Doppler-Derived Myocardial Systolic Strain Rate Is a Strong Index of Left Ventricular Contractility

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Background—Myocardial fiber strain is directly related to left ventricular (LV) contractility. Strain rate can be estimated as the spatial derivative of velocities (dV/ds) obtained by tissue Doppler echocardiography (TDE). The purposes of the study were (1) to determine whether TDE-derived strain rate may be used as a noninvasive, quantitative index of contractility and (2) to compare the relative accuracy of systolic strain rate against TDE velocities alone.

Methods and Results—TDE color M-mode images of the interventricular septum were recorded from the apical 4-chamber view in 7 closed-chest anesthetized mongrel dogs during 5 different inotropic stages. Simultaneous LV volume and pressure were obtained with a combined conductance–high-fidelity pressure catheter. Peak elastance (E\text{max}) was determined as the slope of end-systolic pressure-volume relationships during caval occlusion and was used as the gold standard of LV contractility. Peak systolic TDE myocardial velocities (S\text{m}) and peak (ε') and mean (ε\text{' m}) strain rates obtained at the basal septum were compared against E\text{max} by linear regression. E\text{max} as well as TDE systolic indices increased during inotropic stimulation with dobutamine and decreased with the infusion of esmolol. A stronger association was found between E\text{max} and ε' (r=0.94, P<0.01, y=0.29x+0.46) and ε\text{' m} (r=0.88, P<0.01) than for S\text{m} (r=0.75, P<0.01).

Conclusions—TDE-derived ε' and ε\text{' m} are strong noninvasive indices of LV contractility. These indices appear to be more reliable than S\text{m}, perhaps by eliminating translational artifact. (Circulation. 2002;105:99-105.)

Key Words: strain ■ contractility ■ hemodynamics ■ echocardiography

Tissue Doppler echocardiography (TDE) is a noninvasive imaging modality that allows quantification of myocardial velocities. Pulsed and color Doppler processing have been used to evaluate regional velocities from the apex to the base of the ventricle in either the septum or lateral wall. Systolic wall motion velocities, evaluated using pulsed TDE, have been proposed as a means to assess global left ventricular (LV) function and have been compared with the acceleration of LV pressure (peak dP/dt). One limitation of this method, however, is that regional TDE velocities are affected by heart translation and tethering of adjacent myocardial segments. The myocardial velocity gradient, obtained by analysis of spatiotemporal distribution of myocardial velocities measured by 2D color TDE, has also been evaluated as an index of ventricular contraction that is independent of cardiac translation artifact but is limited to the analysis of circumferential fiber shortening in a few myocardial segments. Gorcsan et al demonstrated that TDE velocities can provide both segmental and global assessment of ventricular contractility.

The LV end-systolic pressure-volume relationship (ESPVR), or peak elastance (E\text{max}), is defined by the slope of the end-systolic pressure-volume points during preload reduction maneuvers, such as caval occlusion, and reflects the operating contractility of the LV. Similarly, preload recruitable stroke work (PRSW), defined by the slope of the linear regression between stroke work (area within the pressure-volume loop) and end-diastolic volume during a preload reduction intervention, has also been proposed as a load-independent index of contractile function. Myocardial fiber strain is also directly related to LV contractility. Strain is defined as relative deformation, whereas strain rate describes the rate of deformation, or how quickly a tissue shortens or lengthens. Strain rate will be decreased when the tissue changes a specific length more slowly or has a decreased change in length in the same time span.

Myocardial strain and strain rate are optimal descriptors of cardiac contraction and relaxation, but until recently they have been available only in invasive experimental settings with implanted sonomicrometers or tantalum markers. Although limited by temporal resolution and image acquisition time, noninvasive strain assessment has been achieved with MRI tagging techniques. Real-time assessment of strain...
rate (\(\epsilon'\)), the first derivative of strain (\(\epsilon\)), has recently been shown by use of ultrasound image processing. Strain rate can be estimated noninvasively as the spatial derivative of velocities (dV/ds) obtained by color M-mode TDE. We have recently developed and implemented offline software to measure strain rate noninvasively as the dV/ds obtained by color M-mode TDE, approximating \(\epsilon'(t) = \frac{V(s_2,t) - V(s_1,t)}{s_2 - s_1}\), where the spatial segment length, \((s_2 - s_1)\), is 1 cm. Strain rate may be more accurate than TDE velocities alone, because they tend to be less affected by translational motion and tethering, since these affect \(V_s\) and \(V_e\) equally and therefore do not affect their difference. The objectives of the following study were (1) to determine whether TDE-derived strain rate may be used as a noninvasive, quantitative index of contractility and (2) to compare the relative accuracy of systolic strain rate against TDE velocities alone.

Methods

Animal Model

The protocol was approved by the Institutional Animal Research Committee and conformed to the position of the American Heart Association on research animal use. Seven mongrel dogs weighing 27.5±0.4 kg (range 26.5 to 29.0 kg) were anesthetized with intravenous sodium pentobarbital (30 mg/kg for induction, 1.0 mg · kg\(^{-1}\) · h\(^{-1}\) for maintenance) and ventilated with room air by a Harvard respirator. The right femoral and carotid arteries and the right internal jugular vein were isolated and cannulated with introducer sheaths (USCI, Hemaquet 8F). Arterial blood pressure and central venous pressure were monitored via fluid-filled catheters together with a single ECG lead coupled to an oscilloscopic transducer sheaths (USCI, Hemaquet 8F). Arterial blood pressure and central venous pressure were monitored via fluid-filled catheters together with a single ECG lead coupled to an oscilloscopic transducer sheaths (USCI, Hemaquet 8F). Arterial blood pressure and central venous pressure were monitored via fluid-filled catheters together with a single ECG lead coupled to an oscilloscopic transducer sheaths (USCI, Hemaquet 8F). Arterial blood pressure and central venous pressure were monitored via fluid-filled catheters together with a single ECG lead coupled to an oscilloscopic transducer sheaths (USCI, Hemaquet 8F).

Five different inotropic-lusitropic conditions were used in each animal: (1) baseline (B), (2) low-dose dobutamine (DL, 5 \(\mu\)g · kg\(^{-1}\) · min\(^{-1}\)), (3) high-dose dobutamine (DH, 10 \(\mu\)g · kg\(^{-1}\) · min\(^{-1}\)), (4) low-dose esmolol (EL, 50 mg · kg\(^{-1}\) · min\(^{-1}\)), and (5) high-dose esmolol (EH, 100 mg · kg\(^{-1}\) · min\(^{-1}\)). A 23-mm Mansfield balloon catheter was introduced through the femoral vein and advanced to the inferior vena cava at the level of the diaphragm under fluoroscopic guidance. Five different inotropic-lusitropic conditions were used in each animal: (1) baseline (B), (2) low-dose dobutamine (DL, 5 \(\mu\)g · kg\(^{-1}\) · min\(^{-1}\)), (3) high-dose dobutamine (DH, 10 \(\mu\)g · kg\(^{-1}\) · min\(^{-1}\)), (4) low-dose esmolol (EL, 50 mg · kg\(^{-1}\) · min\(^{-1}\)), and (5) high-dose esmolol (EH, 100 mg · kg\(^{-1}\) · min\(^{-1}\)). A period of stabilization was allowed between each stage (3 to 20 minutes). Hemodynamic (LV pressure and volume) and myocardial velocity data (TDE color M-mode images) were acquired simultaneously during each occlusion as described below.

Pressure-Volume Measurements

A 6F combination catheter with a multielecetrode (11-pole) conductance configuration and dual high-fidelity pressure sensors (Millar Instruments) was advanced after adequate calibration from the right carotid artery to the LV apex under echocardiographic guidance. The electrical impedance, measured by 5 pairs of conductance electrodes, was analyzed by a conductance data processor (Leycom Sigma 5DF). The position of the catheter and electrodes within the LV cavity was verified by echocardiographic and fluoroscopic visual assessment. In addition, segmental impedance waveforms were examined by use of the ConductPC software (Cardiodynamics) to ensure that appropriate segmental volume data were obtained. The pressure transducers were positioned in the LV cavity and the proximal ascending aorta.

End-diastolic and end-systolic impedance measurements were calibrated by use of echocardiograms obtained during each experimental condition. Volumes were computed from harmonic images providing excellent endocardial definition with the biplane Simpson’s technique, which has been well validated. This approach was previously validated by use of electromagnetic flow measurements in combination with simultaneous impedance data acquired with the conductance catheter. The accuracy in stroke volume by comparison of electromagnetic flow with echocardiographic measurements has been shown previously (y=0.92x+3.8, r=0.86). The approach of using 2D echocardiography to calibrate the conductance data has also been used successfully by other investigators.

LV volume and pressure signals were digitally acquired with 1-ms resolution with a multifunction I/O board (AT-MIO-16, National Instruments) interfaced with a computer workstation (Pentium, 200 MHz) with customized software developed with LabView (National Instruments). A timing signal marker generated by this software was converted to an analog waveform and coupled to the echocardiograph to simultaneously acquire Doppler data.

Invasive Hemodynamic Assessment

LV pressure and volume data obtained during caval occlusion at each stage of acquisition were used to determine \(E_{\text{max}}\) and PRSW. A 5-minute period provided hemodynamic stabilization after inferior vena cava occlusions. \(E_{\text{max}}\) and PRSW were determined during the first 10 to 15 beats during caval occlusion (Figures 1 and 2). The maximum positive rate of ventricular pressure change (dP/dt\(_{\text{max}}\)) was also determined from the LV pressure data.

Echocardiographic Assessment

2D and Doppler echocardiographic studies were performed with an Acuson Sequoia 512 ultrasound machine with a multifrequency transducer (3V2c) and second harmonic imaging. 2D images of the LV were acquired from the apical 4- and 2-chamber views, and volumes were calculated by Simpson’s rule. From the same apical 4-chamber echocardiographic window, the TDE 2D color sector was displayed, and M-mode recordings were acquired after the cursor had been aligned along the ventricular septum, ensuring that the scan line passed through at least the basal segment of the septum (Figure 3). The sample volume size was not chosen from the echocardiograph, as would be standard in pulsed Doppler techniques, but rather by extracting velocity values at a particular depth from the color M-mode images containing velocity samples along the entire scan line. The approximate spatial resolution of the velocity estimates along the scan line (similar to sample volume size) is determined from the imaging depth and the length of each pulse. With a pulse

Figure 1, ESPVR at 3 inotropic conditions (A, esmolol; B, baseline; C, dobutamine) in representative study.
length of ~5 cycles, the spatial resolution of velocity data in the color M-mode is ~3 mm. The location chosen for strain-rate calculation, at a depth of 4.5 to 5.5 cm from the transducer as shown in Figure 4, was selected to avoid sampling at the membranous septum. Color Doppler gain was adjusted to provide a smooth velocity distribution without introducing noise in the color M-mode display.

The TDE color M-mode digital image files were transferred from the Sequoia via optical disk to a computer workstation for conversion to a standard bitmap file format (BMP) by use of MedArchive 2.1, a commercial software package for echocardiographic image analysis (SecureArchive). These BMP files were further processed with customized LabView software developed in our laboratory. The color content in the image representing septal myocardial velocities must be decoded to provide a matrix representation of velocity (V) as a function of depth (s) and time (t), V[s,t]. This is performed with the red-green-blue (RGB) components of the color bar, which displays the relationship between color and velocity on the echocardiographic display. After user identification of a region of interest, the software compares the known RGB values of the velocity color map with each RGB pixel value in the region of interest to assign a velocity and accomplish the transformation to V[s,t]. Peak (ε′) and mean (ε′) strain rates at the basal septum, as well as peak systolic TDE myocardial velocities (S_m), were determined from TDE color M-mode images (Figure 4). Strain rate (ε′) was measured as the spatial derivative of TDE velocity along a scan line (dV/ds) and approximated as [V(s_2,t)−V(s_1,t)]/(s_2−s_1).

**Statistical Analysis**

To minimize the effect of reflex autonomic changes, we analyzed the first 10 to 15 beats of pressure-volume data after the inferior vena"
cava occlusion. The absence of a significant autonomic response was confirmed by the absence of changes in cycle length.

An ANOVA with Student-Newman-Keuls testing was performed to examine the pharmacological effects of \( \beta \)-adrenergic modulation on physiological variables. To test the hypothesis that TDE-derived strain rate can be used as a noninvasive, quantitative index of contractility, \( \epsilon' \) was compared with indices of LV contractility (\( \frac{dP}{dt}_{\text{max}} \), \( E_{\text{max}} \), PRSW) by linear regression analysis. The hypothesis that \( \epsilon' \) provides a more accurate index of LV contractility than \( S_m \) alone was tested by linear regression analysis, with the correlation coefficients compared after Fisher’s Z-transformation. Statistical significance was defined at a value of \( P<0.05 \). Data are expressed as mean±SD.

**Results**

Inotropic effects on heart rate, \( \frac{dP}{dt}_{\text{max}} \), \( E_{\text{max}} \), and \( S_m \) are shown in Figure 5. Mean parameter values are given for the 5 inotropic conditions, and values that were statistically different (\( P<0.05 \)) from baseline are indicated (*). The Table shows the changes in ESPVR observed with the pharmacological interventions. The ESPVR was observed to be linear (\( r>0.86 \) for all stages) in the region described by the change in loading conditions produced with caval occlusion. The negative volume-intercept values (\( V_0 \)) result simply from the extrapolation of this linear relationship and demonstrate a trend of increasing magnitude with the increase in inotropic state. With large loading changes, other investigators have observed that the pressure-volume relationship is nonlinear, and several studies have reported similar findings of negative \( V_0 \) in dogs and in patients.

Heart rate was significantly different from baseline only for the DH (10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \)) condition (heart rate: \( B=90.0\pm22.5 \) versus DH=112.2±32.4 bpm, \( P<0.05 \)). Both dobutamine conditions significantly increased \( \frac{dP}{dt}_{\text{max}} \) from baseline (\( +\frac{dP}{dt}: B=2057\pm497 \) versus DL=3334±1601 and DH=4025±1343 mm Hg/s, \( P<0.05 \)). End-systolic
elastance and systolic myocardial velocities were also significantly greater than baseline with dobutamine infusions ($E_{\text{max}}$: $B = 2.07 \pm 0.81$ versus $DL = 5.33 \pm 2.81$ and $DH = 6.93 \pm 3.03$ mm Hg/mL, $P < 0.05$; $S_m$: $B = 4.24 \pm 1.99$ versus $DL = 6.40 \pm 2.89$ and $DH = 8.53 \pm 2.54$ cm/s, $P < 0.05$).

Figure 6 shows the correlation between $\varepsilon_p$ and the invasive measures of LV contractility: (A) $dP/dt_{\text{max}}$, (B) PRSW, and (C) $E_{\text{max}}$. The relationship is improved for PRSW ($\varepsilon_p'=0.123 \cdot \text{PRSW}+0.134$, $r=0.82$, $P < 0.01$) compared with $dP/dt_{\text{max}}$ ($\varepsilon_p'=0.0006 \cdot \text{PRSW}+0.12$, $r=0.78$, $P < 0.01$) but is best between $E_{\text{max}}$ and $\varepsilon_p'$ ($\varepsilon_p'=0.27 \cdot E_{\text{max}}+0.56$, $r=0.94$, $P < 0.01$).

Figure 7, A and B, shows the relationships between $E_{\text{max}}$ and TDE-derived $S_m$ and $\varepsilon_p$. A stronger relationship was found between $E_{\text{max}}$ and $\varepsilon_p'$ ($\varepsilon_p'=0.27 \cdot E_{\text{max}}+0.56$, $r=0.94$, $P < 0.01$) than between $E_{\text{max}}$ and $S_m$ ($\varepsilon_p'=0.51 \cdot E_{\text{max}}+3.25$, $r=0.68$, $P < 0.01$). A comparison of the correlation coefficients from these relationships demonstrates that a more accurate index of LV contractility is provided by $\varepsilon_p'$ than by $S_m$ ($Z=3.69$, $P<0.001$). Figure 7, C and D, shows Bland-Altman analysis of measured elastance ($E_{\text{max}}$) versus predicted elastance ($E_{\text{max}}$) using (C) systolic velocities and (D) peak strain rate. The mean error was less variable when a prediction of $E_{\text{max}}$ based on strain rate ($\Delta = -0.000012 \pm 1.042$ mm Hg/mL) was used than the estimate using myocardial systolic velocity ($\Delta = 0.0014 \pm 2.336$ mm Hg/mL).

**Discussion**

Assessment of LV function in patients with heart disease is routinely performed by echocardiography. A significant limitation, however, is the subjective visual assessment of wall motion. Although objective, quantitative, echocardiographic indices of ventricular function, such as ejection fraction, end-diastolic volume, stroke volume, and fractional shortening, are often used in routine clinical practice, these parameters are limited by both preload and afterload dependencies. Color kinesis, based on endocardial excursion and myocardial thickening, is another approach to quantify segmental function. Because it is based on detection of endocardial excursion, however, it may fail in patients with technically difficult situations. Moreover, because of cardiac translation, endocardial excursion does not equate to myocardial thickening, the actual parameter of interest. Indices of myocardial contractility that are less load-dependent, such as $E_{\text{max}}$ and PRSW, have been proposed, but a noninvasive tool for their assessment is lacking.

Although echocardiographic approximation of PRSW and $E_{\text{max}}$ can be achieved by determination of serial pressure-area relationships, these methods are cumbersome and are limited by the extrapolation of LV volumes from cross-sectional areas. Furthermore, estimation of $E_{\text{max}}$ from preload-altering maneuvers, particularly in humans with severely impaired cardiovascular function, may be problematic because of vagally mediated physiological responses that may alter contractility. The variation in loading conditions necessary to compute an accurate $E_{\text{max}}$ may also be poorly tolerated in patients with impaired cardiovascular reserve. Consequently, a noninvasive tool that can estimate $E_{\text{max}}$ without the need for alterations in preload could be extremely valuable for serial clinical assessment of ventricular contractility.

LV $dP/dt_{\text{max}}$ has also been shown to be a relatively load-independent index of systolic function. Recently, Yamada and colleagues demonstrated that peak systolic myocardial velocity measured with TDE correlated with $dP/dt_{\text{max}}$ in humans undergoing cardiac catheterization. They
demonstrated a modest but significant correlation between dP/dt max and the peak posterior wall systolic myocardial velocities. A significant limitation of applying pulsed TDE, however, is the confounding influences of ventricular translation and rotation during contraction and the ability to determine the velocities only at a single point within the myocardium.

Myocardial strain has also been proposed as an index of contractility. Myocardial strain reflects the deformation of tissue in response to an applied force. The first temporal derivative of strain, strain rate, is the velocity change in myocardial fiber length. Recent advances in echocardiographic imaging permits real-time strain-rate determination and regional strain rates between the epicardium and endocardium (myocardial velocity gradient) correlated with regional ventricular contractility. When similar techniques were applied to peak diastolic gradients, they found that patients with hypertensive disease and dilated cardiomyopathy had significantly lower diastolic gradients than normal patients.

Limitations
Several limitations of this study should be noted. The invasive assessment of LV function was based on global parameters (Emax, PRSW, dP/dt max) in this experiment, whereas strain rate was measured only in the septum. TDE velocities and strain rates derived from other locations, such as the lateral mitral valve annulus, were not evaluated; therefore, we cannot conclude that septal strain-rate estimates are superior for the assessment of ventricular contractility compared with the full range of TDE velocities. Previous studies have shown that lateral annular TDE velocities correlate better with systolic function and are of greater magnitude than septal values. In our experiment, however, we focused on septal velocities because we could appropriately align the M-mode scan line along the intraventricular septum to measure longitudinal shortening to avoid error due to Doppler angle misalignment, given the technical limitation of visualizing the lateral wall in our animal model.

A fixed sample volume, or spatial region, was used for the strain-rate calculation. During contraction, the myocardial segment moves toward the ventricular apex, and the velocity profile extracted at a specific depth is not truly representative of the same myocardial segment. This measurement does not truly measure the distension of a myocardial segment, because the end points of the segment are not fixed. The addition of an algorithm that could track myocardial segments might improve the noninvasive assessment of strain rate. This algorithm could be based on M-mode gray-scale data obtained simultaneously with the TDE velocities or perhaps realized by use of the recent introduction of tissue tracking methodology that integrates the tissue velocity information.

We recognize that many factors not present in our animal investigation but found in clinical practice may affect septal motion, including bundle-branch block, elevated right heart pressures, and postoperative status. Most of these, however, influence the anteroposterior motion and not longitudinal displacement. One of the advantages of strain rate, a parameter that describes the compression and expansion of the tissue, is that it is translation-independent. Considering TDE data in a small segment of the septum, septal motion would affect the velocity in both locations equally, whereas the difference in velocity (strain rate) would minimize the effects of translation.

Conclusions
Myocardial strain rates (ε′ s and ε′ w) derived by TDE are strong noninvasive indices of LV contractility. These indices appear to be more accurate than S″ s, perhaps by eliminating translational artifact. Potential applications for strain-rate assessment include quantitative assessment of segmental contractility during stress echocardiography in patients with coronary artery disease or in hypertrophic cardiomyopathy.

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