Subclinical left ventricular dysfunction in hypertension and diabetes assessed by tissue Doppler imaging

Niels Holmark Andersen

This review has been accepted as a thesis together with 8 previously published papers by Aarhus University on the 22th of December 2009 and defended on the 16th of April 2010.

Official opponents: Kenneth Egstrup & Per Hildebrandt.

Correspondence: Department of Cardiology, Skejby, Aarhus University Hospital. Brendstrupgaardsvej 100, 8200 N. Denmark.

E-mail: holmark@ki.au.dk

Dan Med Bull 2010; 57: (6) B4150

THE EIGHT ORIGINAL PAPERS ARE:

1. Evaluation of the longitudinal contraction of the left ventricle in normal subjects by Doppler tissue tracking and strain rate
   Andersen NH, Poulsen SH
   J Am Soc Echocardiogr. 2003 Jul;16(7):716-23
2. Influence of preload alterations on parameters of systolic left ventricular long-axis function: a Doppler tissue study.
   Andersen NH, Terkelsen CJ, Sloth E, Poulsen SH
   J Am Soc Echocardiogr. 2004 Sep;17(9):941-7
3. Doppler tissue imaging reveals systolic dysfunction in patients with hypertension and apparent "isolated" diastolic dysfunction
   Poulsen SH, Andersen NH, Ivarsen PI, Mogensen CE, Egeblad H
   J Am Soc Echocardiogr. 2003 Jul;16(7):724-31
4. Diastolic dysfunction after an acute myocardial infarction in patients with antecedent hypertension
   Andersen NH, Karlsen FM, Gerdes JC, Kaltoft A, Bøttcher M, Sloth E, Thuesen L,Bøtker HE, Poulsen SH
   J Am Soc Echocardiogr. 2008 Feb;21(2):171-7
5. Decreased left ventricular longitudinal contraction in normotensive and normoalbuminuric patients with Type II diabetes mellitus: a Doppler tissue tracking and strain rate echocardiography study
   Andersen NH, Poulsen SH, Eiskjaer H, Poulsen PL, Mogensen CE
   Clin Sci (Lond). 2003 Jul;105(1):59-66
6. Left ventricular dysfunction in hypertensive patients with Type 2 diabetes mellitus
   Andersen NH, Poulsen SH, Poulsen PL, Knudsen ST, Helleberg K, Hansen KW, Berg TJ, Flyvbjerg A, Mogensen CE
   Diabet Med. 2005; Sep;22(9):1218-25
7. Effects of blood pressure lowering and metabolic control on systolic left ventricular function in Type II diabetes mellitus
   Andersen NH, Poulsen SH, Poulsen PL, Knudsen ST, Helleberg K, Hansen KW, Dinesen DS, Eiskjaer H, Flyvbjerg A, Mogensen CE
   Clin Sci (Lond). 2006 Jul;111(1):53-9
8. Changes in glycaemic control are related to the systolic function in type 1 diabetes mellitus
   Andersen NH, Hansen TK, Christiansen JS
   Scand Cardiovasc J. 2007 Apr;41(2):85-8

INTRODUCTION

Congestive heart failure (CHF) is a disabling disease with considerable morbidity and mortality rates, despite great advances in heart failure treatment (1;2).

The number of patients with congestive heart failure is rapidly increasing in the western world with a prevalence estimated at 1–2 % and an incidence close to 5–10 per 1000 persons per year (3). The mounting congestive heart failure incidence is closely related to the increasing number of patients with hypertension and diabetes (4). The worldwide estimated number of adults with hypertension was 972 million in 2000; 639 million live in developing countries. By 2025, the total number is expected to increase to 1·56 billion (5). The risk of developing CHF in a hypertensive cohort is about 2-fold in men and 3-fold in women as compared to normotensive individuals (4). Also in population based studies, hypertension is significantly related to development of CHF, accounting for 39 % of cases of CHF in men and 59 % in women (4). A similar exponential increase in type 2 diabetes incidence is evident. According to numbers from the WHO, there will be up to 366 million individuals with type 2 diabetes in 2030.

The prevalence of CHF in a diabetic population is 5-8 fold higher compared to a non-diabetic population (6;7), and the risk of heart failure hospitalization in the UKPDS study was equal to that of non-fatal myocardial infarction, stroke or renal failure (8). Unfortunately, a large number of patients with diabetes mellitus have coexisting hypertension, which significantly increases the risk of heart failure dramatically (9;10).

Hypertension and diabetes are both characterized by long asymptomatic periods, where patients are unaware of their subclinical diseases and thereby remain untreated (11). Recent data derived from the VALUE study showed that hypertensive patients with new-onset diabetes had significantly higher cardiac morbidity, especially increased congestive heart failure incidence, compared to hypertensive patients without diabetes (hazard ratio of 1.43

(95% CI: 1.16 to 1.77))(12). These findings emphasize that hypertensive patients with newly diagnosed diabetes have added morbidity and would benefit considerably from treatment.
However, it is evident that only few of these patients receive recommended treatment, and only a fraction will achieve adequate blood pressure control and normoglycemia (13). For that reason, a large part of these patients are prone to have high incidences of cardiovascular complications, including congestive heart failure (14).
The initial effect of elevated blood pressure, insulin resistance, and hyperglycemia on the left ventricular (LV) function is only sparsely studied, and there may be cardiac functional and structural changes, which support the existence of a subclinical stage of LV dysfunction in patients with hypertension or diabetes.
Recent developments in cardiac imaging techniques, based on tissue Doppler echocardiography, seem able to detect early subclinical changes in LV systolic function in various cardiac diseases. These new echocardiographic modalities may provide an important tool to detect and understand what effects hypertension and diabetes induce on the left ventricular function in the earliest stages of the disease.
The traditional evaluation of left ventricular dimensions and function has been based on 2-Dimensional echocardiography (15). Assessment of systolic function has rested on 2D- modalities like fractional shortening, wall motion index or ejection fraction by Simpson's method of discs (15;16). Whereas spectral Doppler modalities have been a cornerstone in the assessment of diastolic function (17;18).
However, in recent years new imaging modalities have refined non-invasive evaluation of the heart and provided new knowledge about the mechanisms involved in left ventricular function. These new observations have been focused on the fiber orientation of the cardiomyocytes and regional changes in LV function, dependent on different conditions' influence on cardiomyocyte function.
The fiber orientation in the left sided myocardium consists of long axis oriented fibers on the outer and inner layer, whereas the midwall consists of radial oriented fibers. This observation was first described by the famous Danish anatomist Niels Steensen (Observationes Anatomicae, 1662) three centuries ago and relaunched by Streeter in an experimental study on dogs (19).
By the introduction of advanced Magnetic Resonance Imaging (MRI), it became possible to demonstrate the components of systolic and diastolic movement of the left sided myocardium, and to visualize the myocardial fibers structure in humans and document changes in fiber orientation and function in the failing heart (20-22).
Systole consists of a counter directed rotational movement (systolic torsion), a radial shortening combined with a baso-apical long axis shortening (21;23;24), whereas the diastole consists of a counter clockwise rotation and lengthening. This combined twist/untwist provides an efficient function of the left sided myocardium at very low energy expenditure (25;26).
The long axis oriented fibers significantly contribute to the rotation and the baso-apical long axis shortening, whereas the radial and oblique oriented fibers primarily contribute with radial and circumferential shortening (25-27). Consequently, long axis function is not directly evaluated by use of fractional shortening (FS) or LV ejection fraction (LVEF), which primarily depends on the function of the radial oriented fibers (25-27).
However, long axis oriented fibers in the endocardium seem more susceptible to changes in cardiomyocyte function than the radial oriented fibers located in the midwall (28-30). Factors like left ventricular hypertrophy, fibrosis, endo- and subendocardial ischaemia or metabolic changes are all common in patients with hypertension and diabetes, and may all primarily influence function of the long axis oriented fibers in the endocardium.
Therefore, assessment of the systolic function in the long axis plane might be an interesting marker of early deterioration of systolic function in this patient category, which is undetected by conventional echocardiographic methods.
Tissue Doppler echocardiography (TDI), which is a new echocardiographic modality, enables detection of myocardial function in the long axis plane, and provides new information on myocardial function and haemodynamics, which is not possible to obtain by traditional echocardiography. This makes TDI an excellent supplement to traditional measures of left ventricular function.
For that reason, TDI may provide valuable information about subclinical myocardial dysfunction and the relation to common pathophysiological factors seen in asymptomatic patients with hypertension or diabetes.

STUDY AIM

The specific aims of the present thesis were:

To characterize the left ventricular systolic long axis function by tissue Doppler echocardiography in normal subjects, to study the influence from age, gender, and blood pressure, and to assess preload dependency of tissue Doppler derived measures of systolic function.

To examine left ventricular systolic long axis function in patients with essential hypertension and preserved ejection fraction. Furthermore to assess left ventricular systolic long axis and diastolic function in patients with hypertension, suffering from an acute myocardial infarction.

To investigate left ventricular systolic long axis function in patients with diabetes and preserved ejection fraction, and assess the influence from coexisting hypertension, left ventricular hypertrophy and chronic hyperglycemia as well as the effects of blood pressure reduction and improved glycemic control.

METHODOLOGICAL ASPECTS

Participants

Studies I and II consist of 85 normal unmedicated individuals.
Studies III and IV consist of 78 patients with arterial hypertension (40 and 38 patients, respectively), and 38 control patients with myocardial infarction.
Studies V-VIII consist of 143 patients with diabetes mellitus (123 patients with type 2 diabetes and 20 with type 1 diabetes). Thirty-seven of the patients from study VI also chose to participate in study VII.

Patient characteristics

The patients were recruited from the out-patient clinics at the departments of internal medicine in Aarhus, Viborg and Silkeborg, as well as from their general practitioners. Patients with essential hypertension were all recruited from Aarhus Hospital (NBG), whereas patients with hypertension and myocardial infarction were taken from the RESCUE-study (31).
Non-diabetic patients with hypertension fulfilled the criteria's of arterial hypertension according to the JNC VII report (32) or the 2003 ESH guidelines (33).

Antecedent hypertension was defined as such, if the diagnosis was known by the patient, or if the general practitioner or referring cardiologist had indicated a history of hypertension in the admission note (34).
All patients with diabetes mellitus (types 1 and 2) fulfilled the recommended WHO criteria for diabetes (35) upon entering the studies. Patients were classified as normotensive, if their arterial blood pressure from the time of the diabetes diagnosis, had been below 130/85 mmHg at all examinations and they never had been treated with antihypertensive medication.
Diabetic patients with hypertension also fulfilled the hypertension criteria according to the JNC VII report (32) or 2003 ESH guidelines (33).
Albuminuria was classified by assessment of the urine-albumin-creatinine ratio (UACR. Patients were classified as normoalbuminuric, when at least 2 out of 3 urinary UACR's were < 2.5 mg/mmol (men) and < 3.5 mg/mmol (women); as microalbuminuric when their UACR's were between 2.5 and 25 mg/mmol (men) and between 3.5 and 35 mg/mmol (women), and as macroalbuminuric when the UACR's were > 25 mg/mmol (men) or > 35 mg/mmol (women) or dip stick positive proteinuria in at least 2 out of 3 samples)(36). Urinary albumin concentration was determined by an immunoturbidimetric method (Roche Diagnostics, Basel, Switzerland).
All patients were free of any cardiac symptoms (chest pain, dyspnoea) had normal resting ECGs and had no prior history of cardiac disease, except patients from study IV, who all had suffered from a large myocardial infarction.

Measures of glycosylation
In the present studies, the following 3 measures of glycosylation were used.

Fructosamine
Fructosamine was estimated by a commercially available kit, (ABX Pentra fructosamine Montpellier France) based on the tetrazolium method. Serum samples were immediately frozen at -80°C until analysis. Data presented are mean of triplicates and all samples were analyzed in one batch. The intraassay coefficient of variance was less than 5 %. Analyses were done in-house.

Carboxymethyllysine
Carboxymethyllysine- bovine serum albumin (CML-BSA) was prepared according to Reddy et al.(37). The monoclonal anti-CML antibodies (CML-2F8AxB) were identical to the ones described in a previous study (38) supplied by Novo Nordisk A/S (Bagsværd, Denmark). The serum levels of CML were determined by previously published methods using competitive immunoassays with the DELFIA-system (Wallac, Turku, Finland)(38). One CML unit was defined as the competitive activity of 1 µg of CML-BSA standard. Serum samples were immediately frozen at -80°C until analysis. Data presented are mean of triplicates. All samples were analyzed in one batch. The intra-assay coefficient of variation of the CML-assay was 6-12%. The analyses were done at Aker University Hospital, Oslo

Glycosylated hemoglobin (HbA1c)
Glycosylated hemoglobin (HbA1c) was measured, by HPLC (High Pressure Liquid Chromatography). Analyses were performed at each visit by the central lab at Aarhus University Hospital, Denmark.

Echocardiography
To obtain dimensions and conventional measures of systolic and diastolic function, a standard echocardiography was performed in all patients,
Echocardiograms in studies I, V-VIII were performed on a GE Vivid Five (GE Healthcare, Horten, Norway) using a 2.5 MHz transducer. The remaining echocardiograms were performed on the GE Vivid Seven (GE Healthcare, Horten, Norway) using a similar transducer. All echocardiograms were done in the resting stage by one observer, except from some of the echocardiograms in studies III and IV.
Left ventricular dimensions were assessed by M-Mode echocardiography and LV ejection fraction was obtained by Simpson's method of discs (16). In studies II and IV, LV ejection fraction was assessed by a 3D rotational device (39). Wall motion index assessment was also performed in patients from study IV.
Assessment of left ventricular diastolic function
At present, the ESC recommends to base the echocardiographic assessment of diastolic dysfunction on tissue Doppler recordings of the mitral ring displacement velocity during diastole (E') and relate this velocity to the mitral inflow velocity, assessed by spectral Doppler (E) in the E/E' ratio (40). This measure seems very robust, and correlates well with invasive measures of pulmonary capillary wedge pressure (41;42) and the left ventricular end-diastolic pressure (43).
However, there is no consensus about, where the E/E' ratio should be obtained (40), which leaves the observer to a choice between the lateral (42) and medial (41) mitral annulus, which can give different results (44).
Assessment of diastolic function, should be combined with an assessment of the left atrial dimensions, either by measuring the left atrial diameter or by obtaining left atrial volume measurements indexed to body surface area (40).
In the present thesis the diastolic function is mainly assessed by spectral Doppler supplemented by color M-mode flow propagation recordings of the inflow in the LV cavity (45;46), which was the recommended method at that time. In the most recent studies (IV, VIII) assessment of diastolic function is based on the E/E' ratio, due to recent recommendations (40).
There are strengths and weaknesses to all assessment of diastolic dysfunction and a combined assessment using different methods is often advisable.

Tissue Doppler imaging
Tissue Doppler is derived from the traditional Doppler technique. By filtering high velocities from the blood pool Doppler, it is possible to obtain velocity information from a spectrum of lower velocities, which will involve myocardial deformation.
As any other Doppler modality, Tissue Doppler is angle dependent, which requires an optimal insonating angle (47;48). Recordings with high frame rates in narrow sectors improve tissue Doppler data and reduce signal noise (47;48).
Apical views enable assessment of the global LV long axis function, whereas radial contraction can be visualized in the parasternal views. However, the number of measuring points with TDI is limited in the parasternal views compared to the apical views.
Spectral tissue Doppler vs. color-coded tissue Doppler
At present, two different TDI-modalities are available; 1) Spectral tissue Doppler and 2) Color-coded tissue Doppler.
At first, it was only possible to obtain regional spectral tissue Doppler curves (pulse-wave Doppler) by TDI. By placing the region

of interest (ROI) in a specific area like the mitral ring, velocity recording could immediately be obtained.
Spectral TDI has excellent temporal resolution (<4 ms) and provides instantaneous velocity recordings of myocardial deformation in a specific region. This modality was initially introduced, both as a new measure of systolic and diastolic function (41;42;49), but could also provide information about cardiac time intervals and myocardial velocity gradients (50;51).
By the introduction of color-coded tissue Doppler echocardiography, it became possible to obtain velocity information from the whole scanning sector and to digitally store myocardial velocity data for off-line analyses (52).
Temporal resolution in color-coded TDI is lower than spectral Doppler, which means that absolute values derived from myocardial velocities using off-line tissue Doppler are lower than if acquired with spectral tissue Doppler techniques (53;54). This is caused by color coded TDI's autocorrelation analysis, where it is only possible to compute one velocity for each sample volume at each point in time. Therefore, the velocities derived by color coded TDI are only mean values of all velocity components found within the same sample volume (54). Thereby peak values are lost in the sampling and the absolute value becomes lower (53;54). However, the introduction of color-coded tissue Doppler made image acquisition less demanding and enabled calculation of several different TDI modalities from the same heart cycle. This also facilitated assessment of global LV function, which was not possible with spectral TDI.
All TDI data in the present thesis are derived from color-coded tissue Doppler.

Color-coded TDI assessment of systolic function
Systole can be defined as the time span between aortic valve opening and closure. By tissue Doppler imaging, opening and closure of the aortic valve can be defined by a curved anatomical M-mode recording, placed through the aortic valve leaflets in the apical long axis view (event timing). This technique ensures a very precise assessment of the systolic phase in the cardiac cycle.
From tissue velocity recordings, it is possible to compute other tissue Doppler modalities: By numerical integration of the velocity curves, it is possible to create myocardial displacement curves (Tissue Tracking, see below).
Strain rate, which is the rate of change of deformation, can be derived as a spatial derivative of velocity, whereas temporal integration of strain rate can be used for calculating regional strain. The following will provide in detail information about the most commonly used systolic tissue Doppler modalities.

Tissue velocities
Tissue velocities provide an estimate of the myocardial deformation velocity during both systole and diastole. The systolic velocities are often presented as S' (peak systolic velocity), E' (early diastolic velocity), and A' (peak velocity during atrial systole).
The maximum systolic long axis velocities are found in the mitral ring and in the basal segments and lessen gradually through the myocardium to the apex, where minimal or no myocardial shortening is found (55-59). The normal spectrum of systolic mitral ring displacement velocities (S') are 7-10 cm/s and in the apex 2-4 cm/s (55) (*Figure 1*).
The advantage of tissue velocity imaging is the broad applicability of the modality.
Assessment of peak systolic velocities supplements traditional estimation of systolic function in a broad spectrum of diseases (31;60;61), and is an important tool in event timing in cardiac resynchronization (62;63). In addition, it seems that tissue velocity assessment of diastolic dysfunction has simplified a somewhat difficult discipline (40-43). Moreover, tissue velocity imaging upholds prognostic information about patients with cardiovascular disease (64).
The downside of tissue velocities is the influence from tethering by adjacent segments, which can give misleadingly high tissue velocities in specific segments. Due to stretching motions from bordering segments around the ROI, it is not possible to distinguish translational motion from actual contraction which will result in false overestimation of the velocities (65;66).
A second issue is reproducibility, where inter-observer variations can vary from below 10 percent in some studies (56;67), to over 15 percent in others (68).
In experimental and clinical settings, tissue Doppler velocities are considered relatively heart rate independent (55;69;70), but dependent on systolic blood pressure and age (55). However, there are no gender differences in humans (55).
Preload changes within a clinical spectrum do not seem to influence systolic velocities. Influences like nitroglycerine and leg elevation (71), a 500-mL blood donation (72) or fluid retraction from uremic patients undergoing hemodialysis (73) do not alter tissue velocities.
A single study, made in more advanced settings using progressive reductions of preload, obtained by "Lower Body Negative Pressure" during parabolic flight, was able to demonstrate some preload dependence (74). However these findings may have limited value.

Isovolumetric acceleration
The isovolumetric acceleration (IVA) is basically a velocity measure. It reflects the systolic displacement velocity of longitudinally or spirally arranged fibers in the subendocardial and subepicardial layers of the myocardium. These fibers alter the shape of the ventricular cavity into a sphere during the isovolumetric contraction period, thereby enhancing force of contraction (75-78).
The acceleration curve is measured as the slope of the presystolic velocity curve and expressed in centimeters per second^2. In normal subjects the IVA derived from the lateral mitral ring is approximately 1.5 m/s^2 (71) (*Figure 2*).
The IVA is a short-lived entity (< 0.1 sec) that does not appear in recordings at low frame rates (below approximately 140 fps). Therefore, it is often necessary to measure IVA through a narrow sector with frame rates above 200 per second. However, newer equipment can easily obtain high frame rates (> 200 fps) in normal sized scanning sectors, but in dilated hearts it is still necessary to assess one myocardial wall at a time.
Myocardial acceleration during the isovolumetric contraction period correlates well to invasive measures of intraventricular pressure but may also reflect late-diastolic events and possibly also represent wall oscillations, which are related to global LV function (79;80).
The isovolumetric acceleration was for some time considered unaffected by changes in loading within a physiological range (79). This observation was mainly based on findings from experimental settings (79;81), and these results have been disputed ever since (71;80;82-85).
In a different setting in humans, using nitroglycerine to lower preload and leg-lifting to increase preload, the mean IVA obtained in the mitral annulus decreased significantly during increased preload (1.38 ± 0.50 vs.1.60 m/s^2 ± 0.60, $p < 0.01$), whereas the

acceleration curve rises during preload reduction (2.18 ± 0.65 m/s^2 vs.1.60 m/s^2 ± 0.60, p< 0.01) (71).
These data clearly indicated that changes in preload had significant influence on IVA. However, the set-up was criticized for its research design and results, mainly due to theoretical influence from catecholamines, released due to the nitroglycerine stimulus (83). However, two separate studies were later able to confirm these findings, when the IVA measure was tested under different kinds of load changes (80;85). In a study by Lyseggen et al., peak IVA was markedly load dependent and did not reflect impaired myocardial function during ischemia (80), and in a second study regarding patients with reduced LVEF, IVA also seemed significantly dependent on preload (85).
This issue remains controversial and is far from settled. A recent study has yet again claimed IVA to be load stable in healthy subjects during saline infusion (82). Nonetheless, based on the diverse data in human settings, IVA seems to have limited potential in the assessment of myocardial function (71;80).

Tissue tracking
Tissue tracking (TT) displays the integral of myocardial tissue velocity during systole, which equals the distance of motion along the LV long axis. By this technique, up to seven color bands are visualized, which indicate different displacement amplitudes from the base of the heart to the apex. Depending on the LV function, the range of displacement displayed by the seven colour bands can be altered to stretch the color bands between the apex and the mitral annular level (*Figure 1*).
When analyzing the left ventricle in apical views, the lowest distance of motion is at the apex and the greatest at the mitral annulus. In normal subjects, the displacement amplitude in the basal segments is 10 -12 mm and 2-4 mm in the apex (55).
The major advantage of Tissue Tracking is the easy applicability of information about the LV systolic long axis function which is available to the eye at a glance, and can be analyzed within seconds (86). This will provide the observer with supplemental information about long axis function without major efforts in image acquisition.
Tissue tracking analysis of mitral annulus displacement also correlates well with LV ejection fraction in patients with heart failure (86;87) and is reproducible in a broad spectrum of patients (55). Intraobserver and interobserver variabilities have been determined to be 3 ± 2% and 4 ± 3% respectively (55). Tissue Tracking can also be used to detect subtle changes in LV function, which cannot be found by use of the LVEF estimate (88).
Despite these advantages, Tissue Tracking has not earned general recognition and is not widely used for research purposes.
As well as tissue velocities, tissue tracking is influenced by tethering (55).This can be seen as presence of the same systolic displacement amplitude (same colorband) in adjacent myocardial segments, which may reflect stretching e.g. presence of passive movement of the specific myocardial segment (55). Tissue Tracking seems equally influenced by age, blood pressure and heart rate as velocity assessment (55), but has not been preload validated.

Strain and strain rate
Strain and strain rate display myocardial deformation and have shown excellent correlations to tagged magnetic resonance strain measurements (89). Strain and strain rate are also derived from tissue velocity data and can only be assessed by colour-coded images off-line (*Figure 1*).
Strain (ε) describes the relative change in length between two points over a given distance. This means that two adjacent myocardial segments are either being stretched (diastole) or compressed (systole) to a new length or remain unchanged. The strain value is dimensionless and can be presented as a fractional number or as a percentage: positive for lengthening, negative for shortening, and zero for no change in length (71;90;91). The spectrum of strain values derived from the basal myocardial segments range from 15 to 30 per cent in normal subjects (71). Strain values derived from the mitral ring are considerably lower, due to presence of fibrous tissue in the mitral annulus (71).
Strain rate (SR) is the temporal derivative of strain. While strain indicates the amount of deformation, strain rate indicates the rate of deformation. The relation between strain rate and strain can be compared to the relation between velocity and displacement (e.g. Tissue Tracking).
Strain rate is also dimensionless and expressed with the unit per second or s^{-1}.
The strain rate values in the basal segments in normal subjects are approximately -2.5 s^{-1} and -1.5 s^{-1} in apical segments (55).
Strain and strain rate only measure deformation. None are measurements of contractility (stress / strain relation), which involves myocardial tension (stress).
However, from invasive studies, systolic strain seems closely correlated to stroke volume, whereas systolic strain rate being an early systolic event seems more closely correlated to contractility (47;69;92). In experimental settings, strain and strain rate seem heart rate independent within the normal physiological spectrum (heart rate below 140 bpm) (69;70), and there is no correlation between heart rate and strain rate in humans examined in the resting stage (55).
There is general consensus, that strain and strain rate seem superior, compared to other TDI derived measures of systolic function, when it comes to load independency (71;80). When different TDI modalities are compared under the same circumstances, strain and strain rate tend to be less load dependent, compared to velocity parameters like IVA or crude velocity recordings from either the free wall of the left ventricle or the mitral ring (71;93-95).
The reasons, why strain and strain rate remain relatively load stable in the normal myocardium, may be the fact that systolic strain quantifies regional systolic deformation of the LV and is mainly determined by the ejection performance (stroke volume, ejection fraction), which should be unchanged during preload changes (69;71) Similarly, peak strain rates are predominantly related to local contractile function and less on loading conditions (69). Compared to tissue velocities, both entities are uninfluenced by tethering and translational motion (96). However, there are several pitfalls related to these methods, especially when it comes to image acquisition (97-99).

Image acquisition
As in velocity imaging, low frame rates will result in under sampling and loss of data (100). Signal noise should also be diminished by second harmonic imaging and curve smoothing modalities, and reverberation artifacts should be avoided to obtain reliable strain and strain rate curves (47;101).
The strain length (offset for calculating strain and strain rate) is crucial since strain and strain rate values are dependent on, how far the two measuring points are placed apart. The larger the strain length, the higher risk of missing important information or obtaining wrong values (47). The strain length is adjusted by

reducing the ROI, but strain length is rarely mentioned in TDI publications. In the present studies, strain and strain rate was calculated over an offset (strain length) of 6-9 mm.

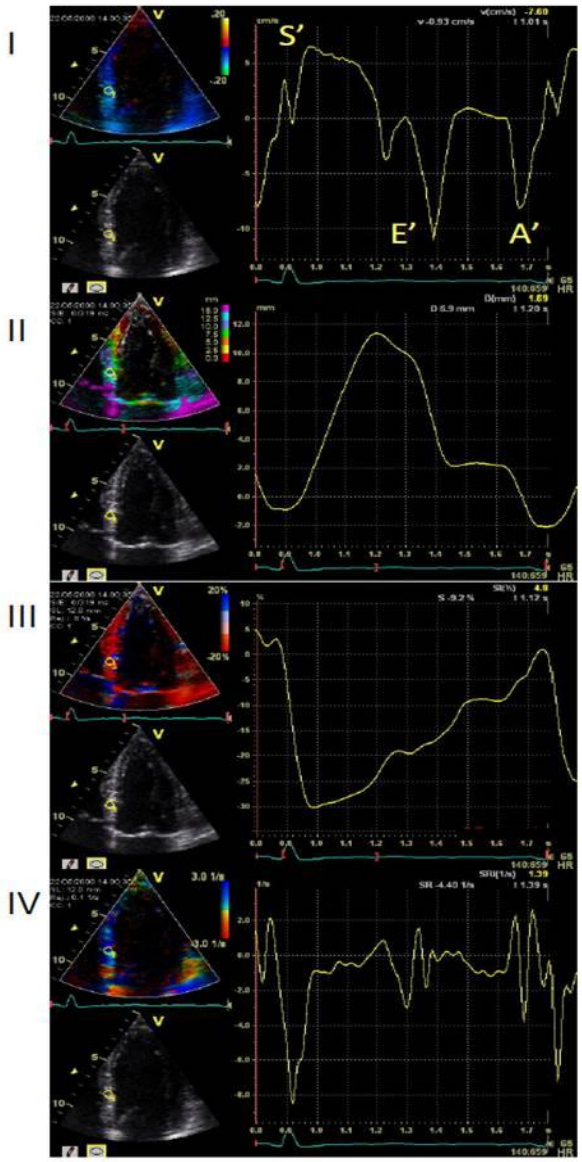

Figure 1.
Four different tissue Doppler modalities from one cineloop.
I) Tissue Velocities. II) Tissue Tracking. III) Strain. IV) Strain rate.
Please notice the R-wave in the ECG (bottom of all images) and the dissimilar timing of the different TDI modalities.

During off-line analysis, another problem appears which is called drift. Drift is a phenomenon in the integrated modalities of displacement and strain. It results from the accumulation of small non random errors in velocity or strain rate values and can be upwards or downwards (47;102). Drift can be compensated in post-processing by numerous maneuvers, but it is questionable how or if drift compensation should be done, since image modulation may result in loss of information or actually "making" wrong values during drift compensation (47;102).
Intra-observer variations of strain and strain rate are acceptable, but inter-observer variations are moderately high (55). In centers where more advanced software is available, the inter-observer variation is still 10-13 percent (103).

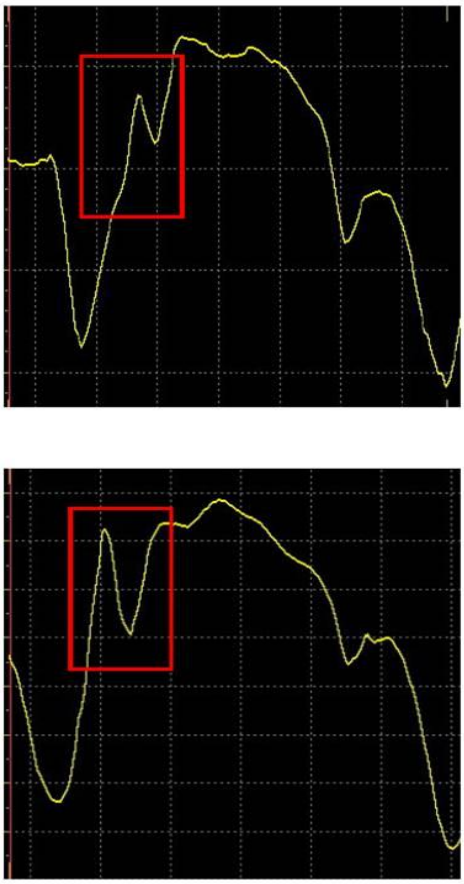

Figure 2
Notice the marked difference in the two different isovolumetric acceleration (IVA) curves obtained in from the same individual with different image acquisition. Above: Tissue velocity curved obtained through a standard size sector at 177 fps. Below: Tissue Velocity curve obtained though a narrow sector at 239 fps.

Choice of tissue Doppler method
Which systolic TDI parameter to choose must depend on the clinical question and the patient category.
Tissue velocity imaging and Tissue Tracking will apply well in on-line settings and provide a quick overview of the LV function as a supplement to LVEF or other 2D methods. In addition, assessment of the patient evaluated for cardiac resynchronization or patients suspected for diastolic dysfunction can easily be handled using tissue velocities.
However, for research purposes a more refined assessment of both global and regional LV contraction may be needed, and here strain or strain rates are generally preferred, due to the relative load independency, heart rate independence, and lack of influence from tethering (98). The most immediate clinical application of strain and strain rate is to identify subclinical LV dysfunction, but barriers to the clinical implementations of these modalities include the requirement for significant understanding of complex methodology, technical challenges of image acquisition and analyses (98).

CLINICAL ASPECTS

Hypertensive heart disease

Arterial hypertension can have significant impact on the heart, involving both the cardiac structure and function. Especially elevated systolic blood pressure and pulse pressure, seem directly related to increased incidence of congestive heart failure (104). Activation of neurohormonal mechanisms may as well have influence on the characteristics of the left sided myocardium (105). There is no specific hypertensive cardiomyopathy, but numerous characteristics that indicate influence from elevated blood pressure on the myocardium. Factors like left ventricular hypertrophy and remodeling as well as myocardial stiffening and fibrosis all induce diastolic dysfunction and left atrial enlargement in hypertensive patients (106-109). Presence of coexisting coronary heart disease will accentuate the condition (110).

Hypertension is highly prevalent in patients with heart failure symptoms and preserved ejection fraction (111;112). Furthermore, many patients hospitalized with acute pulmonary edema have hypertension and apparently normal ejection fractions (113-115), and the general conception is that diastolic dysfunction is the causal mechanism behind pulmonary congestion (115). However, Tissue Doppler imaging may contribute with information about changes in systolic long axis function in hypertensive patients and can elucidate some of the primary interactions between hypertension and the left-sided myocardium. Moreover, TDI may also clarify some of the patophysiological mechanisms behind elevated blood pressure and LV dysfunction. The following sections will provide an overview of the most prevalent consequences of hypertension on the heart and their relation to changes in long axis function.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is defined as thickening of the myocardium due to an increase in the size of its cells (116). Physiological cardiac hypertrophy is often seen in response to exercise training, whereas pathological hypertrophy results from pressure overload, and neurohumoral stress (117).

Left ventricular hypertrophy is mainly found in patients with hypertension (109), obesity (118), diabetes (119) aortic stenosis (76), and in more rare genetic diseases coding for various contractile proteins (120;121).

In hypertension, LVH is a direct indicator of target organ damage and closely associated with increased cardiovascular morbidity and mortality from cardiovascular disease. The risk factor-adjusted relative risk of cardiovascular disease in men is 1.49 (1.20-1.85) for each increment of 50g/m^2 in left ventricular (LV) mass and 1.57 (1.2- 2.04) in women (122).

Echocardiography uses measurements of LV wall thickness and left ventricular diastolic dimensions by a validated cube formula to estimate LV wall volume. When this volume is multiplied by a constant representing the gravity of muscle, the echocardiographic estimate provides a good indication of LV mass (15). Because of normal variations in LV mass, calculations are standardized by indexing for height or body surface area. The arbitrary cut-off for LV mass at the 97th percentile of the population norms has been used to define LVH; However, on the basis of data from the Framingham study, the risk for cardiovascular events appears to increase with LV mass indices even well below this percentile (122).

By echocardiography, LVH can be classified as concentric or eccentric, depending on the ratio of LV wall thickness to chamber diameter.

Concentric hypertrophy is defined as LV hypertrophy with an increased ratio between wall thickness and LV cavity dimension (2 x posterior wall diameter / LV diastolic diameter > 0.43) (108;123). Eccentric hypertrophy is defined as LV hypertrophy without an increased ratio between wall thickness and LV cavity dimension (<0.43). Finally concentric LV remodeling is a condition defined as an increased ratio but with an LV mass within normal limits (123).

The patophysiology behind the appearance of the different LV hypertrophy patterns is not fully understood, but it seems that stimulation of myocardial cell growth and activation of the sympathetic nervous system might preferentially lead to concentric LV hypertrophy through a direct trophic effect and pressure overload, whereas sodium and water retention could lead to eccentric LV hypertrophy due to volume overload (124;125).

There is a close relation between presence of LVH and systolic dysfunction as demonstrated in the large population studies like HyperGen (119) and Strong Heart (126), where patients with LVH have impaired systolic function. Over time, patients with LVH also seem predisposed to develop systolic heart failure, but often in relation to concomitant presence of coronary heart disease and MI (127;128).

However, from clinical hypertension trials there are interesting data which indicate a close relation between LVH and systolic dysfunction which is if blood pressure is lowered and the LV mass is reduced (129).

Myocardial fibrosis

The cardiac tissue composition also changes in hypertension, due to myocardial remodeling in the presence of elevated blood pressure.

While LVH is based on the growth of cardiomyocytes, cardiac fibrosis is accompanied by other iterations in tissue structure, involving heterogeneity and a disproportionate involvement of noncardiomyocyte cells, which accounts for a pathologic remodeling of tissue structure (116;130;131).

The cardiomyocytes become tethered within an exaggerated accumulation of extracellular collagen fibers, endothelial and vascular smooth muscle cells and fibroblasts located in interstitial and perivascular spaces (132).

In post mortem hypertensive hearts, Tanaka et al. observed increasing amounts of cardiac fibrosis from the outer layer of the myocardium to the inner layer, where the fibrosis severity was highest (116). Fibroblasts contribute to accumulation of perivascular fibrosis which seems to impair the vasodilator capacity of the intramyocardial arterioles (116;133). This may further exaggerate accumulation of interstitial fibrosis.

Development of myocardial fibrosis appears to be due to disequilibrium between synthesis and degradation of collagen, caused by disturbance of the normal reciprocal regulation of collagen production (130). It seems that cardiac fibroblasts contribute to an upregulation of collagen type I and III and diminished degradation of collagens when in presence of hemodynamic overload (130;134;135). Fibrosis development seems to represent a reactive process due to overload and shear stress of the inner wall of the left ventricle (130;134;135), and may also be facilitated by neurohormonal activation from the renin-angiotensin system, corticosteroids, catecholamines and endothelial factors

(131;136;137). Here the common denominators are inflammation and tissue repair which will lead to activation of fibroblasts.
A major interest has been focused on assessment of serological markers of collagen turnover and their applicability as markers of cardiac fibrosis.
The main focus has been on detecting collagen turnover by measuring procollagen types I and III in peripheral blood (138). In humans, carboxy-terminal propeptide of procollagen type I (PIP), an index of collagen type I synthesis, correlates well to the level of myocardial fibrosis in endomyocardial biopsies taken from the interventricular septum (139). However, the blood was sampled in the coronary sinus, which makes the results difficult to apply in daily clinics.
However, pro-collagen type I sampled from peripheral blood relates well to ultrasonic reflectivity, evaluated by a real-time integrated backscatter analysis (140) . Ultrasound reflectivity should in these cases indicate fibrosis, i.e. the relation to collagen type I turnover (140), but does not provide any information about myocardial function.
A few studies have focused on whether serological markers of collagen turnover are associated to long axis function. There seems to be a relation between serological collagen markers of collagen III and systolic long axis velocities (141) as well as long axis strain (142) in hypertensive patients. Likewise, decreased levels of circulating collagen markers seem to indicate cardio reparation in hypertensive individuals treated with blood pressure lowering drugs (132;143), including blockade of the renin-angiotensin system (144-146). It is important to emphasize that blood pressure lowering seems superior to any specific drug therapy (147).
There are downsides to assessment of collagen turnover and monitoring of myocardial fibrosis and function in the daily clinic. Tests are relatively expensive, and in some cases there is lack of specificity due to contribution of pro-collagens from larger organs like liver and bone (148;149). Moreover, it is unresolved what consequence should be drawn from positive test results beyond blood pressure lowering. However as a research tool, assessment of collagen turnover in lean patients with essential hypertension still seems quite promising.

Diastolic dysfunction
The term diastolic dysfunction refers to a condition with increased filling pressures and decreased compliance of the left ventricle (17). In hypertension, diastolic dysfunction is a common sequela to elevated blood pressure, closely associated with LVH (150;151).
Diastolic dysfunction is frequent in the ageing population (152), in diabetic patients (153), in systolic heart failure (154), and in patients with acute myocardial infarction (155). Impaired diastolic function is associated with atrial fibrillation (156), aortic stiffness (157;158), and albuminuria (159;160), and has a poor prognosis comparable to that of systolic heart failure (112;161).
Diastolic function is composed of an energy demanding myocardial relaxation and the distensibility of the left ventricle, which is a passive phenomenon (162). Relaxation of the contracted myocardium occurs at the onset of diastole and produces a suction effect, which augments a pressure gradient between the left atrium and the ventricle, facilitating diastolic filling. During the later phases of diastole, the cardiomyocytes in the left ventricle are relaxed and the LV wall is compliant, which as a consequence offers minimal resistance to further LV filling. Therefore, the contribution from the atrium is fairly small in the normal diastole (163;164). Structural changes like LV hypertrophy, and myocardial fibrosis or myocardial ischemia, lead to reduced chamber size and decreased capacitance (reduced volume at a specific pressure) (163), which results in an upward and leftward shift in the diastolic pressure volume curve. As a result, the chamber compliance is reduced, the time course of filling is altered, and LV filling occurs against elevated pressure in the ventricle.
Under such circumstances, small increases in central blood volume can cause a substantial increase in left atrial and pulmonary venous pressures and may result in pulmonary congestion (164). In conditions with long duration, diastolic dysfunction will inevitably lead to left atrial dilation and increased risk of atrial fibrillation, which is a common comorbidity in hypertension (165;166). Furthermore, it is evident that patients with diastolic dysfunction and heart failure symptoms carry a poor prognosis similar to what is found in patients with reduced LVEF (111;167;168).

Treatment of diastolic dysfunction
Despite significant improvements in the medical treatment of systolic heart failure, diastolic dysfunction is still a therapeutic enigma. Many strategies have been challenged, but besides blood pressure lowering (169) or diuretics if congestion is present, no specific treatment strategy has been superior in treating diastolic dysfunction.
The 2005 ACC/AHA CHF guidelines (2), support four approaches:

- Control of systolic and diastolic hypertension
- Control of ventricular rate in patients with atrial fibrillation
- Control of pulmonary congestion and peripheral edema with diuretics
- Coronary revascularization in patients with CHD in whom ischemia is judged to have an adverse effect on diastolic function

Medical treatment should be aimed at regression of LV mass, which theoretically should improve the diastolic function. Reduction of LV mass is primarily related to blood pressure lowering than to a specific drug therapy. There may be a tendency to less LV mass regression with beta-blockers, compared to drug classes like ACE-inhibitors and ARB's or calcium channel blockers, but data are not convincing (170-173).
Another aspect has been whether LV remodeling (ACE/ARB) was superior to slowing the heart rate and prolonging the filling period (beta blockers).
However, no large randomized trial has yet been able to answer this question. The recently published OPTIMIZE-HF study based on beta-blocker therapy failed to show any benefit in patients with diastolic dysfunction (174) and neither the VALIDD trial (169), the CHARM-preserved trial (175) or the I-PRESERVE trial (176) were able to show superiority from an ARB-based regimen. So if a drug should be recommended for specifically treating diastolic dysfunction, it must have benefits beyond simple blood pressure lowering abilities to be superior to good blood pressure control.

Isolated diastolic dysfunction?
Previously, diastolic dysfunction was often taken as an isolated phenomenon, if the LV ejection fraction was above 45 %, and the term "isolated diastolic dysfunction" or "diastolic dysfunction with preserved systolic function" was widely used to characterize these patients (177;178).
However, this conception is not correct, since the systolic function does not appear normal if more advanced echocardiographic modalities are applied (179;180).
For a long time, it has been possible to demonstrate prolonged pre-ejection time and ejection time intervals by use of spectral Doppler (181), which are useful indicators of reduced systolic function, also in hypertension (182). However, these findings did not seem to have significant impact on the conception that diastolic dysfunction was an isolated phenomenon, if the ejection fraction was above 45-50 per cent. By introduction of new TDI based echocardiographic measures, it became obvious that the systolic function was abnormal in a vast majority of this specific patient category, and that isolated diastolic dysfunction was actually quite uncommon (179;180;183-185).
The large amount of data made it necessary to rephrase the term "*isolated diastolic dysfunction*" to "*heart failure with preserved ejection fraction*" (HFNEF), which at present is the most commonly used term (40).

Early systolic dysfunction in hypertension
The early systolic dysfunction in hypertensive HFNEF patients is not fully defined, despite numerous studies. It is unclear whether there is a simultaneous degradation of contraction and relaxation of the cardiomyocyte, or whether these are separate phenomena. Previously, it was generally accepted that the failing midwall function was the earliest sign of systolic failure hypertensive individuals (186;187). This conception was among others derived from the LIFE-study, where midwall fractional shortening was used as a parameter of systolic dysfunction (188).
However, it is worth noticing that the average echo-LIFE patient had considerably elevated blood pressure (mean 174 / 96 mmHg), was approximately 67 years old and overweight, and had eccentric LVH with a considerable enlarged LV mass (average above 230 g)(189). Far from all hypertensive patients apply to these characteristics and reduced midwall fractional shortening may not be among the earliest changes in systolic function in hypertensive individuals.
By use of TDI it is possible to detect subclinical changes in long axis function, which seems to appear even earlier than failure of the midwall. This opens up for a new conception of LV mechanics in hypertensive individuals in the early stages of the disease.
It seems that the earliest involvement is impaired long axis function, often hand in hand with impaired diastolic dysfunction (27;179;183) and can be found in hypertensive patients with only low grade hypertension (179;185). Reduced long axis function can often be seen in conjunction with normal or increased circumferential (midwall) deformation, which in the primary stages preserves the ejection fraction (27;190;191). This pattern of involvement can also be found in diabetic individuals (192;193) and has been interpreted as evidence of the long axis oriented subendocardium, being the primary site of involvement of hypertension (190;191).
Therefore, it must be assumed that dysfunction of the radial oriented fibers must belong to a more advanced stage of myocardial dysfunction (20).
Decreased long axis function is closely related to the presence of LVH in both non-diabetic and diabetic patients (27;160;179;194) and probably more pronounced in patients with concentric hypertrophy (195). Moreover, diminished long axis function is as mentioned associated to myocardial fibrosis, which may contribute significantly to impaired LV function (196), as this phenomenon also can be observed in individuals with diastolic dysfunction without LVH (29;61;142).
Theoretically, heart failure in hypertensive patients may consist of a primary deterioration of the long axis function, followed by failure of the midwall i.e. LIFE-study patients (129). Finally patients will experience reduction in LVEF and overt heart failure. A short cut to this stage could be a large myocardial infarction (MI).
Coronary artery disease and hypertension
Hypertension and coronary artery disease are evidently related, which has been shown in numerous occasions (197-200).
How the coronary circulation and blood flow reserve relate to long axis dysfunction, left ventricular hypertrophy and myocardial fibrosis, is not fully clarified. However, several studies have found an association between diastolic dysfunction and impaired coronary flow reserve in hypertensive individuals (201-203).
In type 2 diabetic patients, a large tissue Doppler based study found decreased long axis function related to the presence of concomitant coronary artery disease (204), but a similar setup has not been made in patients with essential hypertension.
Patophysiological mechanisms beyond the specific effects of ischemia on the cardiomyocyte function could be accumulation of fibrosis. Several small studies have found significant associations between increased collagen turnover, diastolic dysfunction and reduced coronary flow reserve estimated by ultrasound (133;205;206), but to which extent coronary artery disease involves the systolic function in early stage hypertension is unresolved (110).
Myocardial infarction in patients with antecedent hypertension
The ultimate consequence of coronary atherosclerosis is myocardial infarction, which is far the most common cause of overt heart failure in hypertensive patients (127;128;163;207). Presence of clinical heart failure symptoms after an acute myocardial infarction carries a very poor prognosis (208;209), and concomitant hypertension reduces the survival further (210).
The adverse influence of hypertension on the left ventricular function after a myocardial infarction is not well described and there seems to be marked differences depending on the revascularization therapy.
Data derived from large myocardial infarction trails, based on thrombolytic therapy indicate that patients with a history of hypertension have poorer outcome, more evident congestive heart failure symptoms, more pronounced LV dilation than patients without hypertension (211;212).
However, entering the era of primary percutaneous intervention (pPCI), results have slightly changed. In two large studies, patients with antecedent hypertension treated with primary PCI only had minor differences in left ventricular volumes and ejection fractions after an acute MI (34;213) compared to non-hypertensive controls. Nevertheless, these patients had disproportionately higher incidences of congestive heart failure symptoms compared to the control group (34;213). Different revascularization strategies and improved antithrombotic treatment may explain the dissimilar results in LV remodeling, but the consistent high incidences of heart failure symptoms are unexplained. A common denominator could be changes in long axis function, undetected by normal LVEF assessment. Otherwise, it could be caused by

worsened diastolic function in hypertensive patients accentuated by the MI (108;109;182).
These assumptions were investigated in a study involving patients with antecedent hypertension and acute myocardial infarction (44). In this study, both hypertensive patients and a control group of non-hypertensives with myocardial infarction had impaired diastolic function immediately after the acute MI. After 1 month's follow-up, the non-hypertensive patient's diastolic function improved significantly, whereas patients with antecedent hypertension still had elevated E/E' ratios and did not seem to improve their LV filling characteristics assessed by spectral Doppler. This was despite similar changes in LVEF, LV dimensions and long axis systolic strain (44).
Impaired diastolic function will lead to pulmonary congestion and may partially explain why hypertensive patients experience more heart failure symptoms despite similar LVEF after a large MI.
The causal mechanisms should be found in what is already known about the hypertensive heart, where presence of hypertension, LVH and myocardial stiffness leads to reduced chamber size and decreased diastolic capacitance (163;164).
In addition, it seems that the hypertensive patient may suffer from more severe myocardial infarction damage since the myocardium may be more vulnerable (214). As seen in the mentioned study, patients with antecedent hypertension had a significantly poorer post-procedural TIMI-frame count, a larger area at risk measured by SPECT, a slightly higher leak of cardiac troponins, and a strong tendency towards a larger final infarct size (44).
Since any patient suffering from a large MI will experience deterioration of the diastolic function (208;215), hypertensive patients will be worse affected and ought to experience more dyspnea and heart failure symptoms.
Inevitably, presence and degree of abnormal LV filling will increase left atrial size, which will lead to atrial fibrillation and increase the risk of stroke (216;217). Both disorders are far more common in hypertensive patients following an acute MI and will increase the morbidity and mortality of the hypertensive patient (218;219). These mechanisms correspond well with the fact that abnormal LV filling and left atrial size are strong predictors of survival after an acute myocardial infarction (167;220).

DIABETIC HEART DISEASE

Cardiac involvement in diabetes represents a continuum of preclinical stages, which evolve over time into marked structural and functional changes of the myocardium.
The major characteristics of the internal milieu of the patient with diabetes are elevated blood pressure, hyperglycemia and presence of atherosclerosis. In type 2 diabetic patients, hyperinsulinemia must also be considered a major determinant (221).
The presence of diabetes is associated with a population-attributable risk for developing CHF in both men (6%) and women (12%) (4;222).
Presence of congestive heart failure in diabetic patients is very common and is characterized by significantly poorer outcome compared to non-diabetic heart failure patients (6;223-225).
For decades, a diabetes-specific, non-ischemic myocardial disease – referred to as '*diabetic cardiomyopathy'* has been discussed (226-228). In the seventies, Rubler et al. described the presence of CHF among a small group of patients with diabetes and renal involvement (229). In these patients, the presence of CHF could not be attributed to coronary artery disease or hypertension, but seemed solely related to the presence of diabetes. (229). As today, no specific criteria for a diabetic cardiomyopathy exist, and there is no clear definition (227;228;230). Furthermore, the condition seems to have a long subclinical course and possible causative links are immediately interrupted by multifarious treatment algorithms (13).

Diabetes and myocardial dysfunction

The presence of left ventricular diastolic dysfunction in patients with normal LV ejection fraction was for a long time proposed as the initial stage in the development of a diabetic cardiomyopathy (153;226;231;232). Doppler echocardiographic studies demonstrated presence of abnormal LV diastolic filling in as high as 50 % of normotensive patients with type 2 diabetes and a normal ejection fraction (153;231).
In diabetic individuals, diastolic dysfunction is associated with LVH, microalbuminuria (160;233;234), arterial hypertension (151), absence of a nocturnal blood pressure dip (160), endothelial dysfunction (235), and increased carotid intimal thickness (236;237). Strikingly, diabetic patients with diastolic dysfunction and preserved LVEF have similar high mortality rates as diabetic patients with reduced LVEF (223).
Subclinical long axis dysfunction
By TDI, it is possible to visualize subclinical stages of LV dysfunction in diabetic patients. As in hypertensive patients, it seems that subtle changes in systolic dysfunction may occur before or together with presence of diastolic dysfunction, which measures like ejection fraction and fractional shortening are unable to detect.
Tissue Doppler echocardiography reveals a recognizable pattern of functional changes in the LV function in these patients. The primary finding in type 2 diabetic patients is normal ejection fraction, reduced long axis function, compared to normal control subjects (29;160), matched by an increase in radial function, which exceeds that of normal subjects (192;193). Again this explains why these patients have normal LV ejection fraction.
The increase in radial function may be compensatory hyperfunction from midwall derived myocardial fibers, which compensate for the loss of contractile force in the long axis plane, but this issue is not fully clarified. Actually, echocardiographic studies performed before the TDI era have described radial hyperfunction in type 1 diabetic individuals who had significantly higher 2D fractional shortening compared to a control group (238-240). This may have been the same phenomenon.
In diabetic patients as well, reduced long axis function has been interpreted as evidence of the subendocardium being the primary site of involvement of diabetic myocardial disease (241;242).
Numerous theories about patophysiological mechanisms exist (221;226;230), but it has been difficult to connect experimental observations to clinical data, since the estimation of systolic function has been based on crude measures like LVEF ad FS estimates.
However, with TDI it is possible to explore early signs of myocardial involvement and relate these findings to some of the theories behind cardiac dysfunction in diabetic individuals.
One of the primary observations was taken from a small subset of asymptomatic type 2 diabetic patients and relatively short diabetes duration. The patients did not have any of the common complications to diabetes like hypertension, LVH, retinopathy or albuminuria, and had acceptable glucose control (HbA1c 8.3 ± 2 %)(29). In these patients, the long axis function was significantly reduced, especially in the subgroup with diastolic dysfunction. This observation showed that a myocardial involvement was

present in diabetic patients, independent from the presence of hypertension or common markers of small vessel disease (29). Furthermore, these observations pointed out that long axis dysfunction may be equally related to the substrate metabolism (hyperglycemia and hyperinsulinemia) as to LVH, hypertension and myocardial ischemia.
The following sections will focus on the major components in the type 2 diabetic patients' metabolism and their relation to myocardial dysfunction in diabetic patients (*Figure 3*).

Insulin resistance
Insulin resistance is a condition in which normal amounts of insulin are unable to induce a normal insulin response in fatty tissue, skeletal muscle and liver cells. Insulin resistance elevates free fatty acids in the blood stream, reduces glucose uptake in the skeletal muscle and reduces liver glucose storage, all effects serving to elevate blood glucose levels. High plasma levels of insulin and blood glucose resulting from insulin resistance are cornerstones in the metabolic syndrome and in type 2 diabetes (221).
Insulin resistance is linked to obesity, hypertension, left ventricular hypertrophy, endothelial dysfunction, albuminuria and coronary heart disease, and seems to have detrimental effects on cardiomyocyte metabolism as well (243).
Hyperinsulinemia seems to influence cardiomyocyte growth through cellular mechanisms, despite the fact that the cellular mechanisms of insulin are attenuated, if the patient is resistant to insulin (244) Hyperinsulinemia may partially induce LVH and stiffness of the left ventricle and can be linked to diastolic dysfunction (192), but also to early changes in LV systolic function in insulin resistant patients (245-248). However, in normal individuals, the HOMA index (surrogate measure of insulin resistance) is not linked to the LV function (249).
In type 2 diabetic individuals naïve to insulin treatment, there is a negative correlation between fasting insulin levels and LV systolic long axis strain (250). This indicates that myocardial function and insulin resistance are closely associated and insulin resistance may exert a direct effect on the long axis function (250). This hypothesis is supported by a TDI study in obese individuals that showed a direct correlation between HOMA-IR values and systolic strain/SR (251). This could also mean that correction of insulin resistance may have a favorable effect on the long axis function, and data on this matter have recently been reported. In a study including 140 type 2 diabetic patients, randomized to a lifestyle modification programme, there was a significant correlation between improvements in systolic strain and strain rate and improvements in the HOMA index (252). This should mean that myocardial insulin resistance is a potent accessory in the reduction of long axis function, and that treating insulin resistance leads to improved LV function.
The hyperinsulinemia component of insulin resistance can probably account for most of the myocardial changes which occur in obese or type 2 diabetes, but cannot explain the changes seen in lean type 1 diabetic patients, who more or less per definition are insulin sensitive. Therefore, hyperglycemia may be of considerable importance as well.

Hyperglycemia
Both chronic and intermittent hyperglycemia are significantly related to organ damage in both type 1 and type 2 diabetic patients (253-256). The UKPDS study found significantly higher incidences of myocardial infarction and heart failure among patients with type 2 DM with high levels of glycated hemoglobin (HbA1c), and the same association can be found in type 1 diabetic cohorts (253).
However, recent trials on actual intervention have presented disappointing results in preventing cardiovascular disease (257;258).
Several studies have focused on chronic hyperglycemia and long axis dysfunction. Even in non-diabetic individuals, there seems to be a correlation between glycemia and the systolic properties in the long axis plane (249). In a small study in non-diabetic males, a linear correlation was found between fasting plasma glucose within the normal spectrum and systolic strain rate (both values obtained within the same hour), indicative of an association between blood glucose homeostasis and long axis function (249). A similar relation can be found between S-fructosamine and long axis strain rate, however found in a slightly older population (160). Both observations support the conception that glycemia and LV function seem to interplay, even within the normal spectrum.
Concurrent data in type 2 diabetic patients have shown that glycemic control and long axis systolic function are very closely interrelated. Three separate studies have reported correlations between HbA1c, and systolic velocities (192), systolic strain (250) and strain rate (160), demonstrating that glycaemic control over the last 60-80 days is significantly related to the contractile function of the left ventricular long axis plane. The same correlation has also been found with fructosamine, which is regarded as a marker of the last 2 weeks' glycemic control (160).
In type 1 diabetic patients, only few data exist on glycemic control and long axis function. A small magnetic resonance imaging study of the systolic rotational force of the left ventricle, showed that hyperglycemia (HbA1c) and systolic function are interrelated in type 1 diabetes as well (259).
However, cross-sectional data do not clarify whether decreased systolic long axis function depicts generally poor controlled diabetes with organ involvement, or whether it is a more dynamic phenomenon, changeable if glycemic control is improved.
A small number of studies have explored this question. In type 2 diabetic patients, a significant relation between coherent values of HbA1c and LV strain rate can be found over a 12 month observation period (260). Patients with improved glycemic control – defined as a reduction in HbA1c value after 12 months of follow-up (8.3% to 7.4%) – had significantly improved long axis strain rate compared to patients whose HbA1c values were higher than the baseline level (8.2% to 9.1%). The two patient groups had comparable baseline values with regard to long axis function, systolic blood pressure, left ventricular mass, age and duration of diabetes (260).
In the same cohort, coherent values of long axis strain rate (baseline, 3 and 12 months) where significantly correlated to the HbA1c value, obtained at the same time. This correlation eliminated effects from LV mass and blood pressure reduction in a multiple regression analysis (260).
This must be seen as a dynamic relation between blood glucose homeostasis and LV function, and surprisingly LV function is changeable even after several years of diabetes duration (260). Similar findings can be done in type 1 diabetic patients. When type 1 diabetic individuals undergo insulin pump therapy, patients often significantly improve their glycemic control over a short period of time (261). In a small observational study, the initiation of insulin pump therapy led to a significant improvement in HbA1c from 8.6 ± 1.4 % to 7.6 ± 1.1 % ($p < 0.01$) over 45 days (262). During this time span, their mean left ventricular SR ob-

tained in the long axis plane improved significantly from -1.58 ± 0.30 s^{-1} to -1.80 ± 0.4 s^{-1} ($p<0.05$). Interestingly, there was a close correlation between these changes in glycemic control and changes in long axis function (ΔSR vs. Δ HbA1c: r= 0.49, p< 0.01), which emphasizes the connection between hyperglycemia and function of the cardiomyocyte (262).

Patophysiological effects from hyperglycemia

How elevated blood glucose levels interfere with the contractile function of the long axis fibers of the myocardium is unknown, although several theories exist. Hyperglycemia may directly induce apoptotic cell death and myocyte necrosis (263). Cardiomyocyte apoptosis initiated by hyperglycemia and aggravated by oxidative stress (264) results in myocardial cell loss, which may impair the contractile forces of the myocardium. However, the mechanisms that directly mediate hyperglycemia-induced cardiac damage remain poorly understood (265;266), and actual cell death does not correspond well with the reversible manner of long axis dysfunction (260;262).

Chronic hyperglycemia could also affect LV function via the reduction of the sarco(endo)plasmatic reticulum Ca^{2+}-ATPase (267;268), but this issue is far from settled in humans.

A more consistent theory is influence from non-enzymatic glycation of proteins, which induces irreversible formation and deposit of reactive advanced glycation end-products (AGEs). The formation of AGEs on extracellular matrix components accelerates the process of collagen cross linking, contributing to myocardial stiffness and hypertrophy (269). In experimental settings, this phenomenon has been moderated through treatment with a cross link breaker or an AGE receptor antibody (270-274). In human studies, serum levels of AGEs are higher among type 2 diabetic patients with coronary heart disease (275), but little is known about the relation to myocardial function (276;277). Carboxymethyllysine (CML) is known to bind to a specific AGE-receptor (RAGE) and activate NF-κB and proinflammatory cytokine secretion (278), but no significant association has been found between carboxymethyllysine (CML) and long axis systolic strain rate in type 2 diabetic patients (160). The lack of any correlation with the non-cross-linking ligand CML brings into question whether CML is related to the involvement of myocardial function in human type 2 diabetes. Nevertheless, the significant correlation between the levels of glycosylated hemoglobin and long axis function in the same study supports the assumption that glycosylation somehow significantly influences myocardial function (160;226;250).

Another issue is glucose transport through the cellular membrane. Increased glucose uptake in hypertrophied hearts is insulin independent and associated with, on one hand, the increased expression of the basal glucose transporter GLUT1, and on the other, the decreased expression of insulin-regulated glucose transporter GLUT4 (221;279-281). These changes in GLUT expression are also partially related to the mitochondrial dysfunction found in the type 2 diabetic patient (282). Thus changes in GLUT expression can be partially attributed to hyperglycemia, but they are also a result of insulin resistance (283).

Theoretically, if the metabolic control (glycemia and lipids) was optimized, this may directly result in improved cardiac function by increased GLUT expression on the surface of the cardiomyocyte, a process which has been shown to have an effect on cardiac function in experimental studies (284;285). The role of these glucose transporter isoforms and their relation to myocardial function in humans is yet to be clarified.

Hyperlipidaemia

Hyperlipidemia, including cholesterol, triglycerides and free fatty acids (FFA) may all affect LV function.

Lipid overstorage in human cardiac myocytes is an early manifestation in the pathogenesis of type 2 diabetes mellitus, which precedes the presence of heart failure (286), but the actual link between hyperlipidemia and LV dysfunction is not clarified. Nevertheless, several mechanisms have been proposed including impaired coronary flow reserve (287), aortic stiffness (192) and lipotoxicity of the cardiomyocyte attributed by free fatty acids, triglycerides or both (288).

Not much data are available in humans. However, it is well known that lipid levels raise with increasing insulin resistance and impaired glucose tolerance (221). In humans, impaired glucose tolerance is accompanied by cardiac steatosis, which precedes the onset of type 2 diabetes mellitus and left ventricular systolic dysfunction. Lipid overstorage in human cardiomyocytes may be an early manifestation in the pathogenesis of myocardial dysfunction in type 2 diabetes mellitus.

Cholesterol levels significantly correlate to the diastolic properties of the left ventricle in type 2 diabetic patients (192). The relation between cholesterol and diminished myocardial compliance may be explained by stiffness in the great vessels and myocardium due to atherosclerosis (192), but this theory has not been further examined.

However, it seems that this issue may deserve more interest. A small cross-sectional study in healthy males found a highly significant relation between LDL-cholesterol and resting long axis systolic strain rate, whereas the triglyceride levels did not seem to be related to the long axis function at all (249). This finding corresponds well with data from patients with dyslipidemia, in which reduction in cholesterol levels seemed to improve the contractile forces of the myocardium, probably by improving the endothelial function (289) and the coronary flow profile (287;290).

In type 2 diabetic patients, the major problem with assessment of cholesterol levels is influence from statin treatment regimes, or absence of such, which may interfere with the interpretation of the results. Therefore, studies in patients with metabolic syndrome may be the best way to explore this issue further (60).

Hypertension and diabetes

The majority of patients with either type 1 or type 2 diabetes develop hypertension. Patients with type 2 diabetes often suffer from isolated systolic hypertension, partially due to increased stiffening in the large arteries (291). Over time, elevated blood pressure levels can have similar detrimental effects on LV function as non-diabetic patients with hypertension. Perhaps more interesting is the question as to what role the presence of hypertension plays in the early stages of cardiac involvement in diabetic patients. Interestingly, a strong association between systolic blood pressure and long axis dysfunction has not yet been described in type 2 diabetic patients. Vinereanu and colleagues described an inverse correlation to diastolic blood pressure, but also found that a contribution of co-existing arterial hypertension to long axis dysfunction was not significant (192).

Likewise, it also appears that lowering blood pressure cannot directly be related to improved long axis function. A recently published study of 48 type 2 diabetic patients found no connection between a 7 mmHg systolic blood pressure reduction and changes in systolic strain rate in the long axis plane. However, the study demonstrated that significantly improved long axis function

correlated to reductions in LV mass, which partly reflect changes in blood pressure over time (260).
Therefore, the impact of elevated blood pressure levels cannot be fully discounted, as the MYDID study also demonstrated a systolic velocity response to dobutamine stress in type 2 diabetes with hypertension, which ranked lower than normo-hypertensive patients with diabetes, despite similar LV mass estimates (204).
The direct relation between diabetes, long axis function and arterial hypertension requires further elucidation, but from the available data it seems that elevated blood pressure levels may play a less significant role in the mechanism behind the earliest changes in long axis function. Instead it seems that hypertension truly make its presence felt at a later stage.

Coronary artery disease and myocardial microperfusion
Extensive coronary disease is often associated with reduced left ventricular function, and sceptics might argue that early stages of diabetic heart disease are only subclinical manifestations of coronary heart disease.
Nonetheless, according to a large cohort study (292), only 22 per cent of asymptomatic type 2 diabetic patients have silent ischemia assessed by SPECT (292), a number which might be even lower, when patients are subjected to aggressive treatment regimens (293).
Moreover, the large bulk of data in subclinical long axis dysfunction is based upon patients with normal stress echocardiography, which to some extent should exclude patients with severe coronary lesions. One study actually included conduct of coronary angiography in selected cases (294). Furthermore, some of the results from the large MYDID study demonstrated subclinical LV long axis dysfunction in diabetic individuals with normal coronary angiograms (204).
There is also little to justify attribution from abnormalities in the microcirculation. Although postprandial hyperglycemia has proved to decrease myocardial microperfusion (295), a direct connection between myocardial perfusion defects and the loss of long axis function has not been described. Microalbuminuria, a common surrogate for widespread involvement of the microcirculation in diabetic patients, also has not been linked to abnormal long axis function (29;160).
What is known about transmural myocardial blood flow and diabetes is that coronary blood flow is reduced in patients with LVH (296) and possibly also associated with the glycemic control (297), but more studies are needed. Regarding long axis dysfunction, a recent TDI-study did not find any relation between transmural blood flow and subclinical myocardial long axis dysfunction in type 2 diabetic patients (298).
In summary, diabetic cardiomyopathy remains without proper definition, However, TDI studies have contributed with data showing that there is an early involvement of systolic function, which is correlated to the substrate metabolism as well as LVH and to some extent hypertension. Proper treatment of diabetes takes all these components into account (13).
Overt heart failure in hypertensive diabetic patients will probably appear due to similar mechanism as described in non-diabetic hypertension. However, since type 2 diabetes almost has endemic behaviour, in the future we will see patients with dilated cardiomyopathy and a coexisting type 2 diabetes. This coincidence will mistakenly be considered a “diabetic cardiomyopathy”. Whether TDI can help the clinician to distinguish between the two, will be a challenge for the future.

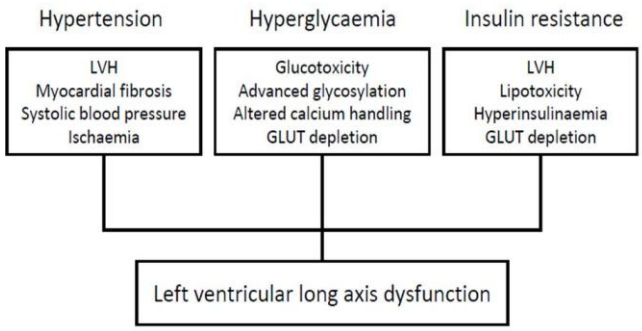

Figure 3. *Tentative mechanisms behind long axis dysfunction, in patients with hypertension and diabetes.*

CONCLUSION
Left ventricular systolic long axis dysfunction seems to be the earliest stage in myocardial disease.
In normal subjects, long axis function deteriorates with age and increasing systolic blood pressure, which emphasizes the importance of age matched control groups with similar blood pressure levels.
In hypertensive individuals long axis function seems mainly dependent on the presence of LVH and myocardial fibrosis, and accordingly also to presence of diastolic dysfunction.
Long axis dysfunction in type 2 diabetic individuals appears before the presence of more well described complications like retinopathy and albuminuria.
In several studies, long axis dysfunction has been closely related to hyperglycemia, observations which can even be found in non-diabetic individuals.
It seems that improved glycemic control improves long axis function, which means that the underlying mechanisms behind hyperglycemia and insulin resistance influence the contractile forces of the myocardium in a reversible manner.

FUTURE PERSPECTIVES
Considerations for the future seem manifold. By introduction of new echocardiographic methods, it may be possible to optimize deformation imaging and thereby make detection of subclinical myocardial dysfunction applicable for the clinician. More advanced off-line analysis software and new entities like Speckle Tracking may be a solution to this problem. Speckle tracking seems less influenced by image acquisition pitfalls and may become the preferred deformation imaging modality (299-301), but such new methods need validation.
In patients with antecedent hypertension and acute myocardial infarction, a new study is being conducted at the department of cardiology, Skejby Hospital, in which more advanced echocardiographic assessment and blood pressure measurements are used. This will provide more data about the relation between hypertension, diastolic dysfunction and myocardial infarction. In addition, more data will make it possible to make a register study on the incidence of atrial fibrillation, stroke and death in this specific cohort of patients.

Prediabetic, prehypertensive individuals should be explored in terms of LV dysfunction, blood pressure and metabolic control, to be able to understand the preclinical stages of LV dysfunction.
In diabetic individuals, a large randomized study on LV function and optimized glycemic control is already under way (252). A similar setup in Denmark is difficult, but other questions could be addressed. Short term alterations in glycemic control may influence LV function, which could be elucidated by studies using clamp-technique.

SUMMARY

The present thesis summarizes studies on subclinical left ventricular dysfunction in patients with hypertension and diabetes. Left ventricular systolic long axis dysfunction seems to be the earliest stage in myocardial disease and therefore an important focus of attention, to determine what causes the myocardium to fail.
At present, imaging of myocardial deformation in the long axis plane by strain or strain rate seems to be the best applicable method, due to its independence of tethering and translational motion, but also considering load stability, reproducibility and heart rate independence.
Long axis function deteriorates with age and increasing systolic blood pressure in normal individuals.
In hypertensive individuals long axis dysfunction seems mainly dependent on the presence of LVH and myocardial fibrosis, and accordingly also to presence of diastolic dysfunction. However, if a hypertensive patient develops a myocardial infarction, no additional loss of long axis function is found, but worsened diastolic function compared to non-hypertensive patients.
In type 2 diabetic individuals, long axis dysfunction appears before the presence of more well described complications like retinopathy and albuminuria.
In several studies, long axis dysfunction is closely related to hyperglycemia, observations which can even be found in non-diabetic individuals.
It seems that improved glycemic control improves long axis function, which means that the underlying mechanisms behind hyperglycemia and insulin resistance influence the contractile forces of the myocardium in a reversible manner.

REFERENCES

1 Chalil S, Stegemann B, Muhyaldeen S, Khadjooi K, Smith RE, Jordan PJ, Leyva F: Intraventricular dyssynchrony predicts mortality and morbidity after cardiac resynchronization therapy: a study using cardiovascular magnetic resonance tissue synchronization imaging. J.Am.Coll.Cardiol. 2007; 50: 243-52
2 Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC, Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B: ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005; 112: e154-e235
3 Mosterd A, Hoes AW: Clinical epidemiology of heart failure. Heart 2007; 93: 1137-46
4 Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK: The progression from hypertension to congestive heart failure. JAMA 1996; 275: 1557-62
5 Hypertension: uncontrolled and conquering the world. Lancet 2007; 370: 539
6 Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB: The Incidence of Congestive Heart Failure in Type 2 Diabetes: An update. Diabetes Care 2004; 27: 1879-84
7 Nichols GA, Hillier TA, Erbey JR, Brown JB: Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. Diabetes Care 2001; 24: 1614-9
8 Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR: Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000; 321: 412-9
9 Tarnow L, Rossing P, Gall MA, Nielsen FS, Parving HH: Prevalence of arterial hypertension in diabetic patients before and after the JNC-V. Diabetes Care 1994; 17: 1247-51
10 Moore WV, Fredrickson D, Brenner A, Childs B, Tatpati O, Hoffman JM, Guthrie R: Prevalence of hypertension in patients with type II diabetes in referral versus primary care clinics. J.Diabetes Complications 1998; 12: 302-6
11 Messerli FH, Williams B, Ritz E: Essential hypertension. Lancet 2007; 370: 591-603
12 Aksnes TA, Kjeldsen SE, Rostrup M, Omvik P, Hua TA, Julius S: Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. Hypertension 2007; 50: 467-73
13 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N.Engl.J.Med. 2003; 348: 383-93
14 Gilbert RE, Connelly K, Kelly DJ, Pollock CA, Krum H: Heart failure and nephropathy: catastrophic and interrelated complications of diabetes. Clin.J.Am.Soc.Nephrol. 2006; 1: 193-208
15 Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, .: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J.Am.Soc.Echocardiogr. 1989; 2: 358-67
16 Schiller NB: Two-dimensional echocardiographic determination of left ventricular volume, systolic function, and mass. Summary and discussion of the 1989 recommendations of the American Society of Echocardiography. Circulation 1991; 84: I280-I287
17 Nishimura RA, Tajik AJ: Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. J.Am.Coll.Cardiol. 1997; 30: 8-18
18 Rakowski H, Appleton C, Chan KL, Dumesnil JG, Honos G, Jue J, Koilpillai C, Lepage S, Martin RP, Mercier LA, O'Kelly B, Prieur T, Sanfilippo A, Sasson Z, Alvarez N, Pruitt R, Thompson C, Tomlinson C: Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. J Am.Soc.Echocardiogr. 1996; 9: 736-60
19 Streeter DD, Jr., Spotnitz HM, Patel DP, Ross J, Jr., Sonnenblick EH: Fiber orientation in the canine left ventricle during diastole and systole. Circ.Res. 1969; 24: 339-47
20 Helm PA, Younes L, Beg MF, Ennis DB, Leclercq C, Faris OP, McVeigh E, Kass D, Miller MI, Winslow RL: Evidence of structural remodeling in the dyssynchronous failing heart. Circ.Res. 2006; 98: 125-32
21 Tseng WY, Reese TG, Weisskoff RM, Brady TJ, Wedeen VJ: Myocardial fiber shortening in humans: initial results of MR imaging. Radiology 2000; 216: 128-39
22 MacGowan GA, Shapiro EP, Azhari H, Siu CO, Hees PS, Hutchins GM, Weiss JL, Rademakers FE: Noninvasive measurement of shortening in the fiber and cross-fiber directions in the normal human left ventricle and in idiopathic dilated cardiomyopathy. Circulation 1997; 96: 535-41
23 Kim HK, Sohn DW, Lee SE, Choi SY, Park JS, Kim YJ, Oh BH, Park YB, Choi YS: Assessment of left ventricular rotation and torsion with two-dimensional speckle tracking echocardiography. J.Am.Soc.Echocardiogr. 2007; 20: 45-53
24 Nakai H, Takeuchi M, Nishikage T, Kokumai M, Otani S, Lang RM: Effect of aging on twist-displacement loop by 2-dimensional speckle tracking imaging. J.Am.Soc.Echocardiogr. 2006; 19: 880-5
25 Teplick R, Haas GS, Trautman E, Titus J, Geffin G, Daggett WM: Time dependence of the oxygen cost of force development during systole in the canine left ventricle. Circ.Res. 1986; 59: 27-38
26 Suga H, Hayashi T, Suehiro S, Hisano R, Shirahata M, Ninomiya I: Equal oxygen consumption rates of isovolumic and ejecting contractions with equal systolic pressure-volume areas in canine left ventricle. Circ.Res. 1981; 49: 1082-91
27 Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF: Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur.Heart J. 2008; 29: 1283-9

28 Vinereanu D, Florescu N, Sculthorpe N, Tweddel AC, Stephens MR, Fraser AG: Differentiation between pathologic and physiologic left ventricular hypertrophy by tissue Doppler assessment of long-axis function in patients with hypertrophic cardiomyopathy or systemic hypertension and in athletes. Am.J.Cardiol. 2001; 88: 53-8
29 Andersen NH, Poulsen SH, Eiskjaer H, Poulsen PL, Mogensen CE: Decreased left ventricular longitudinal contraction in normotensive and normoalbuminuric patients with Type II diabetes mellitus: a Doppler tissue tracking and strain rate echocardiography study. Clin.Sci.(Lond) 2003; 105: 59-66
30 Fang ZY, Schull-Meade R, Leano R, Mottram PM, Prins JB, Marwick TH: Screening for heart disease in diabetic subjects. Am.Heart J. 2005; 149: 349-54
31 Andersen NH, Karlsen FM, Gerdes JC, Kaltoft A, Sloth E, Thuesen L, Botker HE, Poulsen SH: No beneficial effects of coronary thrombectomy on left ventricular systolic and diastolic function in patients with acute S-T elevation myocardial infarction: a randomized clinical trial. J.Am.Soc.Echocardiogr. 2007; 20: 724-30
32 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-72
33 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens. 2003; 21: 1011-53
34 Richards AM, Nicholls MG, Troughton RW, Lainchbury JG, Elliott J, Frampton C, Espiner EA, Crozier IG, Yandle TG, Turner J: Antecedent hypertension and heart failure after myocardial infarction. J.Am.Coll.Cardiol. 2002; 39: 1182-8
35 Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet.Med. 1998; 15: 539-53
36 Mogensen CE, Keane WF, Bennett PH, Jerums G, Parving HH, Passa P, Steffes MW, Striker GE, Viberti GC: Prevention of diabetic renal disease with special reference to microalbuminuria. Lancet 1995; 346: 1080-4
37 Reddy S, Bichler J, Wells-Knecht KJ, Thorpe SR, Baynes JW: N epsilon-(carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins. Biochemistry 1995; 34: 10872-8
38 Berg TJ, Clausen JT, Torjesen PA, Dahl-Jorgensen K, Bangstad HJ, Hanssen KF: The advanced glycation end product Nepsilon-(carboxymethyl)lysine is increased in serum from children and adolescents with type 1 diabetes. Diabetes Care 1998; 21: 1997-2002
39 Kim WY, Sogaard P, Egeblad H, Andersen NT, Kristensen B: Three-dimensional echocardiography with tissue harmonic imaging shows excellent reproducibility in assessment of left ventricular volumes. J.Am.Soc.Echocardiogr. 2001; 14: 612-7
40 Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL: How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur.Heart J. 2007; 28: 2539-50
41 Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, Tajik AJ: Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788-94
42 Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA: Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J.Am.Coll.Cardiol. 1997; 30: 1527-33
43 Liang HY, Cauduro SA, Pellikka PA, Bailey KR, Grossardt BR, Yang EH, Rihal C, Seward JB, Miller FA, Abraham TP: Comparison of usefulness of echocardiographic Doppler variables to left ventricular end-diastolic pressure in predicting future heart failure events. Am.J.Cardiol. 2006; 97: 866-71
44 Andersen NH, Karlsen FM, Gerdes JC, Kaltoft A, Bottcher M, Sloth E, Thuesen L, Botker HE, Poulsen SH: Diastolic Dysfunction After an Acute Myocardial Infarction in Patients with Antecedent Hypertension. J.Am.Soc.Echocardiogr. 2007;
45 Arques S, Ambrosi P, Roux E, Habib G: Potentials and limitations of color M-Mode and tissue Doppler indexes in identifying pseudonormal mitral filling pattern in patients with acute symptoms of heart failure and preserved left ventricular systolic function. Am.J Cardiol. 2004; 93: 1057-60
46 Takatsuji H, Mikami T, Urasawa K, Teranishi J, Onozuka H, Takagi C, Makita Y, Matsuo H, Kusuoka H, Kitabatake A: A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. J.Am.Coll.Cardiol. 1996; 27: 365-71
47 Asbjørn Støylen: Homepage regarding Tissue Doppler Imaging. (http://folk.ntnu.no/stoylen/), Dept. of Circulation and Medical Imaging (ISB) Edition. 2004.
48 Hanekom L, Lundberg V, Leano R, Marwick TH: Optimisation of strain rate imaging for application to stress echocardiography. Ultrasound Med.Biol. 2004; 30: 1451-60
49 Thomas JD, Popovic ZB: Assessment of left ventricular function by cardiac ultrasound. J.Am.Coll.Cardiol. 2006; 48: 2012-25
50 Nagueh SF, Kopelen HA, Lim DS, Zoghbi WA, Quinones MA, Roberts R, Marian AJ: Tissue Doppler imaging consistently detects myocardial contraction and relaxation abnormalities, irrespective of cardiac hypertrophy, in a transgenic rabbit model of human hypertrophic cardiomyopathy. Circulation 2000; 102: 1346-50
51 Zamorano J, Wallbridge DR, Ge J, Drozd J, Nesser J, Erbel R: Non-invasive assessment of cardiac physiology by tissue Doppler echocardiography. A comparison with invasive haemodynamics. Eur.Heart J. 1997; 18: 330-9
52 Heimdal A: Technical principles of tissue velocity and strain imaging methods, Myocardial Imaging. Tissue Doppler and Speckle tracking, 1 Edition. Edited by Marwick T, Yu CM. Oxford, Blackwell, 2007, pp 3-17
53 Tartiere JM, Logeart D, Tartiere-Kesri L, Cohen-Solal A: Color tissue Doppler underestimates myocardial velocity as compared to spectral tissue Doppler: Poor reliability between both methods. Eur.J.Echocardiogr. 2007;
54 McCulloch M, Zoghbi WA, Davis R, Thomas C, Dokainish H: Color tissue Doppler myocardial velocities consistently underestimate spectral tissue Doppler velocities: impact on calculation peak transmitral pulsed Doppler velocity/early diastolic tissue Doppler velocity (E/Ea). J.Am.Soc.Echocardiogr. 2006; 19: 744-8
55 Andersen NH, Poulsen SH: Evaluation of the longitudinal contraction of the left ventricle in normal subjects by Doppler tissue tracking and strain rate. J Am.Soc.Echocardiogr. 2003; 16: 716-23
56 Nikitin NP, Witte KK, Thackray SD, de Silva R, Clark AL, Cleland JG: Longitudinal ventricular function: normal values of atrioventricular annular and myocardial velocities measured with quantitative two-dimensional color Doppler tissue imaging. J.Am.Soc.Echocardiogr. 2003; 16: 906-21
57 Eidem BW, McMahon CJ, Cohen RR, Wu J, Finkelshteyn I, Kovalchin JP, Ayres NA, Bezold LI, O'Brian SE, Pignatelli RH: Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. J.Am.Soc.Echocardiogr. 2004; 17: 212-21
58 Peverill RE, Gelman JS, Mottram PM, Moir S, Jankelowitz C, Bain JL, Donelan L: Factors associated with mitral annular systolic and diastolic velocities in healthy adults. J.Am.Soc.Echocardiogr. 2004; 17: 1146-54
59 Bogaert J, Rademakers FE: Regional nonuniformity of normal adult human left ventricle. Am.J.Physiol Heart Circ.Physiol 2001; 280: H610-H620
60 Andersen NH, Bojesen A, Kristensen K, Birkebaek NH, Fedder J, Bennett P, Christiansen JS, Gravholt CH: Left ventricular dysfunction in Klinefelter syndrome is associated to insulin resistance, abdominal adiposity and hypogonadism. Clin.Endocrinol.(Oxf) 2008; 69: 785-91
61 Andersen NH, Hjerrild BE, Sorensen K, Pedersen EM, Stochholm K, Gormsen LC, Horlyck A, Christiansen JS, Gravholt CH: Subclinical left ventricular dysfunction in normotensive women with Turner's syndrome. Heart 2006; 92: 1516-7
62 Sogaard P, Egeblad H, Kim WY, Jensen HK, Pedersen AK, Kristensen BO, Mortensen PT: Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am.Coll.Cardiol. 2002; 40: 723-30
63 Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ: Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J.Am.Coll.Cardiol. 2004; 44: 1834-40
64 Yu CM, Sanderson JE, Marwick TH, Oh JK: Tissue Doppler imaging a new prognosticator for cardiovascular diseases. J.Am.Coll.Cardiol. 2007; 49: 1903-14
65 Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA: Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. Circulation 2000; 102: 1158-64
66 Yip G, Abraham T, Belohlavek M, Khandheria BK: Clinical applications of strain rate imaging. J.Am.Soc.Echocardiogr. 2003; 16: 1334-42
67 Pauliks LB, Chan KC, Chang D, Kirby SK, Logan L, DeGroff CG, Boucek MM, Valdes-Cruz LM: Regional myocardial velocities and isovolumic contraction acceleration before and after device closure of atrial septal defects: a color tissue Doppler study. Am.Heart J. 2005; 150: 294-301
68 Vinereanu D, Khokhar A, Fraser AG: Reproducibility of pulsed wave tissue Doppler echocardiography. J Am.Soc.Echocardiogr. 1999; 12: 492-9
69 Weidemann F, Jamal F, Sutherland GR, Claus P, Kowalski M, Hatle L, De S, I, Bijnens B, Rademakers FE: Myocardial function defined by strain

rate and strain during alterations in inotropic states and heart rate. Am.J.Physiol Heart Circ.Physiol 2002; 283: H792-H799
70 Weidemann F, Jamal F, Kowalski M, Kukulski T, D'hooge J, Bijnens B, Hatle L, De S, I, Sutherland GR: Can strain rate and strain quantify changes in regional systolic function during dobutamine infusion, B-blockade, and atrial pacing--implications for quantitative stress echocardiography. J Am.Soc.Echocardiogr. 2002; 15: 416-24
71 Andersen NH, Terkelsen CJ, Sloth E, Poulsen SH: Influence of preload alterations on parameters of systolic left ventricular long-axis function: a Doppler tissue study. J.Am.Soc.Echocardiogr. 2004; 17: 941-7
72 Abali G, Tokgozoglu L, Ozcebe OI, Aytemir K, Nazli N: Which Doppler parameters are load independent? A study in normal volunteers after blood donation. J.Am.Soc.Echocardiogr. 2005; 18: 1260-5
73 Hsiao SH, Huang WC, Sy CL, Lin SK, Lee TY, Liu CP: Doppler tissue imaging and color M-mode flow propagation velocity: are they really preload independent? J.Am.Soc.Echocardiogr. 2005; 18: 1277-84
74 Pela G, Regolisti G, Coghi P, Cabassi A, Basile A, Cavatorta A, Manca C, Borghetti A: Effects of the reduction of preload on left and right ventricular myocardial velocities analyzed by Doppler tissue echocardiography in healthy subjects. Eur.J.Echocardiogr. 2004; 5: 262-71
75 Gaasch WH, Carroll JD, Blaustein AS, Bing OH: Myocardial relaxation: effects of preload on the time course of isovolumetric relaxation. Circulation 1986; 73: 1037-41
76 Takeda S, Rimington H, Smeeton N, Chambers J: Long axis excursion in aortic stenosis. Heart 2001; 86: 52-6
77 Rusmer RF: Initial phase of ventricular systole: asynchronous contraction. Am.J.Physiol 1956; 184: 188-94
78 Remme EW, Lyseggen E, Helle-Valle T, Opdahl A, Pettersen E, Vartdal T, Ragnarsson A, Ljosland M, Ihlen H, Edvardsen T, Smiseth OA: Mechanisms of preejection and postejection velocity spikes in left ventricular myocardium: interaction between wall deformation and valve events. Circulation 2008; 118: 373-80
79 Vogel M, Cheung MM, Li J, Kristiansen SB, Schmidt MR, White PA, Sorensen K, Redington AN: Noninvasive assessment of left ventricular force-frequency relationships using tissue Doppler-derived isovolumic acceleration: validation in an animal model. Circulation 2003; 107: 1647-52
80 Lyseggen E, Rabben SI, Skulstad H, Urheim S, Risoe C, Smiseth OA: Myocardial acceleration during isovolumic contraction: relationship to contractility. Circulation 2005; 111: 1362-9
81 Vogel M, Schmidt MR, Kristiansen SB, Cheung M, White PA, Sorensen K, Redington AN: Validation of myocardial acceleration during isovolumic contraction as a novel noninvasive index of right ventricular contractility: comparison with ventricular pressure-volume relations in an animal model. Circulation 2002; 105: 1693-9
82 Dalsgaard M, Snyder EM, Kjaergaard J, Johnson BD, Hassager C, Oh JK: Isovolumic acceleration measured by tissue Doppler echocardiography is preload independent in healthy subjects. Echocardiography. 2007; 24: 572-9
83 Cheung M, Redington A, Vogel M, Schmidt M, Sorensen K: Influence of preload alterations on parameters of systolic left ventricular long-axis function: a Doppler tissue study: flawed methodology leads to spurious results. J.Am.Soc.Echocardiogr. 2005; 18: 298
84 Cheung MM, Redington AN, Schmidt MR, Sorensen KE, Vogel M: Letter regarding article by Lyseggen et al, "Myocardial acceleration during isovolumic contraction: relationship to contractility". Circulation 2005; 112: e135-e136
85 Ruan Q, Nagueh SF: Usefulness of isovolumic and systolic ejection signals by tissue Doppler for the assessment of left ventricular systolic function in ischemic or idiopathic dilated cardiomyopathy. Am.J.Cardiol. 2006; 97: 872-5
86 Pan C, Hoffmann R, Kuhl H, Severin E, Franke A, Hanrath P: Tissue tracking allows rapid and accurate visual evaluation of left ventricular function. Eur J Echocardiogr. 2001; 2: 197-202
87 Borges AC, Kivelitz D, Walde T, Reibis RK, Grohmann A, Panda A, Wernecke KD, Rutsch W, Hamm B, Baumann G: Apical tissue tracking echocardiography for characterization of regional left ventricular function: comparison with magnetic resonance imaging in patients after myocardial infarction. J.Am.Soc.Echocardiogr. 2003; 16: 254-62
88 Vestergaard ET, Andersen NH, Hansen TK, Rasmussen LM, Moller N, Sorensen KE, Sloth E, Jorgensen JO: Cardiovascular effects of intravenous ghrelin infusion in healthy young men. Am.J.Physiol Heart Circ.Physiol 2007;
89 Edvardsen T, Gerber BL, Garot J, Bluemke DA, Lima JA, Smiseth OA: Quantitative assessment of intrinsic regional myocardial deformation by Doppler strain rate echocardiography in humans: validation against three-dimensional tagged magnetic resonance imaging. Circulation 2002; 106: 50-6
90 Heimdal A, Stoylen A, Torp H, Skjaerpe T: Real-time strain rate imaging of the left ventricle by ultrasound. J Am.Soc.Echocardiogr. 1998; 11: 1013-9
91 Stoylen A, Heimdal A, Bjornstad K, Torp HG, Skjaerpe T: Strain Rate Imaging by Ultrasound in the Diagnosis of Regional Dysfunction of the Left Ventricle. Echocardiography. 1999; 16: 321-9
92 Abraham TP, Nishimura RA: Myocardial strain: can we finally measure contractility? J Am.Coll.Cardiol. 2001; 37: 731-4
93 Caiani EG, Weinert L, Takeuchi M, Veronesi F, Sugeng L, Corsi C, Capderou A, Cerutti S, Vaida P, Lang RM: Evaluation of alterations on mitral annulus velocities, strain, and strain rates due to abrupt changes in preload elicited by parabolic flight. J.Appl.Physiol 2007; 103: 80-7
94 Kjaergaard J, Snyder EM, Hassager C, Oh JK, Johnson BD: Impact of preload and afterload on global and regional right ventricular function and pressure: a quantitative echocardiography study. J.Am.Soc.Echocardiogr. 2006; 19: 515-21
95 Eyskens B, Ganame J, Claus P, Boshoff D, Gewillig M, Mertens L: Ultrasonic strain rate and strain imaging of the right ventricle in children before and after percutaneous closure of an atrial septal defect. J.Am.Soc.Echocardiogr. 2006; 19: 994-1000
96 D'hooge J, Heimdal A, Jamal F, Kukulski T, Bijnens B, Rademakers F, Hatle L, Suetens P, Sutherland GR: Regional strain and strain rate measurements by cardiac ultrasound: principles, implementation and limitations. Eur J Echocardiogr. 2000; 1: 154-70
97 Marwick TH: Straining to detect ischaemia. Eur.Heart J. 2007; 28: 1407-8
98 Marwick TH: Measurement of strain and strain rate by echocardiography: ready for prime time? J.Am.Coll.Cardiol. 2006; 47: 1313-27
99 Kowalski M, Kukulski T, Jamal F, D'hooge J, Weidemann F, Rademakers F, Bijnens B, Hatle L, Sutherland GR: Can natural strain and strain rate quantify regional myocardial deformation? A study in healthy subjects. Ultrasound Med.Biol. 2001; 27: 1087-97
100 Stoylen A, Skjaerpe T: Systolic long axis function of the left ventricle. Global and regional information. Scand.Cardiovasc.J. 2003; 37: 253-8
101 Slordahl SA, Bjaerum S, Amundsen BH, Stoylen A, Heimdal A, Rabben SI, Torp H: High frame rate strain rate imaging of the interventricular septum in healthy subjects. Eur J Ultrasound 2001; 14: 149-55
102 D'hooge J, Konofagou E, Jamal F, Heimdal A, Barrios L, Bijnens B, Thoen J, Van De WF, Sutherland G, Suetens P: Two-dimensional ultrasonic strain rate measurement of the human heart in vivo. IEEE Trans.Ultrason.Ferroelectr.Freq.Control 2002; 49: 281-6
103 Weidemann F, Eyskens B, Jamal F, Mertens L, Kowalski M, D'hooge J, Bijnens B, Gewillig M, Rademakers F, Hatle L, Sutherland GR: Quantification of regional left and right ventricular radial and longitudinal function in healthy children using ultrasound-based strain rate and strain imaging. J.Am.Soc.Echocardiogr. 2002; 15: 20-8
104 Haider AW, Larson MG, Franklin SS, Levy D: Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann.Intern.Med. 2003; 138: 10-6
105 Olsen MH, Wachtell K, de Simone G, Palmieri V, Dige-Petersen H, Devereux RB, Ibsen H, Rokkedal J: Is inappropriate left ventricular mass related to neurohormonal factors and/or arterial changes in hypertension? A LIFE substudy. J.Hum.Hypertens. 2004; 18: 437-43
106 Perlini S, Muiesan ML, Cuspidi C, Sampieri L, Trimarco B, Aurigemma GP, Agabiti-Rosei E, Mancia G: Midwall mechanics are improved after regression of hypertensive left ventricular hypertrophy and normalization of chamber geometry. Circulation 2001; 103: 678-83
107 Maurer MS, Burkhoff D, Fried LP, Gottdiener J, King DL, Kitzman DW: Ventricular structure and function in hypertensive participants with heart failure and a normal ejection fraction: the Cardiovascular Health Study. J.Am.Coll.Cardiol. 2007; 49: 972-81
108 Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JH: Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am.Coll.Cardiol. 1992; 19: 1550-8
109 Devereux RB, Roman MJ: Left ventricular hypertrophy in hypertension: stimuli, patterns, and consequences. Hypertens.Res. 1999; 22: 1-9
110 Galderisi M, de Simone G, Cicala S, De Simone L, D'Errico A, Caso P, de Divitiis O: Coronary flow reserve in hypertensive patients with appropriate or inappropriate left ventricular mass. J.Hypertens. 2003; 21: 2183-8
111 Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP: Outcome of heart failure with preserved ejection fraction in a population-based study. N.Engl.J.Med. 2006; 355: 260-9
112 Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM: Trends in prevalence and outcome of heart failure with preserved ejection fraction. N.Engl.J.Med. 2006; 355: 251-9
113 Gandhi SK, Powers JC, Nomeir AM, Fowle K, Kitzman DW, Rankin KM, Little WC: The pathogenesis of acute pulmonary edema associated with hypertension. N.Engl.J.Med. 2001; 344: 17-22
114 Dabbah S, Reisner SA, Aronson D, Agmon Y: Left ventricular filling hemodynamics in patients with pulmonary edema and preserved versus reduced left ventricular ejection fraction: a prospective Doppler echocardiographic study. J.Am.Soc.Echocardiogr. 2006; 19: 733-43

115 Little WC: Hypertensive pulmonary oedema is due to diastolic dysfunction. Eur.Heart J. 2001; 22: 1961-4
116 Tanaka M, Fujiwara H, Onodera T, Wu DJ, Hamashima Y, Kawai C: Quantitative analysis of myocardial fibrosis in normals, hypertensive hearts, and hypertrophic cardiomyopathy. Br.Heart J. 1986; 55: 575-81
117 Berenji K, Drazner MH, Rothermel BA, Hill JA: Does load-induced ventricular hypertrophy progress to systolic heart failure? Am.J.Physiol Heart Circ.Physiol 2005; 289: H8-H16
118 de Simone G, Palmieri V, Bella JN, Celentano A, Hong Y, Oberman A, Kitzman DW, Hopkins PN, Arnett DK, Devereux RB: Association of left ventricular hypertrophy with metabolic risk factors: the HyperGEN study. J.Hypertens. 2002; 20: 323-31
119 de Simone G, Kitzman DW, Palmieri V, Liu JE, Oberman A, Hopkins PN, Bella JN, Rao DC, Arnett DK, Devereux RB: Association of inappropriate left ventricular mass with systolic and diastolic dysfunction: the HyperGEN study. Am.J.Hypertens. 2004; 17: 828-33
120 Hoedemaekers YM, Caliskan K, Majoor-Krakauer D, van dL, I, Michels M, Witsenburg M, ten Cate FJ, Simoons ML, Dooijes D: Cardiac {beta}-myosin heavy chain defects in two families with non-compaction cardiomyopathy: linking non-compaction to hypertrophic, restrictive, and dilated cardiomyopathies. Eur.Heart J. 2007; 28: 2732-7
121 Monserrat L, Hermida-Prieto M, Fernandez X, Rodriguez I, Dumont C, Cazon L, Cuesta MG, Gonzalez-Juanatey C, Peteiro J, Alvarez N, Penas-Lado M, Castro-Beiras A: Mutation in the alpha-cardiac actin gene associated with apical hypertrophic cardiomyopathy, left ventricular non-compaction, and septal defects. Eur.Heart J. 2007; 28: 1953-61
122 Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N.Engl.J Med. 1990; 322: 1561-6
123 Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB: Relation of arterial structure and function to left ventricular geometric patterns in hypertensive adults. J Am.Coll.Cardiol. 1996; 28: 751-6
124 Izzo JL, Jr., Gradman AH: Mechanisms and management of hypertensive heart disease: from left ventricular hypertrophy to heart failure. Med.Clin.North Am. 2004; 88: 1257-71
125 Verdecchia P, Reboldi G, Schillaci G, Borgioni C, Ciucci A, Telera MP, Santeusanio F, Porcellati C, Brunetti P: Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. Circulation 1999; 100: 1802-7
126 Devereux RB, Roman MJ, Paranicas M, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Rodeheffer RJ, Cowan LD, Howard BV: A population-based assessment of left ventricular systolic dysfunction in middle-aged and older adults: the Strong Heart Study. Am.Heart J. 2001; 141: 439-46
127 Drazner MH, Rame JE, Marino EK, Gottdiener JS, Kitzman DW, Gardin JM, Manolio TA, Dries DL, Siscovick DS: Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. J.Am.Coll.Cardiol. 2004; 43: 2207-15
128 Rame JE, Ramilo M, Spencer N, Blewett C, Mehta SK, Dries DL, Drazner MH: Development of a depressed left ventricular ejection fraction in patients with left ventricular hypertrophy and a normal ejection fraction. Am.J.Cardiol. 2004; 93: 234-7
129 Wachtell K, Palmieri V, Olsen MH, Gerdts E, Papademetriou V, Nieminen MS, Smith G, Dahlof B, Aurigemma GP, Devereux RB: Change in systolic left ventricular performance after 3 years of antihypertensive treatment: the Losartan Intervention for Endpoint (LIFE) Study. Circulation 2002; 106: 227-32
130 Weber KT, Jalil JE, Janicki JS, Pick R: Myocardial collagen remodeling in pressure overload hypertrophy. A case for interstitial heart disease. Am.J Hypertens. 1989; 2: 931-40
131 Weber KT, Brilla CG: Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991; 83: 1849-65
132 Diez J, Lopez B, Gonzalez A, Querejeta R: Clinical aspects of hypertensive myocardial fibrosis. Curr.Opin.Cardiol. 2001; 16: 328-35
133 Brilla CG, Janicki JS, Weber KT: Impaired diastolic function and coronary reserve in genetic hypertension. Role of interstitial fibrosis and medial thickening of intramyocardial coronary arteries. Circ.Res. 1991; 69: 107-15
134 Weber KT: Cardioreparation in hypertensive heart disease. Hypertension 2001; 38: 588-91
135 Diez J, Panizo A, Gil MJ, Monreal I, Hernandez M, Pardo MJ: Serum markers of collagen type I metabolism in spontaneously hypertensive rats: relation to myocardial fibrosis. Circulation 1996; 93: 1026-32
136 Ohkubo N, Matsubara H, Nozawa Y, Mori Y, Murasawa S, Kijima K, Maruyama K, Masaki H, Tsutumi Y, Shibazaki Y, Iwasaka T, Inada M: Angiotensin type 2 receptors are reexpressed by cardiac fibroblasts from failing myopathic hamster hearts and inhibit cell growth and fibrillar collagen metabolism. Circulation 1997; 96: 3954-62
137 Weber KT: Fibrosis and hypertensive heart disease. Curr.Opin.Cardiol. 2000; 15: 264-72
138 Querejeta R, Varo N, Lopez B, Larman M, Artinano E, Etayo JC, Martinez Ubago JL, Gutierrez-Stampa M, Emparanza JI, Gil MJ, Monreal I, Mindan JP, Diez J: Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. Circulation 2000; 101: 1729-35
139 Querejeta R, Lopez B, Gonzalez A, Sanchez E, Larman M, Martinez Ubago JL, Diez J: Increased collagen type I synthesis in patients with heart failure of hypertensive origin: relation to myocardial fibrosis. Circulation 2004; 110: 1263-8
140 Maceira AM, Barba J, Varo N, Beloqui O, Diez J: Ultrasonic backscatter and serum marker of cardiac fibrosis in hypertensives. Hypertension 2002; 39: 923-8
141 Sciarretta S, Ferrucci A, Ciavarella GM, De Paolis P, Venturelli V, Tocci G, De Biase L, Rubattu S, Volpe M: Markers of inflammation and fibrosis are related to cardiovascular damage in hypertensive patients with metabolic syndrome. Am.J.Hypertens. 2007; 20: 784-91
142 Poulsen SH, Andersen NH, Heickendorff L, Mogensen CE: Relation between plasma amino-terminal propeptide of procollagen type III and left ventricular longitudinal strain in essential hypertension. Heart 2005; 91: 624-9
143 Lopez B, Querejeta R, Varo N, Gonzalez A, Larman M, Martinez Ubago JL, Diez J: Usefulness of serum carboxy-terminal propeptide of procollagen type I in assessment of the cardioreparative ability of antihypertensive treatment in hypertensive patients. Circulation 2001; 104: 286-91
144 Ciulla MM, Paliotti R, Esposito A, Diez J, Lopez B, Dahlof B, Nicholls MG, Smith RD, Gilles L, Magrini F, Zanchetti A: Different effects of antihypertensive therapies based on losartan or atenolol on ultrasound and biochemical markers of myocardial fibrosis: results of a randomized trial. Circulation 2004; 110: 552-7
145 Diez J, Querejeta R, Lopez B, Gonzalez A, Larman M, Martinez Ubago JL: Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002; 105: 2512-7
146 Brilla CG, Matsubara L, Weber KT: Advanced hypertensive heart disease in spontaneously hypertensive rats. Lisinopril-mediated regression of myocardial fibrosis. Hypertension 1996; 28: 269-75
147 Christensen MK, Olsen MH, Wachtell K, Tuxen C, Fossum E, Bang LE, Wiinberg N, Devereux RB, Kjeldsen SE, Hildebrandt P, Rokkedal J, Ibsen H: Does long-term losartan- vs atenolol-based antihypertensive treatment influence collagen markers differently in hypertensive patients? A LIFE substudy. Blood Press 2006; 15: 198-206
148 Anttila P, Jarvi K, Latvala J, Romppanen J, Punnonen K, Niemela O: Biomarkers of alcohol consumption in patients classified according to the degree of liver disease severity. Scand.J.Clin.Lab Invest 2005; 65: 141-51
149 Pagani F, Francucci CM, Moro L: Markers of bone turnover: biochemical and clinical perspectives. J.Endocrinol.Invest 2005; 28: 8-13
150 Aeschbacher BC, Hutter D, Fuhrer J, Weidmann P, Delacretaz E, Allemann Y: Diastolic dysfunction precedes myocardial hypertrophy in the development of hypertension. Am.J.Hypertens. 2001; 14: 106-13
151 Bella JN, Palmieri V, Liu JE, Kitzman DW, Oberman A, Hunt SC, Hopkins PN, Rao DC, Arnett DK, Devereux RB: Relationship between left ventricular diastolic relaxation and systolic function in hypertension: The Hypertension Genetic Epidemiology Network (HyperGEN) Study. Hypertension 2001; 38: 424-8
152 Yamada H, Oki T, Mishiro Y, Tabata T, Abe M, Onose Y, Wakatsuki T, Ito S: Effect of aging on diastolic left ventricular myocardial velocities measured by pulsed tissue Doppler imaging in healthy subjects. J Am.Soc.Echocardiogr. 1999; 12: 574-81
153 Poirier P, Bogaty P, Garneau C, Marois L, Dumesnil JG: Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. Diabetes Care 2001; 24: 5-10
154 Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ: Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003; 289: 194-202
155 Poulsen SH, Jensen SE, Egstrup K: Longitudinal changes and prognostic implications of left ventricular diastolic function in first acute myocardial infarction. Am.Heart J. 1999; 137: 910-8
156 Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB: Risks for atrial fibrillation and congestive heart failure in patients >/=65 years of age with abnormal left ventricular diastolic relaxation. Am.J.Cardiol. 2004; 93: 54-8
157 Abhayaratna WP, Barnes ME, O'Rourke MF, Gersh BJ, Seward JB, Miyasaka Y, Bailey KR, Tsang TS: Relation of arterial stiffness to left ventricular diastolic function and cardiovascular risk prediction in patients > or =65 years of age. Am.J.Cardiol. 2006; 98: 1387-92
158 Tsioufis C, Chatzis D, Dimitriadis K, Stougianos P, Kakavas A, Vlasseros I, Tousoulis D, Stefanadis C, Kallikazaros I: Left ventricular diastolic dys-

function is accompanied by increased aortic stiffness in the early stages of essential hypertension: a TDI approach. J.Hypertens. 2005; 23: 1745-50
159 Grandi AM, Santillo R, Bertolini A, Imperiale D, Broggi R, Colombo S, Selva E, Jessula A, Guasti L, Venco A: Microalbuminuria as a marker of preclinical diastolic dysfunction in never-treated essential hypertensives. Am.J.Hypertens. 2001; 14: 644-8
160 Andersen NH, Poulsen SH, Poulsen PL, Knudsen ST, Helleberg K, Hansen KW, Berg TJ, Flyvbjerg A, Mogensen CE: Left ventricular dysfunction in hypertensive patients with Type 2 diabetes mellitus. Diabet.Med. 2005; 22: 1218-25
161 Varadarajan P, Pai RG: Prognosis of congestive heart failure in patients with normal versus reduced ejection fractions: results from a cohort of 2,258 hospitalized patients. J.Card Fail. 2003; 9: 107-12
162 Aurigemma GP, Gaasch WH: Clinical practice. Diastolic heart failure. N.Engl.J.Med. 2004; 351: 1097-105
163 Maurer MS, King DL, El Khoury RL, Packer M, Burkhoff D: Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. J.Card Fail. 2005; 11: 177-87
164 Zile MR, Baicu CF, Gaasch WH: Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N.Engl.J Med. 2004; 350: 1953-9
165 Okin PM, Wachtell K, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Julius S, Lindholm LH, Nieminen MS, Edelman JM, Hille DA, Dahlof B: Regression of electrocardiographic left ventricular hypertrophy and decreased incidence of new-onset atrial fibrillation in patients with hypertension. JAMA 2006; 296: 1242-8
166 L'Allier PL, Ducharme A, Keller PF, Yu H, Guertin MC, Tardif JC: Angiotensin-converting enzyme inhibition in hypertensive patients is associated with a reduction in the occurrence of atrial fibrillation. J.Am.Coll.Cardiol. 2004; 44: 159-64
167 Moller JE, Pellikka PA, Hillis GS, Oh JK: Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. Circulation 2006; 114: 438-44
168 Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ: Trends in heart failure incidence and survival in a community-based population. JAMA 2004; 292: 344-50
169 Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP: Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet 2007; 369: 2079-87
170 Agabiti-Rosei E, Ambrosioni E, Dal Palu C, Muiesan ML, Zanchetti A: ACE inhibitor ramipril is more effective than the beta-blocker atenolol in reducing left ventricular mass in hypertension. Results of the RACE (ramipril cardioprotective evaluation) study on behalf of the RACE study group. J Hypertens. 1995; 13: 1325-34
171 Malmqvist K, Kahan T, Edner M, Held C, Hagg A, Lind L, Muller-Brunotte R, Nystrom F, Ohman KP, Osbakken MD, Ostergern J: Regression of left ventricular hypertrophy in human hypertension with irbesartan. J Hypertens. 2001; 19: 1167-76
172 Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Dahlof B: Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: The Losartan Intervention for Endpoint reduction in Hypertension (LIFE) Study. Circulation 2003; 108: 684-90
173 Gottdiener JS, Thurmann PA, Kenedi P, Schmidt A, Harder S, Rietbrock N: Influence of the angiotensin II antagonist valsartan on left ventricular hypertrophy in patients with essential hypertension. Circulation 1999; 100: 685-8
174 Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC: Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. J.Am.Coll.Cardiol. 2009; 53: 184-92
175 Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362: 777-81
176 Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A: Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N.Engl.J.Med. 2008;
177 Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP: Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002; 288: 2144-50
178 Devereux RB, Roman MJ, Liu JE, Welty TK, Lee ET, Rodeheffer R, Fabsitz RR, Howard BV: Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study. Am.J.Cardiol. 2000; 86: 1090-6
179 Poulsen SH, Andersen NH, Ivarsen PI, Mogensen CE, Egeblad H: Doppler tissue imaging reveals systolic dysfunction in patients with hypertension and apparent "isolated" diastolic dysfunction. J Am.Soc.Echocardiogr. 2003; 16: 724-31
180 Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW: Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002; 105: 1195-201
181 Burwash IG, Otto CM, Pearlman AS: Use of Doppler-derived left ventricular time intervals for noninvasive assessment of systolic function. Am.J Cardiol. 1993; 72: 1331-3
182 Andersen NH, Poulsen SH, Helleberg K, Ivarsen P, Knudsen ST, Mogensen CE: Impact of essential hypertension and diabetes mellitus on left ventricular systolic and diastolic performance. Eur.J.Echocardiogr. 2003; 4: 306-12
183 Yip G, Wang M, Zhang Y, Fung JW, Ho PY, Sanderson JE: Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? Heart 2002; 87: 121-5
184 Bruch C, Gradaus R, Gunia S, Breithardt G, Wichter T: Doppler tissue analysis of mitral annular velocities: evidence for systolic abnormalities in patients with diastolic heart failure. J Am.Soc.Echocardiogr. 2003; 16: 1031-6
185 Vinereanu D, Nicolaides E, Tweddel AC, Fraser AG: "Pure" diastolic dysfunction is associated with long-axis systolic dysfunction. Implications for the diagnosis and classification of heart failure. European Journal of Heart Failure 2005; 7: 820-8
186 Ballo P, Mondillo S, Guerrini F, Barbati R, Picchi A, Focardi M: Midwall mechanics in physiologic and hypertensive concentric hypertrophy. J.Am.Soc.Echocardiogr. 2004; 17: 418-27
187 Verdecchia P, Schillaci G, Reboldi G, Ambrosio G, Pede S, Porcellati C: Prognostic value of midwall shortening fraction and its relation with left ventricular mass in systemic hypertension. Am.J Cardiol. 2001; 87: 479-82
188 Wachtell K, Papademetriou V, Smith G, Gerdts E, Dahlof B, Engblom E, Aurigemma GP, Bella JN, Ibsen H, Rokkedal J, Devereux RB: Relation of impaired left ventricular filling to systolic midwall mechanics in hypertensive patients with normal left ventricular systolic chamber function: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. Am.Heart J. 2004; 148: 538-44
189 Wachtell K, Smith G, Gerdts E, Dahlof B, Nieminen MS, Papademetriou V, Bella JN, Ibsen H, Rokkedal J, Devereux RB: Left ventricular filling patterns in patients with systemic hypertension and left ventricular hypertrophy (the LIFE study). Losartan Intervention For Endpoint. Am.J.Cardiol. 2000; 85: 466-72
190 Przewlocka-Kosmala M, Kosmala W, Mazurek W: Left ventricular circumferential function in patients with essential hypertension. J.Hum.Hypertens. 2006; 20: 666-71
191 Ballo P, Quatrini I, Giacomin E, Motto A, Mondillo S: Circumferential versus longitudinal systolic function in patients with hypertension: a nonlinear relation. J.Am.Soc.Echocardiogr. 2007; 20: 298-306
192 Vinereanu D, Nicolaides E, Tweddel AC, Madler CF, Holst B, Boden LE, Cinteza M, Rees AE, Fraser AG: Subclinical left ventricular dysfunction in asymptomatic patients with Type II diabetes mellitus, related to serum lipids and glycated haemoglobin. Clin.Sci.(Lond) 2003; 105: 591-9
193 Fang ZY, Leano R, Marwick TH: Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. Clin.Sci.(Lond) 2004; 106: 53-60
194 Yuda S, Short L, Leano R, Marwick TH: Myocardial abnormalities in hypertensive patients with normal and abnormal left ventricular filling: a study of ultrasound tissue characterization and strain. Clin.Sci.(Lond) 2002; 103: 283-93
195 Hare JL, Brown JK, Marwick TH: Association of myocardial strain with left ventricular geometry and progression of hypertensive heart disease. Am.J.Cardiol. 2008; 102: 87-91
196 Kang SJ, Lim HS, Choi BJ, Choi SY, Hwang GS, Yoon MH, Tahk SJ, Shin JH: Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. J.Am.Soc.Echocardiogr. 2008; 21: 907-11
197 Marwick TH, Case C, Sawada S, Vasey C, Thomas JD: Prediction of outcomes in hypertensive patients with suspected coronary disease. Hypertension 2002; 39: 1113-8
198 Weitzman D, Goldbourt U: The significance of various blood pressure indices for long-term stroke, coronary heart disease, and all-cause mortality in men: the Israeli Ischemic Heart Disease study. Stroke 2006; 37: 358-63
199 Lawes CM, Vander HS, Rodgers A: Global burden of blood-pressure-related disease, 2001. Lancet 2008; 371: 1513-8
200 Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. JAMA 2002; 287: 2570-81

201 Galderisi M, Cicala S, Caso P, De Simone L, D'Errico A, Petrocelli A, de Divitiis O: Coronary flow reserve and myocardial diastolic dysfunction in arterial hypertension. Am.J.Cardiol. 2002; 90: 860-4
202 Galderisi M, de Simone G, Cicala S, Parisi M, D'Errico A, Innelli P, de Divitiis M, Mondillo S, de Divitiis O: Coronary flow reserve in hypertensive patients with hypercholesterolemia and without coronary heart disease. Am.J.Hypertens. 2007; 20: 177-83
203 Galderisi M, de Simone G, D'Errico A, Sidiropulos M, Viceconti R, Chinali M, Mondillo S, de Divitiis O: Independent association of coronary flow reserve with left ventricular relaxation and filling pressure in arterial hypertension. Am.J.Hypertens. 2008; 21: 1040-6
204 Govind S, Brodin LA, Nowak J, Quintana M, Raumina S, Ramesh SS, Keshava R, Saha S: Isolated type 2 diabetes mellitus causes myocardial dysfunction that becomes worse in the presence of cardiovascular diseases: results of the myocardial doppler in diabetes (MYDID) study 1. Cardiology 2005; 103: 189-95
205 Di B, V, Pedrinelli R, Giorgi D, Bertini A, Talini E, Mengozzi G, Palagi C, Nardi C, Dell'omo G, Paterni M, Mariani M: Coronary microcirculation in essential hypertension: a quantitative myocardial contrast echocardiographic approach. Eur.J.Echocardiogr. 2002; 3: 117-27
206 Youn HJ, Ihm SH, Lee JM, Park CS, Cho EJ, Jung HO, Jeon HK, Oh YS, Chung WS, Kim JH, Choi KB, Hong SJ: Relation between flow reserve capacity of penetrating intramyocardial coronary arteries and myocardial fibrosis in hypertension: study using transthoracic Doppler echocardiography. J.Am.Soc.Echocardiogr. 2006; 19: 373-8
207 Benetos A, Thomas F, Bean K, Gautier S, Smulyan H, Guize L: Prognostic value of systolic and diastolic blood pressure in treated hypertensive men. Arch.Intern.Med. 2002; 162: 577-81
208 Moller JE, Brendorp B, Ottesen M, Kober L, Egstrup K, Poulsen SH, Torp-Pedersen C: Congestive heart failure with preserved left ventricular systolic function after acute myocardial infarction: clinical and prognostic implications. Eur.J.Heart Fail. 2003; 5: 811-9
209 Torabi A, Cleland JG, Khan NK, Loh PH, Clark AL, Alamgir F, Caplin JL, Rigby AS, Goode K: The timing of development and subsequent clinical course of heart failure after a myocardial infarction. Eur.Heart J. 2008; 29: 859-70
210 Hellermann JP, Jacobsen SJ, Redfield MM, Reeder GS, Weston SA, Roger VL: Heart failure after myocardial infarction: clinical presentation and survival. Eur.J.Heart Fail. 2005; 7: 119-25
211 Kenchaiah S, Pfeffer MA, St John SM, Plappert T, Rouleau JL, Lamas GA, Sasson Z, Parker JO, Geltman EM, Solomon SD: Effect of antecedent systemic hypertension on subsequent left ventricular dilation after acute myocardial infarction (from the Survival and Ventricular Enlargement trial). Am.J.Cardiol. 2004; 94: 1-8
212 Spargias K, Ball S, Hall A: The prognostic significance of a history of systemic hypertension in patients randomised to either placebo or ramipril following acute myocardial infarction: evidence from the AIRE study. Acute Infarction Ramipril Efficacy. J.Hum.Hypertens. 1999; 13: 511-6
213 Parodi G, Carrabba N, Santoro GM, Memisha G, Valenti R, Buonamici P, Dovellini EV, Antoniucci D: Heart failure and left ventricular remodeling after reperfused acute myocardial infarction in patients with hypertension. Hypertension 2006; 47: 706-10
214 Nass O, Yang XP, Liu YH, Carretero OA, Khaja F, Goldstein S, Sabbah HN: Effects of pre-existing left ventricular hypertrophy on ventricular dysfunction and remodeling following myocardial infarction in rats. J.Heart Lung Transplant. 2002; 21: 1113-9
215 Poulsen SH, Moller JE, Norager B, Egstrup K: Prognostic implications of left ventricular diastolic dysfunction with preserved systolic function following acute myocardial infarction. Cardiology 2001; 95: 190-7
216 Bertomeu V, Cabades A, Morillas P, Cebrian J, Colomina F, Valencia J, Frutos A, Sanjuan R, Ruiz-Nodar JM, Gonzalez-Hernandez E: Clinical course of acute myocardial infarction in the hypertensive patient in Eastern Spain: the PRIMVAC registry. Heart Lung 2006; 35: 20-6
217 Abrignani MG, Dominguez LJ, Biondo G, Di Girolamo A, Novo G, Barbagallo M, Braschi A, Braschi G, Novo S: In-hospital complications of acute myocardial infarction in hypertensive subjects. Am.J.Hypertens. 2005; 18: 165-70
218 Witt BJ, Ballman KV, Brown RD, Jr., Meverden RA, Jacobsen SJ, Roger VL: The incidence of stroke after myocardial infarction: a meta-analysis. Am.J.Med. 2006; 119: 354-9
219 Mooe T, Eriksson P, Stegmayr B: Ischemic stroke after acute myocardial infarction. A population-based study. Stroke 1997; 28: 762-7
220 Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, Park SW, Bailey KR, Pellikka PA: Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation 2003; 107: 2207-12
221 Witteles RM, Fowler MB: Insulin-resistant cardiomyopathy clinical evidence, mechanisms, and treatment options. J.Am.Coll.Cardiol. 2008; 51: 93-102
222 Lloyd-Jones DM: The risk of congestive heart failure: sobering lessons from the Framingham Heart Study. Curr.Cardiol.Rep. 2001; 3: 184-90
223 Gustafsson I, Brendorp B, Seibaek M, Burchardt H, Hildebrandt P, Kober L, Torp-Pedersen C: Influence of diabetes and diabetes-gender interaction on the risk of death in patients hospitalized with congestive heart failure. J Am.Coll.Cardiol. 2004; 43: 771-7
224 Fox CS, Coady S, Sorlie PD, D'Agostino RB, Sr., Pencina MJ, Vasan RS, Meigs JB, Levy D, Savage PJ: Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. Circulation 2007; 115: 1544-50
225 From AM, Leibson CL, Bursi F, Redfield MM, Weston SA, Jacobsen SJ, Rodeheffer RJ, Roger VL: Diabetes in heart failure: prevalence and impact on outcome in the population. Am.J.Med. 2006; 119: 591-9
226 Guha A, Harmancey R, Taegtmeyer H: Nonischemic heart failure in diabetes mellitus. Curr.Opin.Cardiol. 2008; 23: 241-8
227 Fein FS, Sonnenblick EH: Diabetic cardiomyopathy. Prog.Cardiovasc.Dis. 1985; 27: 255-70
228 Francis GS: Diabetic cardiomyopathy: fact or fiction? Heart 2001; 85: 247-8
229 Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A: New type of cardiomyopathy associated with diabetic glomerulosclerosis. Am.J.Cardiol. 1972; 30: 595-602
230 Fang ZY, Prins JB, Marwick TH: Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. Endocr.Rev. 2004; 25: 543-67
231 Zabalgoitia M, Ismaeil MF, Anderson L, Maklady FA: Prevalence of diastolic dysfunction in normotensive, asymptomatic patients with well-controlled type 2 diabetes mellitus. Am.J.Cardiol. 2001; 87: 320-3
232 Boudina S, Abel ED: Diabetic cardiomyopathy revisited. Circulation 2007; 115: 3213-23
233 Salmasi AM, Jepson E, Grenfell A, Kirollos C, Dancy M: The degree of albuminuria is related to left ventricular hypertrophy in hypertensive diabetics and is associated with abnormal left ventricular filling: a pilot study. Angiology 2003; 54: 671-8
234 Liu JE, Robbins DC, Palmieri V, Bella JN, Roman MJ, Fabsitz R, Howard BV, Welty TK, Lee ET, Devereux RB: Association of albuminuria with systolic and diastolic left ventricular dysfunction in type 2 diabetes: the Strong Heart Study. J Am.Coll.Cardiol. 2003; 41: 2022-8
235 Charvat J, Michalova K, Chlumsky J, Valenta Z, Kvapil M: The association between left ventricle diastolic dysfunction and endothelial dysfunction and the results of stress myocardial SPECT in asymptomatic patients with type 2 diabetes. J.Int.Med.Res. 2005; 33: 473-82
236 Fernandes VR, Polak JF, Edvardsen T, Carvalho B, Gomes A, Bluemke DA, Nasir K, O'Leary DH, Lima JA: Subclinical atherosclerosis and incipient regional myocardial dysfunction in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis (MESA). J.Am.Coll.Cardiol. 2006; 47: 2420-8
237 Bertoni AG, Goff DC, Jr., D'Agostino RB, Jr., Liu K, Hundley WG, Lima JA, Polak JF, Saad MF, Szklo M, Tracy RP, Siscovick DS: Diabetic cardiomyopathy and subclinical cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2006; 29: 588-94
238 Thuesen L, Christiansen JS, Mogensen CE, Henningsen P: Cardiac hyperfunction in insulin-dependent diabetic patients developing microvascular complications. Diabetes 1988; 37: 851-6
239 Thuesen L, Christiansen JS, Schmitz O, Christensen NJ, Orskov H, Henningsen P: Increased myocardial contractility during intravenous insulin infusion in type 1 (insulin-dependent) diabetic patients: an echocardiographic study. Scand.J.Clin.Lab Invest 1988; 48: 275-84
240 Gotzsche O, Darwish A, Gotzsche L, Hansen LP, Sorensen KE: Incipient cardiomyopathy in young insulin-dependent diabetic patients: a seven-year prospective Doppler echocardiographic study. Diabet.Med. 1996; 13: 834-40
241 Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH: Echocardiographic detection of early diabetic myocardial disease. J Am.Coll.Cardiol. 2003; 41: 611-7
242 Marwick TH: Diabetic heart disease. Heart 2006; 92: 296-300
243 Sasso FC, Carbonara O, Cozzolino D, Rambaldi P, Mansi L, Torella D, Gentile S, Turco S, Torella R, Salvatore T: Effects of insulin-glucose infusion on left ventricular function at rest and during dynamic exercise in healthy subjects and noninsulin dependent diabetic patients: a radionuclide ventriculographic study. J.Am.Coll.Cardiol. 2000; 36: 219-26
244 Poornima IG, Parikh P, Shannon RP: Diabetic cardiomyopathy: the search for a unifying hypothesis. Circ.Res. 2006; 98: 596-605
245 Fujino T, Ishii Y, Takeuchi T, Hirasawa K, Tateda K, Kikuchi K, Hasebe N: Recovery of BMIPP uptake and regional wall motion in insulin resistant patients following angioplasty for acute myocardial infarction. Circ.J. 2003; 67: 757-62
246 Peterson LR, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, Dence C, Klein S, Marsala J, Meyer T, Gropler RJ: Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation 2004; 109: 2191-6
247 Monti LD, Landoni C, Setola E, Galluccio E, Lucotti P, Sandoli EP, Origgi A, Lucignani G, Piatti P, Fazio F: Myocardial insulin resistance associated

with chronic hypertriglyceridemia and increased FFA levels in Type 2 diabetic patients. Am.J.Physiol Heart Circ.Physiol 2004; 287: H1225-H1231
248 Mule G, Nardi E, Cottone S, Cusimano P, Volpe V, Piazza G, Mongiovi R, Mezzatesta G, Andronico G, Cerasola G: Influence of metabolic syndrome on hypertension-related target organ damage. J.Intern.Med. 2005; 257: 503-13
249 Andersen NH, Bojesen A, Christiansen JS, Gravholt CH: Glycemia, lipidemia and systolic left ventricular function evaluated by myocardial strain rate: a tissue Doppler echocardiographic study. Ultrasound Med.Biol. 2008; 34: 151-4
250 Fang ZY, Schull-Meade R, Downey M, Prins J, Marwick TH: Determinants of subclinical diabetic heart disease. Diabetologia 2005; 48: 394-402
251 Di B, V, Santini F, Di Cori A, Pucci A, Palagi C, Delle Donne MG, Giannetti M, Talini E, Nardi C, Pedrizzetti G, Fierabracci P, Vitti P, Pinchera A, Balbarini A: Relationship between preclinical abnormalities of global and regional left ventricular function and insulin resistance in severe obesity: a Color Doppler Imaging Study. Int.J.Obes.(Lond) 2006; 30: 948-56
252 Marwick T, Zhang N, Sharman J, Hordern M, Smith L, Prins J: Response of subclinical myocardial dysfunction in diabetes mellitus to lifestyle modification. Circulation 2005; 112: U487
253 Kilpatrick ES, Rigby AS, Atkin SL: Mean blood glucose compared with HbA(1c) in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia 2007;
254 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N.Engl.J.Med 2005; 353: 2643-53
255 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-12
256 Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH: Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann.Intern.Med. 2004; 141: 421-31
257 Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. N.Engl.J.Med. 2008; 358: 2545-59
258 Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N.Engl.J.Med. 2008; 358: 2560-72
259 Chung J, Abraszewski P, Yu X, Liu W, Krainik AJ, Ashford M, Caruthers SD, McGill JB, Wickline SA: Paradoxical increase in ventricular torsion and systolic torsion rate in type I diabetic patients under tight glycemic control. J.Am.Coll.Cardiol. 2006; 47: 384-90
260 Andersen NH, Poulsen SH, Poulsen PL, Knudsen ST, Helleberg K, Hansen KW, Dinesen DS, Eiskjaer H, Flyvbjerg A, Mogensen CE: Effects of blood pressure lowering and metabolic control on systolic left ventricular function in Type II diabetes mellitus. Clin.Sci.(Lond) 2006; 111: 53-9
261 Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. The Study Group for the Development of Pump Therapy in Diabetes. Diabetes Care 2000; 23: 1232-5
262 Andersen NH, Hansen TK, Christiansen JS: Changes in glycaemic control are related to the systolic function in type 1 diabetes mellitus. Scand.Cardiovasc.J. 2007; 41: 85-8
263 Cai L, Li W, Wang G, Guo L, Jiang Y, Kang YJ: Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway. Diabetes 2002; 51: 1938-48
264 Bojunga J, Nowak D, Mitrou PS, Hoelzer D, Zeuzem S, Chow KU: Antioxidative treatment prevents activation of death-receptor- and mitochondrion-dependent apoptosis in the hearts of diabetic rats. Diabetologia 2004; 47: 2072-80
265 Kobayashi S, Mao K, Zheng H, Wang X, Patterson C, O'Connell TD, Liang Q: Diminished GATA4 protein levels contribute to hyperglycemia-induced cardiomyocyte injury. J.Biol.Chem. 2007; 282: 21945-52
266 Fiordaliso F, Bianchi R, Staszewsky L, Cuccovillo I, Doni M, Laragione T, Salio M, Savino C, Melucci S, Santangelo F, Scanziani E, Masson S, Ghezzi P, Latini R: Antioxidant treatment attenuates hyperglycemia-induced cardiomyocyte death in rats. J.Mol.Cell Cardiol. 2004; 37: 959-68
267 Bidasee KR, Zhang Y, Shao CH, Wang M, Patel KP, Dincer UD, Besch HR, Jr.: Diabetes increases formation of advanced glycation end products on Sarco(endo)plasmic reticulum Ca2+-ATPase. Diabetes 2004; 53: 463-73
268 Abe T, Ohga Y, Tabayashi N, Kobayashi S, Sakata S, Misawa H, Tsuji T, Kohzuki H, Suga H, Taniguchi S, Takaki M: Left ventricular diastolic dysfunction in type 2 diabetes mellitus model rats. Am.J.Physiol Heart Circ.Physiol 2002; 282: H138-H148
269 Candido R, Forbes JM, Thomas MC, Thallas V, Dean RG, Burns WC, Tikellis C, Ritchie RH, Twigg SM, Cooper ME, Burrell LM: A breaker of advanced glycation end products attenuates diabetes-induced myocardial structural changes. Circ.Res. 2003; 92: 785-92
270 Vaitkevicius PV, Lane M, Spurgeon H, Ingram DK, Roth GS, Egan JJ, Vasan S, Wagle DR, Ulrich P, Brines M, Wuerth JP, Cerami A, Lakatta EG: A cross-link breaker has sustained effects on arterial and ventricular properties in older rhesus monkeys. Proc.Natl.Acad.Sci.USA 2001; 98: 1171-5
271 Asif M, Egan J, Vasan S, Jyothirmayi GN, Masurekar MR, Lopez S, Williams C, Torres RL, Wagle D, Ulrich P, Cerami A, Brines M, Regan TJ: An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. Proc.Natl.Acad.Sci.U.S.A 2000; 97: 2809-13
272 Liu J, Masurekar MR, Vatner DE, Jyothirmayi GN, Regan TJ, Vatner SF, Meggs LG, Malhotra A: Glycation end-product cross-link breaker reduces collagen and improves cardiac function in aging diabetic heart. Am.J Physiol Heart Circ.Physiol 2003; 285: H2587-H2591
273 Cao Z, Bonnet F, Candido R, Nesteroff SP, Burns WC, Kawachi H, Shimizu F, Carey RM, de Gasparo M, Cooper ME: Angiotensin type 2 receptor antagonism confers renal protection in a rat model of progressive renal injury. J Am.Soc.Nephrol. 2002; 13: 1773-87
274 Flyvbjerg A, Denner L, Schrijvers BF, Tilton RG, Mogensen TH, Paludan SR, Rasch R: Long-term renal effects of a neutralizing RAGE antibody in obese type 2 diabetic mice. Diabetes 2004; 53: 166-72
275 Kilhovd BK, Berg TJ, Birkeland KI, Thorsby P, Hanssen KF: Serum levels of advanced glycation end products are increased in patients with type 2 diabetes and coronary heart disease. Diabetes Care 1999; 22: 1543-8
276 Simm A, Casselmann C, Schubert A, Hofmann S, Reimann A, Silber RE: Age associated changes of AGE-receptor expression: RAGE upregulation is associated with human heart dysfunction. Exp.Gerontol. 2004; 39: 407-13
277 He CJ, Koschinsky T, Buenting C, Vlassara H: Presence of diabetic complications in type 1 diabetic patients correlates with low expression of mononuclear cell AGE-receptor-1 and elevated serum AGE. Mol.Med. 2001; 7: 159-68
278 Schalkwijk CG, Baidoshvili A, Stehouwer CD, van Hinsbergh VW, Niessen HW: Increased accumulation of the glycoxidation product Nepsilon-(carboxymethyl)lysine in hearts of diabetic patients: generation and characterisation of a monoclonal anti-CML antibody. Biochim.Biophys.Acta 2004; 1636: 82-9
279 Paternostro G, Clarke K, Heath J, Seymour AM, Radda GK: Decreased GLUT-4 mRNA content and insulin-sensitive deoxyglucose uptake show insulin resistance in the hypertensive rat heart. Cardiovasc.Res. 1995; 30: 205-11
280 Nuutila P, Maki M, Laine H, Knuuti MJ, Ruotsalainen U, Luotolahti M, Haaparanta M, Solin O, Jula A, Koivisto VA, .: Insulin action on heart and skeletal muscle glucose uptake in essential hypertension. J.Clin.Invest 1995; 96: 1003-9
281 Gaudreault N, Scriven DR, Moore ED: Characterisation of glucose transporters in the intact coronary artery endothelium in rats: GLUT-2 upregulated by long-term hyperglycaemia. Diabetologia 2004; 47: 2081-92
282 Lowell BB, Shulman GI: Mitochondrial dysfunction and type 2 diabetes. Science 2005; 307: 384-7
283 Hammarstedt A, Sopasakis VR, Gogg S, Jansson PA, Smith U: Improved insulin sensitivity and adipose tissue dysregulation after short-term treatment with pioglitazone in non-diabetic, insulin-resistant subjects. Diabetologia 2005; 48: 96-104
284 Belke DD, Larsen TS, Gibbs EM, Severson DL: Altered metabolism causes cardiac dysfunction in perfused hearts from diabetic (db/db) mice. Am.J.Physiol Endocrinol.Metab 2000; 279: E1104-E1113
285 Belke DD, Larsen TS, Gibbs EM, Severson DL: Glucose metabolism in perfused mouse hearts overexpressing human GLUT-4 glucose transporter. Am.J.Physiol Endocrinol.Metab 2001; 280: E420-E427
286 McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS: Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. Circulation 2007; 116: 1170-5
287 Bountioukos M, Rizzello V, Krenning BJ, Bax JJ, Kertai MD, Vourvouri EC, Schinkel AF, Biagini E, Boersma E, Roelandt JR, Poldermans D: Effect of atorvastatin on myocardial contractile reserve assessed by tissue Doppler imaging in moderately hypercholesterolemic patients without heart disease. Am.J.Cardiol. 2003; 92: 613-6
288 Borradaile NM, Schaffer JE: Lipotoxicity in the heart. Curr.Hypertens.Rep. 2005; 7: 412-7
289 Strey CH, Young JM, Lainchbury JH, Frampton CM, Nicholls MG, Richards AM, Scott RS: Short-term statin treatment improves endothelial function and neurohormonal imbalance in normocholesterolaemic patients with non-ischaemic heart failure. Heart 2006; 92: 1603-9

290 Kondo I, Mizushige K, Hirao K, Nozaki S, Tsuji T, Masugata H, Kohno M, Matsuo H: Ultrasonographic assessment of coronary flow reserve and abdominal fat in obesity. Ultrasound Med.Biol. 2001; 27: 1199-205
291 Smulyan H, Safar ME: The diastolic blood pressure in systolic hypertension. Ann.Intern.Med. 2000; 132: 233-7
292 Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE: Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 2004; 27: 1954-61
293 Wackers FJ, Chyun DA, Young LH, Heller GV, Iskandrian AE, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Filipchuk N, Ratner RE, Inzucchi SE: Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. Diabetes Care 2007; 30: 2892-8
294 Kosmala W, Kucharski W, Przewlocka-Kosmala M, Mazurek W: Comparison of left ventricular function by tissue Doppler imaging in patients with diabetes mellitus without systemic hypertension versus diabetes mellitus with systemic hypertension. Am.J.Cardiol. 2004; 94: 395-9
295 Scognamiglio R, Negut C, De Kreutzenberg SV, Tiengo A, Avogaro A: Postprandial myocardial perfusion in healthy subjects and in type 2 diabetic patients. Circulation 2005; 112: 179-84
296 Galderisi M, Capaldo B, Sidiropulos M, D'Errico A, Ferrara L, Turco A, Guarini P, Riccardi G, de Divitiis O: Determinants of reduction of coronary flow reserve in patients with type 2 diabetes mellitus or arterial hypertension without angiographically determined epicardial coronary stenosis. Am.J.Hypertens. 2007; 20: 1283-90
297 Miyazaki C, Takeuchi M, Yoshitani H, Otani S, Sakamoto K, Yoshikawa J: Optimum hypoglycemic therapy can improve coronary flow velocity reserve in diabetic patients: demonstration by transthoracic doppler echocardiography. Circ.J. 2003; 67: 945-50
298 Moir S, Hanekom L, Fang ZY, Haluska B, Wong C, Burgess M, Marwick TH: The relationship between myocardial perfusion and dysfunction in diabetic cardiomyopathy: A study of quantitative contrast echocardiography and strain rate Imaging. Heart 2006;
299 Tops LF, Suffoletto MS, Bleeker GB, Boersma E, van der Wall EE, Gorcsan J, III, Schalij MJ, Bax JJ: Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. J.Am.Coll.Cardiol. 2007; 50: 1180-8
300 Winter R, Jussila R, Nowak J, Brodin LA: Speckle tracking echocardiography is a sensitive tool for the detection of myocardial ischemia: a pilot study from the catheterization laboratory during percutaneous coronary intervention. J.Am.Soc.Echocardiogr. 2007; 20: 974-81
301 Gjesdal O, Hopp E, Vartdal T, Lunde K, Helle-Valle T, Aakhus S, Smith HJ, Ihlen H, Edvardsen T: Global longitudinal strain measured by two-dimensional speckle tracking echocardiography is closely related to myocardial infarct size in chronic ischaemic heart disease. Clin.Sci.(Lond) 2007; 113: 287-96