Charles University, Prague
1ˢᵗ Faculty of Medicine

Synopsis of PhD thesis

ASSESSMENT OF MYOCARDIAL ENERGETICS
BY STRAIN ECHOCARDIOGRAPHY

THE RELATIONSHIP BETWEEN CHANGES IN REGIONAL MYOCARDIAL
DEFORMATION ASSESSED BY ECHOCARDIOGRAPHY AND IMPAIRED
MYOCARDIAL ENERGETICS INDUCED BY ISCHEMIA OR
PHARMACOLOGICAL INHIBITION IN ANIMAL MODELS

HODNOCENÍ MYOKARDIÁLNÍ ENERGETIKY
POMOCÍ STRAIN ECHOKARDIOGRAFIE

VZTAH MEZI ECHOKARDIOGRAFICKY DETEKOVATELNÝMI ZMĚNAMI
LOKALNÍ DEFORMACE MYOKARDU A STUPNI ISCHÉMIE VČETNĚ
FARMAKOLOGICKÉ INHIBICE ENERGETICKÉHO METABOLISMU MYOKARDU
STUDOVANÉ NA ZVÍŘECÍCH MODELECH

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Autoreferát byl rozeslán dne

Obhajoba se koná dne ....v............hod...........kde

S disertací je možno se seznámit na děkanátě 1. lékařské fákulty
University Karlovy v Praze

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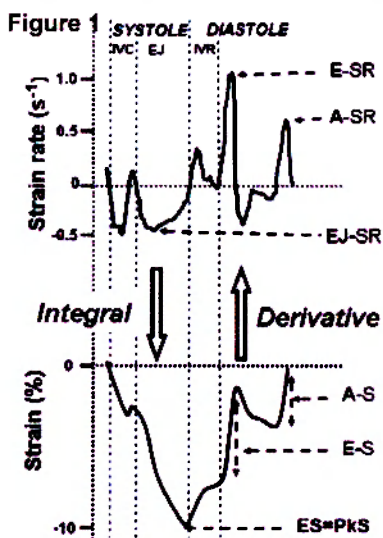# Contents:

Abbreviations

ADP,	- Adenosine diphosphate
ANOVA	- Analysis of variance
A ~ A-SR	- Late diastolic filling (atrial contraction) strain rate
A-S	- atrial strain
ATP	- Adenosine triphosphate
CK	- Creatine kinase
dP/dt	- Time derivative of left ventricular pressure
2D	- Two dimensional
2DSE	- 2D speckle tracking strain echocardiography
2D-HRT	- 2D high spatial resolution speckle tracking echocardiography
E ~ E-SR	- Early diastolic filling strain rate
EJ	- Ejection (systolic) strain rate
EJ-SR	- Ejection strain rate
ES ~ esS	- End-systolic strain
E-S	- Early relaxation strain
IAA	- Iodoacetamide
IVC	- Isovolumic contraction
IVR	- Isovolumic relaxation
LAD	- Left Anterior Descendent Coronary Artery
L	- Length
LV	- Left Ventricle
LVP	- Left Ventricular Pressure
LVPS	- Peak systolic left ventricular pressure
LVPD	- End diastolic left ventricular pressure
MRS	- Magnetic resonance spectroscopy
PET	- Positron emission tomography
PkS	- Peak shortening Strain
PSS	- Postsystolic Shortening Strain
psSR	- Peak systolic strain rate
SCs	- Sonomicrometry crystals
SL	- Systolic Lengthening strain
SPECT	- Single photon emission computed tomography
TDSE	- Tissue Doppler strain echocardiography
TTC	- Triphenyltetrazolium chloride

1. Introduction

Despite significant advances in the diagnosis, prevention and treatment; cardiovascular diseases and ischemic heart disease in particular remain a major cause of mortality in the developed countries. Therefore, further improvement of current and development of novel diagnostic approaches for ischemic heart disease have been one of the most important research focuses.

Myocardial ischemia is primarily a metabolic event characterized by multiple alterations of myocardial energetic metabolism with an impaired myocardial contractile performance that may eventually lead to myocardial necrosis. Various aspects of myocardial energetics can be directly or indirectly evaluated by several imaging techniques, including magnetic resonance spectroscopy (MRS), single photon emission computed tomography (SPECT) and positron emission tomography (PET). Echocardiography, as the last imaging technique, has not been shown to assess myocardial energetic status. Unlike MRS, SPECT, or PET, the nature of ultrasound does not allow direct evaluation of myocardial energetic status by cardiac echocardiography.

However, echocardiography is an outstanding technique for quantification of regional myocardial function by analysis of deformation (strain).[1] Myocardial strain is dimensionless quantity which can be assessed in longitudinal, circumferential and radial directions. Longitudinal myocardial strain is defined as the deformation of the myocardium normalized to its length and calculated throughout the cardiac cycle as $= (L-L_0)/L_0$ where L is the instantaneous length and L_0 is the original length.[1,2] Similarly, circumferential and radial strain can be derived. By convention, shortening (circumferential or longitudinal) is represented by a negative and radial thickening by a positive value.[2] Strain rate is a temporal derivative of strain (and vice versa strain is a temporal integral of strain rate) and expresses

Figure 1

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the speed at which the deformation (i.e. strain) occurs. Strain and strain rate can be depicted as waveforms throughout cardiac cycle (Figure 1). Currently two ultrasound methods are used for strain evaluation, tissue Doppler strain, and two-dimensional strain speckle tracking echocardiography (2DSE) without or with high spatial resolution library (2D-HRT). Several deformational parameters can be assessed from the curves during systole and diastole. As the myocardium contracts during isovolumic contraction (IVC) and ejection (EJ), EJ strain rate (EJ-SR) and endsystolic strain (ES) and peak systolic strain (PkS) can be measured. During diastole, early relaxation is characterized by E wave and atrial contraction by A wave on the strain rate curves that correspond to deformation on strain curves (E-S and A-S). In normal myocardium, small systolic lengthening (SL) and postsystolic shortening (PSS) deformation can occur and has been related to myofiber orientation and reshaping of LV during IVC and IVR. However, during ischemia and reperfusion, SL and PSS also occur but with higher magnitudes (Figure 2).'

Myocardial systole and active diastole are very energetically demanding with high consumption of energy fuels such as adenosine triphosphate (ATP). ATP is predominantly produced in the mitochondria and transported mainly by the creatine kinase (CK) shuttle system from mitochondria to sarcomere via conversion to creatine phosphate.[4,5] During the consumption of ATP, adenosine diphosphate (ADP) and inorganic phosphate are produced, and thereafter converted back to ATP, thus the ATP/ADP ratio is a sensitive indicator of mismatch between ATP production and consumption.[4,6,7] ATP levels at the sarcomere may decrease due to reduced production (ischemia) or due to diminished energy transport (inhibition of CK by iodoacetamide[8]). The ATP decrease may reach a certain threshold associated with inhibition of myosin ATPase and subsequently the myocardial contraction stops. This is followed by the development of ischemic contracture and rigor that is associated and modulated by ADP levels.[6,7] A Certain level of ATP is also required for the preservation of myocardial cell survival linking the ATP/ADP ratio values with myocardial cell viability and myocardial necrosis. Thus the decrease in ATP/ADP ratio is associated with functional alteration of sarcomere and may be linked to regional myocardial dysfunction as well as myocardial viability of ischemia. Nevertheless, how to translate the information obtained from strain curves during alterations of myocardial energetics into the ATP/ADP ratio values has not been elucidated.

2. Hypotheses and Aims:

Based on the close mechanoenergetic relationship, we hypothesized that the computational analysis of strain parameters obtained by reproducible strain echocardiographic technique would enable quantitative estimates of energetic impairment (estimation of the ATP/ADP ratio based on strain parameters) for the spectrum of normal, ischemic and reperfused myocardium. Six consecutive aims and objectives were defined as follows:

1) To investigate if TDSE reflects alterations in myocardial contractile function caused by isolated impairment of myocardial energetics induced by nonischemic inhibition energetics (inhibition of CK energy transfer by IAA) without alteration of myocardial viability in a porcine model (**Study 1**).

2) To study the relationship between myocardial strains and energetics in a porcine model of acute progressive myocardial ischemia. Based on the close strain patterns-ATP/ADP ratio relationships we aimed to derive a mathematical formula estimating the ATP/ADP ratio using strain parameters measured by TDSE for acutely ischemic myocardium (**Study 2**).

3) To test an impact of sonomicrometry crystals ("gold standard technique" for myocardial function validation studies) implantation on regional myocardial deformation assessed by TDSE prior SCs use for validation of new stain echocardiography techniques (2DSE and 2D-HRT). (**Study 3**).

4) To validate novel Doppler independent 2DSE with gold standard technique SCs in vitro using tissue mimicking phantom and in vivo in porcine model of acute myocardial ischemia (**Study 4**).

5) To test whether new version of 2DSE upgraded with high spatial resolution analysis improves accuracy and precision of 2DSE in vitro using tissue mimicking phantom (**Study 5**)

6) To extend findings from aim two and define a mathematical formula for prediction of the ATP/ADP ratio based on strain parameters measured by 2D-HRT not only in ischemic but also in normal and reperfused myocardium and in this way to broaden the potential future application of this echo-computational approach (**Study 6**).

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3. Methods

All studies were approved by the Institutional Animal Care and Use Committee of the Mayo Clinic.

Overview of methods used for each study is in table 1

In Vivo Experiments (Studies 1, 2, 3, 4 and 6)

Animal Preparation

Anesthesia was induced with an intramuscular injection of ketamine HCl and xylazine and maintained with a ketamine HCl, fentanyl and etomidate. Each animal was intubated and mechanically ventilated. Following sternotomy, the heart was exposed on a pericardial cradle, 7Fr pressure catheters (Millar Instruments, Inc., Houston, TX for studies, 2, 3, 4 and 6) or fluid-filled 5F pigtail catheters (Boston Scientific, Natick, Mass for study 1) were inserted into the LV and the ascending aorta via common carotid artery access and the animals were fully anticoagulated with heparin. Pressure and electrocardiographic monitoring continued throughout the study.

Tissue Doppler Strain Echocardiography (Study 1, 2 and 3)

An ultrasound system (Vivid 5 or 7; GE Healthcare) was used to obtain narrow sector epicardial long-axis tissue velocity projections ($\geq$220 frames/s) for offline strain rate and strain analysis (EchoPAC; GE Healthcare). Strain-rate measurements were obtained from tissue velocity data, and strains were integrated from strain rates over the period of an electrocardiographic RR interval.

2DSE (Study 4) and 2D-HRT (Study 5 and 6)

An ultrasound system (Vivid 7, GE Healthcare) was used to obtain wide sector epicardial long axis (study 4 and 6), short axis images (study 4) or gelatin phantom (study 4 and 5) images at frame rates ranged from 75 to 79 frames/s. Strain curves were obtained with dedicated software (EchoPAC PC-2D strain, GE Healthcare) which performed speckle tracking. For studies 5 and 6 the software included analysis high spatial resolution library to improve strain assessment.

Strain Rate or Strain Parameters Measured by TDSE (study 1, 2 and 3) or 2DSE (Study 4, 5 and 6)

Peak ejection SRs and early (E) and late (A) diastolic SRs were measured (Study 1 and 3, Figure 1). Longitudinal systolic lengthening (SL) strain, end-systolic (ES) strain, and peak shortening (PkS) strain were expressed as percentage deformation with respect to the preceding end-diastolic state. Postsystolic shortening (PSS) strain was expressed as the difference between ES and PkS strain magnitudes (Study 1,2 and 3). The lengthening/shortening (L/S) ratio was calculated as SL/(SL - PkS) (Study 2 and 6). Measurements of 3 consecutive cardiac cycles were averaged to reduce the influence of noise.

Sonomicrometry (Study 3, 4 and 5)

A pair of spherical SCs (~2 mm in diameter) was inserted into the inner half of the myocardial apical anterior and midposterior wall segments (approximately 10 to 15 mm apart and oriented along the LV long axis to measure predominantly longitudinal motion). Mutual motion of SCs was recorded at a rate of 250 Hz.

Hemodynamic Data Analysis (Study 1, 2, 3 4 and 6)

Peak (LVPS) and end diastolic (LVPD) left ventricular pressure, the peak positive and negative time derivatives of pressure (+dP/dt and -dP/dt, respectively) and heart rate were calculated from ventricular pressure tracings.

Viability Analysis by Tissue Staining (Study 2 and 6)

The heart was dissected into transverse slices approximately 1 cm thick that were incubated in 2% triphenyltetrazolium chloride (TTC) solution at 37°C for 5 minutes. Viable myocardium became brick red, whereas necrotic myocardium remained unstained. A radial extent of necrosis >90% was considered transmural infarction. The spatial extent of infarction was measured as a percentage of planimetry.

Myocardial Histological and Enzymatic Analysis (Study 1)

Histological samples from 5 animal studies were obtained using a colposcopy biopsy device and used for electron microscopy analysis. Other samples were rapidly frozen by brief immersion into liquid nitrogen to preserve enzyme activities. Creatine kinase (CK) activity and protein content were measured using the commercially available assay kit (No. 47-20, Sigma-Aldrich, St Louis, Mo) and protein assay (D-c, Bio-Rad Laboratories, Hercules, Calif). CK activities were expressed in μmol/min/mg of protein.

Myocardial High-Energy Phosphate Analysis (Study 2 and 6)

Myocardial samples (100-200 mg) from the testing and control regions were rapidly dissected and immediately immersed into liquid nitrogen to avoid the loss of high-energy nucleotides. Nucleotide concentrations were determined by high-performance liquid chromatography (HPLC Series 1100; Hewlett-Packard Corporation, Waldbronn, Germany). ATP and ADP values (nmol/mg protein), their ratio were calculated.

In Vitro Experiments (Studies 4 and 5)

In Vitro Model (Studies 4 and 5)

Tissue-mimicking phantom simulating stiffness and acoustic backscatter properties of myocardium (9- x 9- x 10-cm (width x diameter x height) consisted of 13% gelatin, 10% graphite, and 10% formaldehyde. Two sonomicrometry crystals were embedded 15 mm from the bottom and 20 mm apart vertically before the gelatin cured to measure longitudinal strain. An ultrasound probe for 2DSE (study 4) or 2D-HRT (study 5) scanning was positioned vertically through the platform A servo-hydraulic, programmable compression system (MTS Systems Corp) was used to generate cyclic compressions of the gelatin block in the longitudinal direction with respect to the transducer at defined strains and frequencies of piston compressions to mimic a wide range of magnitudes and rates of cardiac muscle deformations.

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Statistical Analysis

Data is presented as mean ± SD. Using JMP and SAS/STAT (SAS Institute, Inc., Cary, NC) software, paired and unpaired t-test, ANOVA, repeated measures ANOVA, linear and multivariate regression analysis were used as appropriate to compare animal groups or to show relationships among various echocardiographic, hemodynamic, and energetic parameters. Linear regression analysis with a least squares method and Bland-Altman test was performed to assess the precision and accuracy, in validation studies (4 and 5). Multivariate regression analysis with backward elimination was used to explore all strain parameters measured at different time points of acute progressive ischemia (study 2) and normal and reperfused myocardium (study 6) and define a formula for estimating the ATP/ADP ratio from strain values. The intraobserver and interobserver variability of strain measurements were assessed in 10 randomly picked animals in the apical anterior midposterior segments and are presented as the difference between measurements expressed as a percentage of the mean. P values less than .05 were considered statistically significant.

Table 1 **List of Methods Used in Each Study**

	Hemody namics	TDSE	2DSE	2D-HRT	SCs	CK	ATP/ADP	TTC
Study 1	*	*				*		
Study 2	*	*					*	*
Study 3	*	*			*			
Study 4	*		*		*			
Study 5				*	*			
Study 6	*			*			*	*

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Study Protocols

Study 1: In 12 animals, baseline and at 60 minutes after intracoronary perfusion of IAA, hemodynamic recording, TDSE, myocardial biopsy samples for analysis of CK enzyme activities were obtained. Peripheral blood samples were obtained in 5 animals at the start and end of the study to examine whether there was any cellular disruption evidenced by enzyme leakage (CK-MB, troponin I).

Study 2: Twenty-eight animals were assigned into 7 subgroups of 4 animals each. One subgroup was used for baseline measurements. In 4 subgroups, the middle LAD was occluded for 12, 40, 120, and 200 minutes, respectively, without reperfusion. In the remaining 2 subgroups, the LAD was occluded for 12 and 120 minutes, respectively, followed by 100-minute reperfusion. At the end of each time period, hemodynamic recording, TDSE and myocardial tissue samples (for ATP and ADP analysis) were promptly obtained, the animal was euthanized, and the heart was excised and dissected into slices for TTC staining.

Study 3: In 12 animals, first blood draw for troponin I analysis, hemodynamic recordings and TDSE were performed before embedding nay of the SCs. Subsequently, SCs were carefully inserted into the inner half of the myocardial apical anterior and midposterior wall segments (10 to 15 mm apart) and oriented along the LV long axis and measure longitudinal deformation. The midlateral wall represented a control region with no SC implanted. Approximately 90 to 120 minutes after SC insertion, all TDSE and hemodynamic measurements were repeated along with sonomicrometry recordings and the second blood draw for troponin I analysis.

Study 4: Study 4 was consisted of 2 sets of experiments: in vitro and in vivo

In vivo: In 13 animals, one triplet of ultrasonic crystals was implanted into the inner (subendocardial) layer of the apical anterior or anteroseptal LV wall (testing region) and another triplet was placed into the midposterior wall (control region). Two crystals in each triplet were aligned approximately 15 mm in direction parallel to the LV long axis to measure longitudinal strains. The third crystal in each triplet was placed approximatelly 15 mm next to the proximal crystal of the longitudinal pair to form a right triangle and allow the measurement of circumferential strains. Mid LAD was ligated for 45 to 60 minutes to induce acute myocardial ischemia and regional wall-motion abnormalities. Regional

longitudinal and circumferential strains were obtained by 2DSE (apical 2-chamber and 3-chamber long axis views and apical and midventricular short-axis views) and by SCs at baseline and at the end of the ischemic period.

In vitro: The cyclic compressions of the gelatin block in the longitudinal direction were performed at defined strains (5.4%, 10.8%, 16.1%, 21.5%) to mimic a wide range of magnitudes of myocardial strains and frequencies of piston compressions (0.8, 1.2, 1.6, 2.0, 2.4, 2.8, 3.2 Hz) to simulate a wide range of heart rates. 2DSE and sonomicrometry data were obtained during the compressions and regional strain were measured off line.

Study 5: Similar study protocol as for in vitro in study 4 was used and 0.4 frequencies of piston compressions were added to simulate even lower heart rates than in study 4. 2D-HRT and sonomicrometry data were obtained during the compressions and regional as well as global strain were measured off line.

Study 6: Thirty two animals were randomly assigned to 5 groups and studied under general anesthesia. One group (7 animals) served as the control group and was used for baseline measurements. In two groups (6 and 6 animals), the mid LAD was occluded for different time periods (20 and 150 minutes,) without reperfusion. In the remaining two subgroups, the LAD was occluded for 20 minutes (6 animals) and 150 minutes (7 animals), followed by 90-minute reperfusion in both groups. Hemodynamic measurements, 2D-HRT and myocardial biopsies from testing and control regions were performed at the end of each experiment. After euthanasia, the hearts were excised, dissected into slices and TTC staining was performed.

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4. Results

The most important echocardiographic, hemodynamic and energetic findings are shown.

Study 1

Hemodynamics
Within 60 minutes after the IAA administration LVPS decreased and LVPD increased significantly.

TDSE
As shown in table 1, all strain and strain rate parameters decreased with IAA administration, while remained unchanged in control region (data not shown).

Table 2 Strain echocardiographic data

Parameter	Baseline	IAA inhibition	P value
psSR (l/s)	-0.81 ± 0.17	-0.32 ± 0.16	< 001
ES (%)	-13.1 ± 3.5	-2.6 ± 1.5	< 0001
E-SR (l/s)	1.19 ± 0.46	0.34 ± 0.22	<.0001
A-SR (l/s)	1.48 ± 0.47	0.55 ± 0.57	<.0001

Biochemical and Histological Findings
After IAA administration, neither plasma troponin I or CK-MB were elevated CK activity in the testing region decreased to 0.5% of its baseline level, whereas in control region remained unchanged. Electron microscopy demonstrated tissue contracture with a marked shortening of sarcomere length whereas mitochondria remained normally appearing.

Study 2

Hemodynamics

LVPS, +dP/dt, LVPD had a decreasing trend during progressive ischemia and tended toward an increase in both reperfusion groups.

TDSE

Both SL and PSS strain developed in the testing region at 12 minutes of ischemia and decreased nearly exponentially thereafter (Figure 2). The mean negative value of ES strain at baseline changed to a positive value, with a decreasing trend toward 200 minutes of ischemia, whereas absolute values of PkS strain decreased in a monophasic manner towards their minimal magnitudes at 200 minutes of ischemia (Figure 2, Table 3). The L/S ratio significantly increased from baseline to 12 minutes of ischemia and remained stable with longer duration of ischemia. After 12 minutes of ischemia and 100 minutes of reperfusion, SL and PSS strain decreased significantly compared with 12 minutes of ischemia without reperfusion; the ES strain shifted back negative values, although never reaching the baseline magnitude; PkS strain improved; the L/S ratio tended to be lower (Table 3). After 120 minutes of ischemia and 100 minutes of reperfusion, strain parameters remained without significant changes compared with 120 or 200 minutes of ischemia without reperfusion.
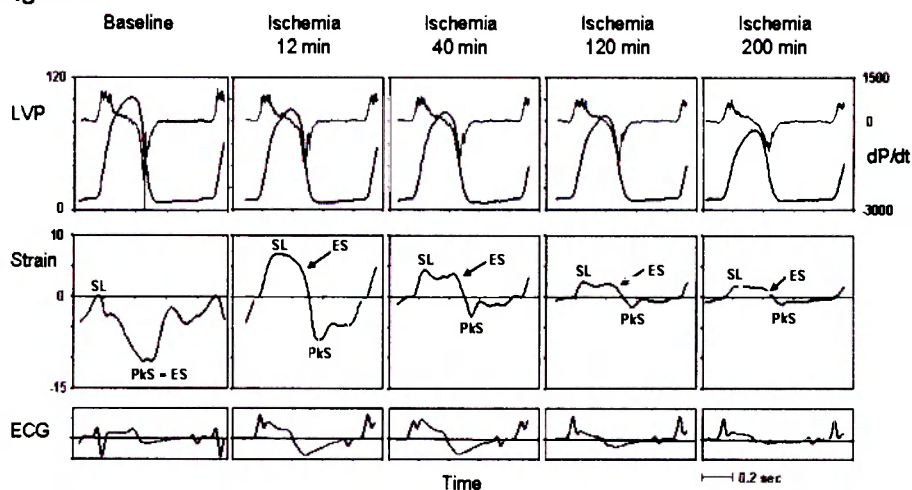
Figure 2

Table 3 Strain echocardiographic data – testing region

Parameter	Baseline	No reperfusion				100-min reperfusion	
		12 min Ischemia	40 min Ischemia	120 min Ischemia	200 min Ischemia	12 min Ischemia	120 min Ischemia
Strain							
SL strain (%)	0.1±0.2	6.0±1.2*	4.3±0.6*†	3.3±0.5*†	3.1±0.3*†	3.9±0.2†	2.5±0.4*†‡
ES strain (%)	-9.7±1.5	2.9±1.2*	3.4±1.3*	1.6±0.4*	1.3±1.4*	-2.4±1.2*†‡§||	1.3±0.3*|
PkS strain (%)	-9.7±1.5	-5.8±1.0*	-3.5±2.8*	-2.5±1.5*	-2.7±1.1-	-7.7±1.6*§||	-1.4±0.9*|
PSS strain (%)	0.1±0.2	9.1±1.0*	6.9±1.6*	4.1±1.6*†	3.5±1.3*†‡	5.3±0.6*†	1.3±0.3†‡|
I/S	0.01±0.03	0.51±0.05*	0.6±0.18*	0.6±0.15*	0.6±0.08*	0.34±0.04	0.67±0.19*
High energy phosphates							
ATP	28.0±2.7	20.2±1.8*	8.0±3.3†	2.2±2.0†	1.6±0.6*†‡	19.8±1.8*†§||	2.4±1.9*†|
ATP/ADP ratio	4.1±0.3	2.6±0.4*	1.5±0.6*†	0.6±0.3*†	0.6±0.1*†	4.3±0.1†‡§||	0.8±0.4*†|

*$P < .05$ vs baseline.
†$P < .05$ vs 12-minute ischemia
‡$P < .05$ vs 40-minute ischemia
§$P < .05$ vs 120-minute ischemia.
||$P < .05$ vs 12-minute ischemia and 100-minute reperfusion.

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Course of High-Energy Phosphate Levels during Progressive Ischemia and Reperfusion

In the testing region, ATP and the ATP/ADP ratio declined exponentially with increasing duration of ischemia. Following 12 minutes of ischemia and 100 minutes of reperfusion the ATP level did not increase while the ATP/ADP ratio increased due to a decrease of ADP Following 120 minutes of ischemia and 100 minutes of reperfusion there was no change in ATP or ADP as compared to 120 minutes of ischemia without reperfusion. No change in ATP or ATP/ADP ratio was observed in the control region (Table 3).

Figure 3
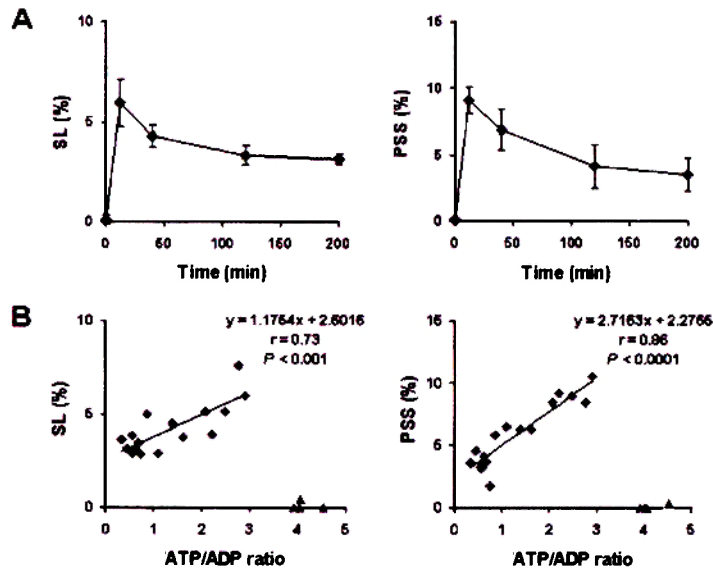
Regression Analysis of High-Energy Phosphates and Strain Parameters

During ischemia, the ATP/ADP ratio was correlated closely with SL strain (r = 0.73, P < .001) and PSS strain (r = 0.86, P < 0.0001) (Figure 2), as well as with PkS strain (r = -0.70, P < .003), the L/S ratio (r = -0.52, P < .05), and systolic compliance (r = 0.67, P < .005). There was no correlation between ES strain and the ATP/ADP ratio (r = 0.37, P = .15)

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Mathematical Formula for Estimating the ATP/ADP Ratio

Through multivariate linear regression analysis of all permutations of strain parameters described in this study and using backward statistical elimination, we arrived at the following formula that estimated best ($r = 0.94$, $P < .05$) the ATP/ADP ratio during the course of persisting acute ischemia:

$$ATP/ADP = -0.97 + 0.25 \times PSS \; strain + 0.20 \times SL \; strain.$$

Viability Evaluation

No necrosis was detectable at baseline and after 12 minutes of ischemia with and without reperfusion. After 40 minutes of ischemia, small subendocardial necrosis (<10%) was identified in 1 animal. Transmural necrosis was detected in all animals at 12 minutes of ischemia with or without reperfusion and 200 minutes of ischemia.

Intraobserver and interobserver variability

Intraobserver and interobserver variability were, respectively, 14.5% and 15.4% for SL strain, 12.4% and 16.1% for ES strain, 13.2% and 15.3% for PkS strain, 12.7% and 14.3% for PSS strain, and 11.0% and 17.2% for the L/S ratio.

Study 3

Hemodynamics

There was no statistically significant difference between the hemodynamic parameters before and after insertion of SCs into myocardium.

TDSE

Table summarizes the strain data obtained by TDSE (strain rate data not shown). No changes were observed in patterns of strain or SR curves after implantation of crystals in the testing and control regions and there was no difference in any of the strain or strain rate parameters before or after SC insertion.

Table 4 Strain parameters by echocardiography and sonomicrometry

Segment	Parameter	Baseline, %	After SC insertion. %
Apical anterior	SL	0.1 ± 0.2	0.1 ± 0.1
	ES	-11.5 ± 1.3	-11.1 ± 2.4
	PkS	-11.6 ± 1.2	-11.3 ± 2.3
	PSS	0.1 ± 0.3	0.2 ± 0.5
Midposterior	SL	0.2 ± 0.4	0.2 ± 0.4
	ES	-15.9 ± 1.5	-15.5 ± 1.2
	PkS	-16.6 ± 2.1	-16.0 ± 1.3
	PSS	0.7 ± 1.3	0.5 ± 0.8
Midlateral	SL	0.1 ± 0.2	0.1 ± 0.3
	ES	-18.7 ± 2.1	-18.3 ± 2.0
	PkS	-19.1 ± 2.4	-18.8 ± 2.4
	PSS	0.5 ± 0.8	0.5 ± 0.8

Biochemical Detection of Myocardial Injury

At baseline, the troponin I levels were below 0.01 μg/L, but increased significantly to 0.129 ± 0.138 μg/L ($P < .005$) after SC insertion.

Intraobserver and Interobserver Variability

Intra- and inter-observer variabilities were, respectively, 13.6% and 16.6% for SL, 11.4% and 12.7% for ES, 10.9% and 13.1% for PkS, 10.7% and 12.8% for PSS.
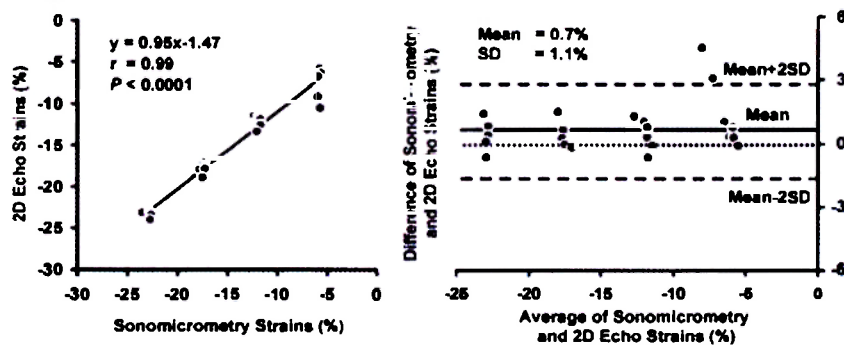
Study 4

In Vitro Study (Tissue Mimicking Phantom)

2DSE vs. Sonomicrometry

Linear regression analysis demonstrates high correlation (Figure 4) and the Bland-Altman plot of strains derived by 2DSE and Sonomicrometry documents a close overall agreement (bias ± 2SD, 0.7 ± 2.2%) of the pooled measurements (Figure 4). One-way analysis of variance showed that there was a statistically significant difference across the 4 strain settings ($P = .003$) when analyzing the difference between 2DSE and sonomicrometry crystals. To supplement this analysis, pairwise comparisons were performed between each strain level. The 5.4% strain was significantly different than the 3 other testing strains ($P < .002$ in each case); there was no difference between 10.8%, 16.1%, and 21.5% strains ($P > .900$ in each case). From 2-way analysis of variance, significantly ($P < .001$) greater differences were observed between 2DSE and sonomicrometry at lower strains and lower piston excursion rates (simulating heart rate).

Figure 4


In Vivo Study (Porcine Ischemic Model)

Hemodynamics

LVPS and peak negative dP/dt significantly increased in absolute value, whereas heart rate, positive dP/dt, and LVPD remained unchanged.

2DSE vs. Sonomicrometry

In the testing region, dyskinesis developed after LAD occlusion and strains were statistically different from baseline values, but remained unchanged in the control region. At baseline, linear regression analysis of 2DSE and sonomicrometry showed regional correlation of peak systolic longitudinal and peak systolic circumferential strains as follows: anteroseptal region, $r = 0.71$ ($P < .0001$) and $r = 0.68$ ($P < .0001$), respectively; and midposterior region, $r = 0.73$ ($P < .01$) and $r = 0.65$ ($P < .05$), respectively. After LAD occlusion (n = 13), the correlation of peak systolic longitudinal and peak systolic circumferential strains was as follows: anteroseptal (ischemic) region, $r = 0.65$ ($P < .05$) and $r = 0.19$ ($P =$ not significant), respectively; and midposterior region, $r = 0.81$ ($P < .0005$) and $r = 0.65$ ($P < .05$), respectively. Figure 5 demonstrates that the correlation for 2DSE and sonomicrometry data pooled from all strain measurements (i.e., longitudinal and circumferential strains, both at baseline and after ischemia) was very close ($r = 0.94$, $P < .0001$). The Bland-Altman agreement analysis (Figure 5) reflects the effect of scaling from negative to positive strain values and shows only a small bias (bias ± 2SD, -1.1 ± 7.5%). The variability of the mean differences is larger compared with that obtained from the in vitro study.

Figure 5
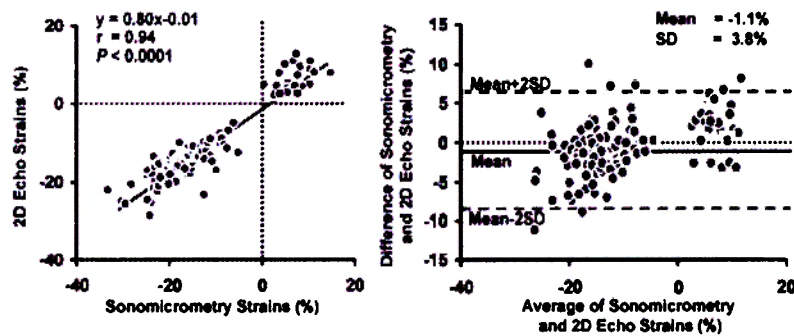
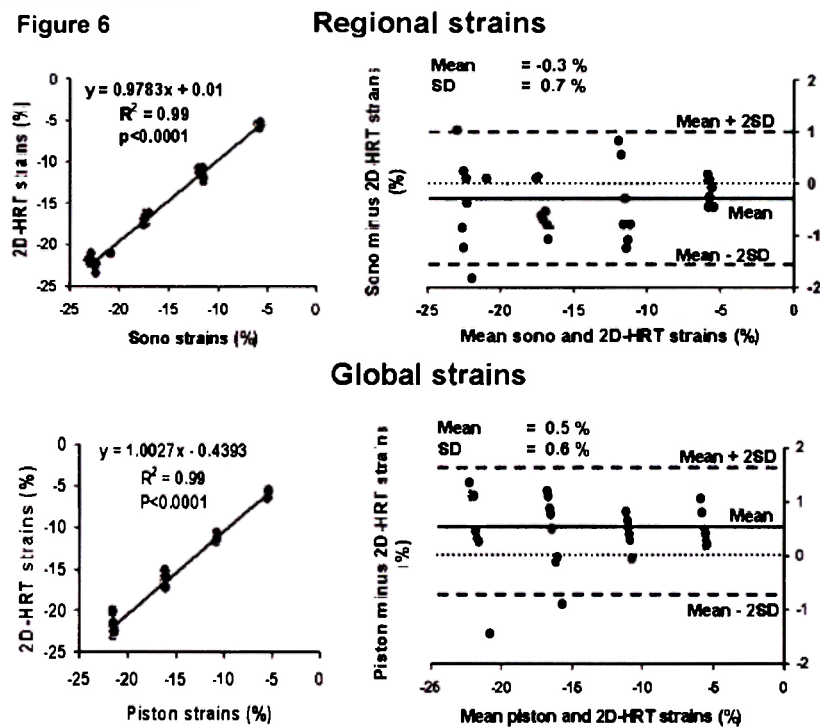### Intraobserver and Interobserver Variability

There was good reproducibility of all tests: intra- and interobserver variability was 3.6% and 5.3% for in vitro and 8.8% and 11.8% for in vivo experiments, respectively.

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Study 5

2D-HRT

Linear regression analysis demonstrates high correlation and the Bland-Altman plot documents a close overall agreement (bias ± 2SD, -0.3 ± 1.3%) of the pooled regional (Figure 6) and global measurements (Figure 6). The strain differences ranged only from -1.9% to 1.0% for regional and from -1.5% to 1.3% for global strains with random distribution in all permutations of deformation magnitudes across the data set.

Figure 6   **Regional strains**


Global strains

Intraobserver and Interobserver Variability

There was good reproducibility of all tests: interobserver and intraobserver variabilities were 3.2% and 3.4% for regional strain and 3.1% and 3.5% for global strains, respectively.

Study 6

Hemodynamics, 2D-HRT Derived Strains and the ATP/ADP ratio

The myocardial viability results, hemodynamics, the course of strain and the ATP/ADP ratio changes from baseline to 20 minutes and 150 minutes of ischemia with or without reperfusion were similar to the previous study 2 when compared to changes from baseline to 12 minutes and 120 minutes of ischemia with or without reperfusion (page 16). For all pooled animal groups, quadratic regression model analyses were shown to be the best fit to describe the relationship between SL, PSS or ES and the ATP/ADP ratio among the various models (Figure 7). The relationship between PkS and the ATP/ADP ratio was nearly linear.

Figure 7
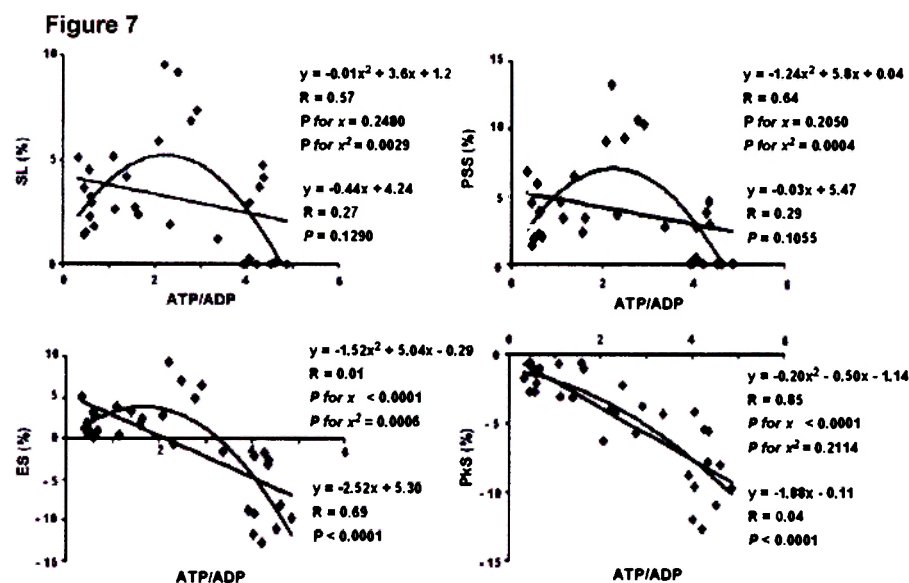
Mathematical Formula for Estimating the ATP/ADP Ratio

For all pooled data, the final multivariate regression analyses included all permutations of strain parameters, their quadratic and linear values. Using stepwise elimination techniques, a mathematical formula was derived and was the best predictive of the ATP/ADP ratio $(= -0.91*ES + 0.57*PSS + 0.04*SL^2 -0.05*PkS^2 -0.55)$ for normal, ischemic and reperfused myocardium (with $p<0.0001$ for ES, $p=0.0003$ for PSS, $p=0.0023$ for SL^2 and $p<0.0001$ for PkS^2; respectively).

5. Discussion

Study 1: IAA inhibits CK but does not inhibit adenylate kinase[8], which catalyzes an alternative path in cellular energetics that contributes by about 10% to the overall phosphotransfer,[9] thus, maintaining basal myocyte metabolism and viability in the IAA-inhibited myocardium. Diastolic dysfunction after myocyte energy metabolism inhibition is primarily associated with persistent binding of ADP to the actomyosin complex caused by the depletion of ATP from the sarcomere and, consequently, its inadequate availability to displace ADP from the binding. The resulting impairment of relaxation ultimately culminates in contracture, documented in our study by electron microscopy. These changes were detected by TDSE as decreased E and A waves on strain rate curves. The lack of ATP for myosin ATPase impaired contraction.[10] The systolic dysfunction manifested as a significant decrease in psSR and esS. The preserved negativity or near zero values of longitudinal psSR and esS document that hypokinesis or akinesis– but not dyskinesis–developed after the energy metabolism inhibition.

Study 2: The myosin ATPase function is inhibited at the free energy of ATP hydrolysis decreased by 25% at approximately 12 minutes of severe ischemia[4,11] with good myocyte survival, which corresponds to our results (the ATP/ADP ratio decreased by 37% and ATP by 28% at 12 mnutes of ischemia) while viability was preserved and myocardial function was severly dysfucntional (high SL and PSS). The noncontracting myocardium was stretched during systole by the rising LVP, which resulted in SL strain. Then, during late systole and early diastole, when LVP declines, the myocardium passively recoiled and produced PSS strain.[3,12] As ischemia continued, strain parameters, including SL and PSS strain, progressively decreased in magnitude, and were closely correlated with a decline in the ATP/ADP ratio and accompanied by nontransmural necrosis (1 animal) at 40 minutes and transmural necrosis at 120 and 200 minutes of ischemia. We speculate that the observed decrease in strain parameters was related to increasing myocardial stiffness.[5,13] The noncontracting, progressively less compliant myocardium increasingly resists the stretching forces generated by systolic ventricular pressure. As a consequence, SL strain decreases in its magnitude, and the passive recoil following aortic valve closure also becomes limited resulting in decreased PSS.

The development of ischemic contracture and the formation of rigor bonds have been associated with decreases in both ATP levels and the ATP/ADP ratio[4,5,14,15] and might explain the close correlations of SL strain, PSS strain to the ATP/ADP ratios. Following the reperfusion of stunned myocardium (ie, after 12 minutes of ischemia), SL strain, PSS strain, and the L/S ratio decreased and suggested partially active myocardial motion[12] which was associated with normalization of the ATP/ADP ratio (this was driven more by a decrease in the ADP level than by an increase in the ATP level [4]). It has also been previously described that a stunned muscle maintains ATP consumption in spite of the lower force development and that its calcium responsiveness decreases.[16] The changes in strain patterns could thus be explained on the basis of force generation, which (although low) would decrease the magnitude of SL strain and contribute to active contraction (expressed as negative values of ES strain and a decrease of the PSS strain component) during the ejection phase. As expected, the reperfusion of a necrotic myocardium has not resulted in change in strains or energetics. On the basis of the described relationship between high-energy phosphate levels and strain magnitudes, a mathematical formula for estimating the energetic status was derived that reflects a linear relation of mathematically combined SL and PSS strain magnitudes to the ATP/ADP ratio as contractile failure develops following 12 minutes of acute ischemia. The presence of SL and PSS strain at baseline and the progression of SL and PSS strain magnitudes during the initial 12 minutes of ischemia to their peak values would lead to an underestimation of the ATP/ADP ratio. However, using ES strain as an independent parameter would differentiate nonischemic (a highly negative ES strain value) from acutely ischemic (a positive or nearly zero ES strain value) myocardium.

Study 3:

The initial epicardial puncture and the following SC insertion and tunneling can injure both myofibers and vessels. Some damage to myocyte integrity was present and signaled by a significant increase of troponin I levels in peripheral blood. However, 2-dimensional echocardiography, which is suitable for identification of intramural hematoma, did not reveal any noticeable intramural bleeding. Therefore, there were no alteration of strain or strain rate magnitudes or patterns in the implantation region as assessed by TDSE.

Study 4: Contrary to 1-dimensional strain estimations obtained TDSE, the new method is inherently 2-dimensional and independent of interrogation angle as it tracks speckle patterns (acoustic markers) within serial 2D sector scans. A wide view provided by the 2DSE method allowed simultaneous analysis of strains in multiple myocardial segments. Results from experiments in vitro suggested that for combinations of low strains and low rates of piston excursion, the 2DSE technique had a tendency to overestimate the reference values. This can be explained by a likely occurrence of subpixel displacements at low strain magnitudes and rates. Under such circumstances, acoustic markers cannot be reliably tracked. For cycling of 1.6 Hz or higher, 2DSE measured compression strains precisely and accurately for all testing magnitudes. Also, for compressive strains of approximately 12% or more, 2DSE was precise and accurate independently of the testing rates. In experimental animal studies, pooled 2DSE measurements correlated and agreed well with those by reference sonomicrometry. After separating the data into groups by time point (baseline vs ischemia), region (testing vs control), and orientation of strains (longitudinal vs circumferential), good correlation of 2DSE with sonomicrometry remained except for the circumferential strains in the testing region after acute ischemia. Here the 2DSE method showed no correlation with the reference; nevertheless, identification of dyskinesis by change to positive values of strains was consistent with measurements by sonomicrometry. We speculate that tracking in the circumferential orientation was more affected by bulging in ischemia as a result of fiber orientation (which affects acoustic properties).[17] Mean absolute values of strains measured by 2DSE in vivo were slightly lower than those measured by sonomicrometry. We propose two explanations. Firstly, the sonomicrometry crystals were placed closer to the endocardium, where measured deformations were likely higher compared with those captured by the 2DSE method (which encompasses the whole thickness of myocardium). Secondly, crystals may have approximated the principal strain along fiber orientation better than tracking by the 2DSE method in standard projections. We tested an early version of 2DSE, however, and further development toward higher frame rates and better tracking alogorhytm was expected.

Study 5: Study experimental setting allowed testing of low deformation rates and the current tests with the 2D-HRT method show close correlation and tight

agreement limits as compared with the reference sonomicrometry for the entire broad range of testing deformation rates. Both regional strains measured by 2D-HRT and sonomicrometry were a little higher than deformations defined by piston motion. We propose that this difference is a consequence of unavoidable residual friction on contact surfaces of the gel phantom resulting in a heterogeneous distribution of strains along the scan axis. Global left ventricular strain measured by 2D-HRT was introduced as a novel index of overall systolic function and proposed as a possible alternative to a broadly used ejection function.[18] However, until the current study, validation of global strain by 2D-HRT had not been performed. We found excellent correlation of global strains assessed by 2D-HRT across the cyclically changing thickness of the entire gelatin phantom with those calculated from motion of the piston that subjected the phantom to the compression-expansion deformations.

Study 6: Relatinships between strains and the ATP/ADP ratio were similar like in the Study 2. However, the formula described in Study 2 could not estimate ATP/ADP ratio for normal and reperfused myocardium. The relationships between the strain parameters and the ATP/ADP ratio for the spectrum of normal, progressively ischemic and reperfused myocardium were predominantly quadratic. The quadratic relationships can be problematic if only one strain parameter would be used in isolation for prediction of the ATP/ADP ratio. The decrease of SL and PSS or a decrease of ES from highly positive values towards zero could be understood as improvement of function upon early reperfusion associated with improvement (increase) of the ATP/ADP ratio as well as worsening of myocardial dysfunction with progression of ischemia associated with a decrease of the ATP/ADP ratio. PkS was the only parameter with nearly linear relationship with the ATP/ADP ratio. However, significant overlap of the PkS values were present especially between the ischemic groups with and without reperfusion. Thus interpretation of the decrease in SL, PSS, ES, L/S ratio or PkS in isolation can be ambiguous and can mean both the improvement and the worsening of myocardial energetic status. Because the quadratic relationship differed for each strain parameter, the combination of parameters is more useful and in this way strengthens the estimation of the ATP/ADP ratio. Indeed, we arrived to formula which included linear as well as square strain parameters.

6. Conclusions

Study 1: Experimentally induced inhibition of phosphotransfer by IAA led to the impairment of regional myocardial function characterized by non-ischemic contracture with preserved myocardial viability. TDSE was able to detected selective energy metabolism inhibition by characterizing regional myocardial systolic and diastolic dysfunction.

Study 2: TDSE derived strain measurements closely reflect serial changes in high-energy phosphate metabolism that occur in acute myocardial ischemia. We introduce a conceptual approach for the noninvasive estimation of the ATP/ADP ratio as a marker of myocardial energetic status during acute persisting ischemia. The mathematical formula was derived based on TDSE derived strain parameters.

Study 3: Careful insertion of sonomicrometry crystals into myocardium does not cause alterations in regional systolic or diastolic myocardial function measurable by TDSE, although the related micro-injury can be detected with elevated troponin I levels in peripheral blood. These results support applicability of the SCs use as reference "gold standard" method for strain evaluation in validation studies.

Study 4: 2DSE closely correlated with sonomicrometry derived regional strains in vitro and in vivo. At low simulated deformations and heart rates 2DSE tended to overestimate strain measured by sonomicrometry, but the overall precision and accuracy of the 2DSE method is promising for prospective clinical use.

Study 5: 2D-HRT with the combined 2-stage speckle tracking algorithm allowed a precise and accurate evaluation of strains at low deformations and heart rates, where the previous 2D-SE overestimated the true strain magnitudes.

Study 6: This study advances our previous findings and defines a mathematical model for estimation of the ATP/ADP ratio which combines linear and square values of several strain parameters measured by 2D-HRT reflecting the non-linear character of the relationship between changes of the ATP/ADP ratio and strains.

Thesis conclusion: In this thesis, we show that validated 2D-HRT enables to indirectly estimate myocardial energetic status for spectrum of normal, ischemic and reperfused myocardium. Thus, 2D-HRT could be complimentary alternative to PET, SPECT or MRS for evaluation of myocardial energetics. However, further validation is warranted to confirm the applicability of this echo-computational approach in clinical practice.

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8. List of Author's Manuscripts and Abstracts

The doctoral thesis consists of manuscripts 1.-5. and abstract no 1. Impact factor (IF) of the published manuscripts is denoted in parentheses. Total IF of published manuscripts is 117 as of September 2008.

Manuscripts

1. **Korinek J.**, Anagnostopoulos P.C., Pislaru C., Dzeja P.P., Seward J.B., Terzic A., Belohlavek M. **Both systolic and diastolic dysfunction characterize nonischemic inhibition of myocardial energy metabolism: an experimental strain rate echocardiographic study.** J Am Soc Echocardiogr. 2004 Dec;17(12):1239-44.
    (IF **1.513** 2005)

2. **Korinek J.**, Wang J., Sengupta P.P., Miyazaki C., Kjaergaard J., McMahon E.M., Abraham T.P., Belohlavek M. **2D Strain - A Doppler Independent Ultrasound Method for Quantitation of Regional Deformation: Validation In-vitro and In-vivo.** J Am Soc Echocardiogr. 2005 Dec;18(12):1247-53.   (IF **1.513** 2005)

3. **Korinek J**, Kjaergaard J, Sengupta PP, Yoshifuku S, McMahon EM, Cha SS, Khandheria BK, Belohlavek M. **High spatial resolution speckle tracking improves accuracy of two-dimensional strain measurements: an update on a new method in functional echocardiography.** J Am Soc Echocardiogr. 2007 Feb;20(2):165-70.
    (IF **2.062** 2007)

4. **Korinek J.**, Vitek J., Sengupta P.P., Romero-Corral A., Krishnamoorthy V.K., McMahon E.M., Khandheria B.K., Belohlavek M. **Does implantation of sonomicrometry crystals alter regional cardiac muscle function?** J Am Soc Echocardiogr.2007 Jun 29   (IF **2.062** 2007)

5. **Korinek J**, Sengupta PP, Wang J, Romero-Corral A, Boukatina AE, Vitek J, Krishnamoorthy VJ, Cha S, Dzeja PP, Terzic A, Khandheria BK, Belohlavek M. **Strain Imaging by Ultrasound Estimates Myocardial Energetic Status in Acute Progressive Ischemia and Indicates its Recovery upon Reperfusion.** J Am Soc Echocardiogr.2008 Mar 4;[Epub ahead of print]   (IF **2.062** 2007)

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