Doppler derived measures of regional contractility and deformation in basal segment of RV free wall before and after induction of severe pulmonary regurgitation by percutaneous insertion of a stent in the pulmonary valvular orifice. Mean±SD are illustrated by horizontal lines and vertical error bars, respectively.
Adapted from Kjaergaard et al. Eur J Echocardiogr 2010;11: 19-26

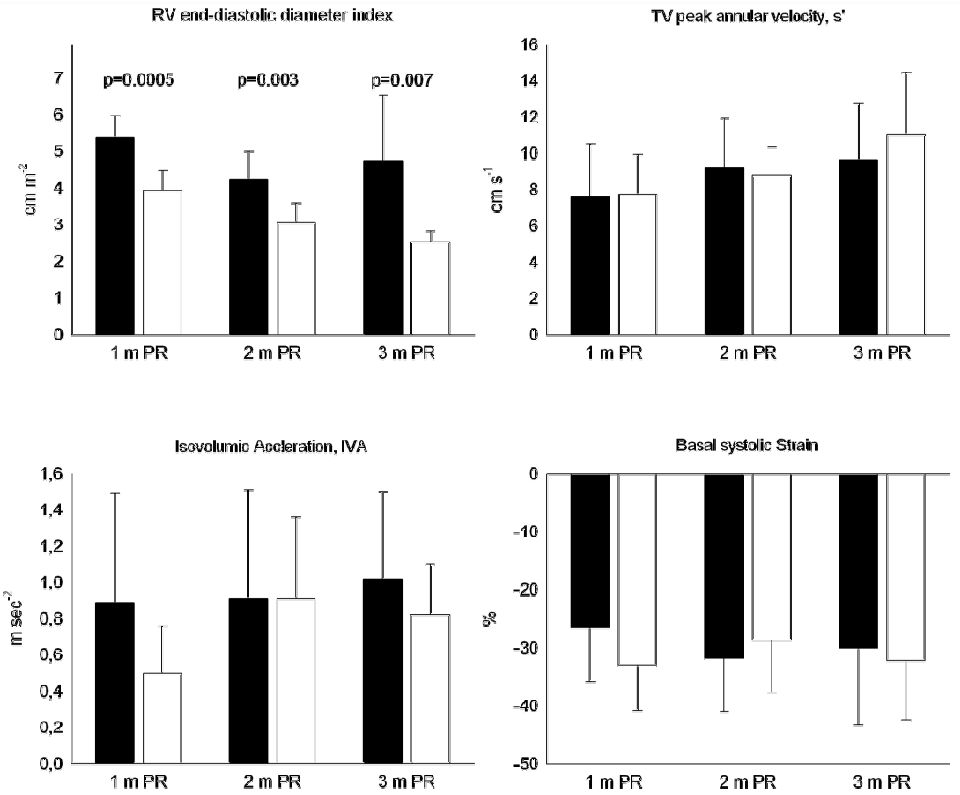

Figure 11
Mean values of RV end-diastolic diameter indexed to BSA, peak tricuspid annular plane systolic velocity (s'), Isovolumic acceleration (IVA) and peak systolic strain in pig with 1, 2 or 3 month (m) of severe pulmonary regurgitation (PR) induced by a stent in the pulmonary valve orifice (black bars), compared to control animals at similar time point (white bars). Error bars, SD.
Adapted from Kjaergaard et al. Eur J Echocardiogr 2010;11: 19-26.

increased after 3 months follow-up [192]. RV myocardial contractility was assessed by conductance catheters at rest and during dobutamine stress, and the study showed that while contractility at rest was similar to a group of control animals, the response to pharmacological stress was blunted resulting in reduced dP/dt_{max} and maximal elastance (E_{max}) [192].
In a porcine model using echocardiographic indices of myocardial performance I performed a study aiming to look at temporal changes in measures of contractility over time, after percutaneously inserting a stent in the pulmonary valve orifice similar to the model described above, Figure 9. After induction of free pulmonary regurgitation the animals were randomized into three groups and followed for one, two or three months, respectively. As a comparison group, nine animals that underwent right heart catheterization were included examined using serial monthly echocardiographic examinations.

As can be appreciated from Figure 11, RV dilation is present already after one month, and to an extent similar to that found immediately after induction of free PR [IX]. No difference in global RV longitudinal function is seen and measures of global and regional contractility showed no differences compared to the control group [X]. In conclusion, free PR seem to be well tolerated, and even in the setting of significant RV remodeling no signs of decreased myocardial contractility can be found at rest by tissue Doppler echocardiography after 3 months of free PR. These findings are in agreement with a previous study, where decreased myocardial contractility was apparent only during dobutamine stress testing [192]. Previous studies have evaluated the incremental benefit of bicycle stress testing in patients with repaired ToF, finding that these patients have a lower baseline value of peak systolic velocity, as well as a blunted increase during stress testing compared to healthy controls [183], which indicates that stress testing could be a valuable adjunct to the resting echocardiography. However, the effect of Dobutamine or similar drugs could be an increase in RV contractility as well as decreasing RV afterload as seen in pressure overloaded RV [193]. The data from our animal models showed the impact of free PR on RV contractility was low although PR was present for a significant part of the normal lifespan of the animal, and this may indicate that our model was sub-optimal for illustrating the RV failure resulting from chronic volume overload [**X**]. Also differences in response to PR may be different in patients with restrictive RV physiology and patients with normal RV filling [194]. In the case of humans with ToF repaired by a trans-annular patch, several decades may pass before signs of RV failure are present, and therefore extended follow-up in the animal models or development of new models with stenosis preconditioning the RV should be considered for studying the mechanisms of RV failure in chronic volume overload.

Monitoring treatment effects in diseases associated with right ventricular volume overload
Measures of RV deformation and contractility are unchanged before and after percutaneous closure of atrial septal defects [188,195,196], while myocardial velocities may be changed due to

the changes in RV loading [195]. Surgical closure can limit the usefulness of tissue Doppler based assessment of regional deformation [187,196].
Echocardiography is a pivotal examination in the serial follow up of grown-ups with congenital heart disease [174], not least in the group with repaired TOF who do well for many years without signs of de-conditioning [197]. However, chronic PR is associated with progressive RV dilatation and heart failure and the clinician must balance the peri-operative risks of repeated cardiac surgery and limited durability of the prosthetic valves available against the progressive deterioration of the patients, that results in irreversible heart failure [198]. Even though percutaneus pulmonary valve replacement is increasingly available, feasible and has shown excellent results over the last few years [176], indication for intervention still depend largely on clinical status of the patient including exercise capacity, QRS duration, and RV end-diastolic volumes assessed by magnetic resonance imaging [174,177,199-203].
As previously reported, I studied the long-term effects of pulmonary regurgitation in a porcine model, where free PR was induced by percutaneus stenting of the pulmonary valvular orifice at baseline. The animals were then randomized to a follow-up interval of one, two or three months, respectively, before percutaneus pulmonary valve repair (PPVR) was performed. After PPVR, the animals were followed for one month to allow for reverse remodeling and were subsequently euthanized. A control group examined every month served as normal reference [**X**]. I found that long-term PR is associated with RV dilation and increasing leftward septal shift as clear markers of RV volume overload, and that these factors normalized after PPVR. Measures of RV ejection fraction, however, remain unchanged after chronic PR as well as after PPVR regardless of duration of PR [**X**]. Results from the subgroup of animals exposed to three months of free PR are shown in Figure 12.

IVA as a measure of RV contractility has previously been shown to be related to severity of PR in patients with repaired ToF [37], and may thus be an interesting marker of RV dysfunction with potential clinical importance. In our study, however, IVA remained unchanged after long-term PR as well as after PPVR, Figure 12, and even though higher IVA pre-PPVR was associated with a higher risk of incomplete reverse remodeling 1 month following PPVR, this parameter may not be as clinically useful as expected. SR remained unchanged; while a trend towards a reduction in peak systolic strain after PPVR was seen, corresponding to the decrease in volume load [**X**]. A limitation to the model deserves mentioning: no clear signs of RV failure in spite of longstanding significant RV volume overload could be detected, despite the

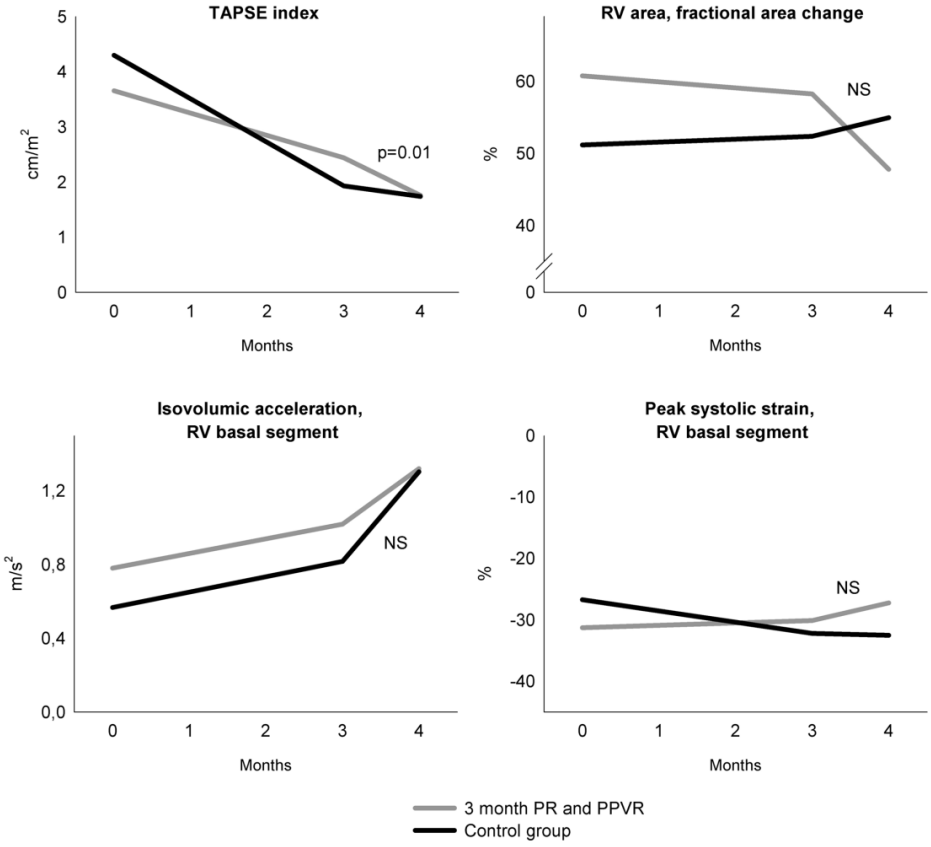

Figure 12
Mean values of Tricuspid Annular Plane Systolic Excursion (TAPSE), fractional area change of RV area (top panels), Isovolumic acceleration and basal peak systolic deformation (strain) (bottom panels) at baseline, after 3 months of free pulmonary regurgitation (PR) and 1 month following after percutaneus pulmonary valve repair. Comparison to a sham operated group of animals (control group) are made, testing differences in response to valve repair.
Adapted from from Kjaergaard et al, Echocardiography 2010

fact that this has previously been associated with decreasing RV function [192]. Repair of PR in ToF is associated with a reduction of RV strain immediately following surgery, which subsequently improves, but strain values remain reduced compared to healthy controls [190]. An improvement in RV free wall strain following PPVR was reported in 10 patients in a recent study of percutaneus pulmonary valve repair in a GUCH population, while strain rate remained unchanged [204], both in agreement with our findings.

Prognostic importance in diseases associated with right ventricular volume overload

Congenital heart diseases associated with chronic volume overload as a result of left to right shunting or (iatrogenic) valvular incompetence, may eventually lead to RV dysfunction, exercise intolerance, arrhythmias, and sudden death [173,174,202]. The importance of maintaining a competent valve has been emphasized, and preservation or reconstruction of pulmonary valve competence at an appropriate time has resulted in hemodynamic improvements of patients with severe pulmonary regurgitation after repair of ToF [198]. RV failure is an adverse sign, and thus usually an indication for intervention [173]. Echocardiography is an essential part of the serial follow-up in these patients, but the potential as a pivotal modality in these patients has yet to be fully established, and thus further research in the echocardiographic markers of impending irreversible RV overload are needed. If able to accurately show signs of imminent RV failure, echocardiography including deformation analysis by tissue Doppler or by speckle tracking technologies could be proven to be valuable adjuncts in the management of these patients.

DIAGNOSTIC AND PROGNOSTIC POTENTIAL OF TISSUE DOPPLER ECHOCARDIOGRAPHY OF THE RIGHT VENTRICLE – KEY FINDINGS

- RV mid wall longitudinal strain and TAPSE are significantly reduced in patients with non-massive pulmonary embolism compared to patients with no obstruction of the pulmonary vasculature. Longitudinal strain or TAPSE however, did not provide additional diagnostic information over conventional echocardiographic parameters in this population.
  Paper IV. Patients suspected of first non-massive pulmonary embolism, N=300
- Extent of pulmonary embolism is inversely related to global and regional longitudinal RV systolic function as estimated by TAPSE and mid-wall systolic strain. RV dysfunction is found only in patients with perfusion defects equal to 25% of the pulmonary vascular tree or more.
  Paper V. Patients with confirmed first non-massive pulmonary embolism. N=58 compared to 58 age and gender matched controls without pulmonary embolism. Subgroups of population presented in paper IV
- While reduced global longitudinal motion of the RV annular plane is associated with adverse outcome, RV free wall strain adds no additional prognostic information over conventional echocardiography either in patients suspected of first non-massive pulmonary embolism, or in patients in whom pulmonary embolism is confirmed. The LV ejection fraction and pulmonary artery flow pattern are independent predictors of outcome in this population.
  Paper VI. Patients suspected of first non-massive pulmonary embolism, N=300, as presented in paper IV.
- RV systolic function as assessed by global longitudinal motion of the RV annular plane (TAPSE) is an important predictor of mortality in patients with heart failure, independent of the degree of pulmonary hypertension and other clinical and echocardiographic variables. Tissue Doppler based measures of RV systolic function in relation to mortality in heart failure remains to be studied, but may prove to be a valuable adjunct to prognostication in these patients, and perhaps even a target for therapy.
- Sildenafil significantly reduces RV pressure at rest in acute hypoxia, while limited effect is seen during exercise. However RV function, as estimated by RV annular IVA during hypoxic exercise, seems to be improved and normalized by sildenafil
  Paper VII. Double blind cross-over trial in healthy subjects. N=14
- RV mid-wall and apical longitudinal strain is reduced in patients with Arrhythmogenic Right Ventricular Cardiomyopathy and no sign of heart failure. The diagnostic application of strain analysis for screening or follow-up in these patients is limited by wide variation in the measurements and a substantial overlap with normal values.
  Paper VIII. Patients with confirmed diagnosis of ARVC, N=20, compared to age and gender matched healthy subjects, N=32
- While volume overload of the RV is associated with significant a change in RV chamber geometry, no change is seen in tissue Doppler based measures of longitudinal deformation or ejection fraction. This may imply that deformation analysis may not be a sensitive marker of RV function or pending dysfunction in acute volume overload by pulmonary regurgitation in normal hearts.
  Paper IX. Porcine animal model of acute 'free' pulmonary regurgitation. N=32 and sham operated controls, N=9
- No changes in measures of longitudinal deformation assessed by tissue Doppler echocardiography occurs with chronic pulmonary regurgitation despite significant changes in RV chamber size. Also after percutaneous insertion of a pulmonary valve no changes in these parameters occur, suggesting a limited sensitivity for assessment of pending RV failure indicative of intervention in chronic pulmonary regurgitation.
  Paper X. Porcine animal model of chronic severe pulmonary regurgitation and corrective valve replacement after 1, 2 or 3 months of pulmonary regurgitation. N=23 in total and sham operated controls, N=9

SUMMARY

This thesis summarizes a series of studies performed in order to assess the clinical usefulness of a novel echocardiographic technology that allows non-invasive assessment of regional right ventricular myocardial velocities and deformation: tissue Doppler echocardiography. While the technology is a promising tool for improving our understanding of right ventricular hemodynamics, several aspects of the technology must be evaluated. The accuracy and reproducibility of the technology is evaluated in vitro, and normal values, impact of changes in loading of the right ventricle, response to exercise and pharmacological pulmonary vasodilatation is established in normal subjects. The diagnostic and prognostic importance of adding tissue Doppler echocardiography to conventional echocardiographic and clinical parameters was evaluated in studies on patients with diseases associated with different modes of impact on right ventricular hemodynamics:

pulmonary embolism, Arrhythmogenic right ventricular cardiomyopathy and pulmonary regurgitation, the latter in an animal model.

The conclusions of the thesis are:

- Color tissue Doppler echocardiography accurately measures velocities, SR and strain in vitro. No systematic bias between ultrasound systems can be found, and accuracy of the measurements is good. However, the reproducibility of measurements in a test-retest design can limit the usefulness of the technology in daily clinical use, as 25% to 80% of change would be needed for the technology to identify a change in individual patients [**I**].
- Normal values of tissue Doppler based measurements of RV regional velocities, SR and strain exist, and apply to both sexes and in all age groups with the exception of slightly decreasing values in strain with increasing age. Increasing preload and afterload changes regional myocardial velocities, but no changes in SR, strain or isovolumic acceleration could be observed [**II**&**III**].
- Tissue Doppler echocardiography of the RV free wall in non-massive pulmonary embolism quantifies degree of RV dysfunction, and supports the existence of the 'McConnell sign' of mid-ventricular RV dysfunction. Echocardiographic signs of RV dysfunction are present if >25% of the pulmonary vascular bed is obstructed. However, Tissue Doppler echocardiography and deformation analysis has no independent value over other clinical and quantitative echocardiographic measures of RV size, pressure and function in these patients [**IV**&**V**].
- Regional deformation of the RV free wall has significant prognostic importance in a population suspected of first non-massive pulmonary embolism, and is significantly associated with adverse events in patients with proven pulmonary embolism, however, it does not add to the information gained from other quantitative echocardiographic measures of LV and RV function and pressure [**VI**].
- Changes in tissue Doppler based measures of RV systolic function can be used to monitor the effect of selective vasodilation by phosphodiestares-5 inhibition in hypoxic pulmonary hypertension and exercise in normal individuals. Phosphodiestares-5 inhibition by sildenafil may predominantly be effective during hypoxia in resting conditions, and may improve the blunted response in RV contractility seen with exercise in hypoxia [**VII**].
- Reduced RV free wall deformation can be quantified by tissue Doppler echocardiography in patients with confirmed Arrhythmogenic Right Ventricular Cardiomyopathy, but the clinical application of the technique may be limited by considerable overlap with normal values [**VIII**].
- Acute RV volume loading in free pulmonary regurgitation is associated with abrupt geometric changes in the RV structure including significant dilatation, but is well tolerated with only mild reduction in measures of global RV systolic function as estimated by 2D echocardiography in an experimental animal model. Regional RV myocardial function is also only mildly reduced. Also no differences in global or regional RV function can be observed after 1-3 months of pulmonary regurgitation [**IX**&**X**].
- Relief of free pulmonary regurgitation by percutaneus pulmonary valve replacement in an animal model is associated with immediate reverse remodeling of the RV. No changes in tissue Doppler based measures of RV contractility can be identified [**X**].

Perspective

The present thesis summarizes a series of studies in the application of an echocardiographic technology in a setting outside of which it was originally intended and validated, namely in the LV. Applying the technology in RV evaluation seemed to be a logical step, and had the potential to overcome some of the challenges conventional 2D and Doppler echocardiography have faced in providing quantitative measures of RV dysfunction in humans. The conclusion based on the thesis, discouraging as it may seem, is that it is unlikely that color tissue Doppler derived measures of myocardial deformation or contractility will have a significant impact on the management of individual patients with cardiac diseases with RV involvement. The diagnostic potential of the technology is not ideal due to the wide variation seen in normal subjects as well as relatively small differences between healthy controls and patients. For follow-up of patients, the sub-optimal reproducibility will limit the sensitivity of the techniques to detect the majority of changes achieved by treatment or induced by the natural history of disease, requiring large changes in these measures before the technique allows for unambiguous detection of response or change in disease.

But despite a seemingly low yield in the clinical application of the technology in individual patients, tissue Doppler echocardiography technology remains a promising tool for improving our understanding of RV hemodynamics in many different settings when groups of subjects are investigated. By the introduction of Tissue Doppler based assessment of myocardial deformation, cardiac imaging clinicians were offered a user-friendly tool for direct, quantitative assessment of human circulatory physiology that has strengthened the field of echocardiography.
Following the introduction of tissue Doppler echocardiography, speckle tracking of the 2D echocardiographic imaging has emerged, which has a high degree of accuracy in in vitro experiments, may have better reproducibility and signal to noise ratio in the LV, but is limited by a lower frame rate [205,206]. A comparative study of tissue Doppler and 2D speckle tracking techniques in the RV found only moderate correlation and relatively wide limits of agreement between the two [57]. Still the combination of the two techniques could improve sensitivity [207].

Future studies

There is still a great deal to be learned about RV physiology and its adaptation to changes in loading and disease. One area of interest is further understanding RV filling, which seems at least as difficult to fully assess as LV filling [208-210], but more knowledge of the diastolic function of the RV will be essential for further improving our knowledge. Secondly, the role of the RV in left heart failure could be further clarified, not only in the setting of backward failure and increased pulmonary pressures as previously mentioned, but also in clarifying the role of the RV function in patients with symptomatic heart failure with bundle branch block often considered for bi-ventricular pacing. The role of the RV in the development of symptoms, potential for predicting the response to therapy and relation of improvement in RV performance to symptoms and potentially to outcome, are interesting topics, which have barely been touched upon in the literature [211].

Yet another field is the understanding the RV hemodynamics during exercise. The wealth of current echocardiographic studies have been performed at rest with the patients examined in static and relatively un-physiological positions, i.e. left decumbent position, which may impact RV hemodynamics systematically and bias our knowledge. The need for redoing a series of basic studies in various diseases under some degree of physiological stress is appearent and for simple comparison studies of the effects of supine exercise versus upright exercise is obvious, preferably including assessment of the interaction of pulmonary function and preferably with the application of valid reference methods, invasive if needed.

Tissue Doppler and echocardiographic techniques for quantitative analysis of myocardial performance still offer advantages over conventional imaging for these purposes. Tissue Doppler has been the first of a series of developmental leaps in the quantification of myocardial (dys-)function, which will likely prove to be essential for the development of our understanding of these mechanisms. The significant prognostic impact of the RV dysfunction in many cardiac diseases calls for studies aimed at specifically improving RV hemodynamics and at present very few therapies for this purpose are available outside the area of pulmonary hypertension.

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