Influence of heart rate, preload, afterload, and inotropic state on myocardial ultrasonic backscatter

KIRAN B. SAGAR, M.D., LORI E. PELC, PH.D., THEODORE L. RHYNE, PH.D., L. SAMUEL WAN, M.D., AND DAVID C. WALTER, M.D., PH.D.

ABSTRACT Ultrasonic backscatter is substantially modified by pathologic changes in myocardium. Influence of physiologic changes in heart rate, mean arterial pressure, preload, and inotropic state were studied in 17 anesthetized open-chest dogs. Heart rate was changed with atrial pacing/ULFS'49 (a selective bradycardic agent). Mean arterial pressure was varied with aortic constriction/nitroprusside, preload was altered with nitroglycerin/volume infusion, and inotropic states were altered with dobutamine (10 μg/kg)/esmolol (100 μg/kg). IBR5, an optimum weighted frequency average (4 to 6.8 MHz) of the squared envelope of diffraction corrected for absolute backscatter, and the Fourier coefficient of amplitude modulation (FAM), an index of cardiac cycle–dependent variation, were measured from six sequential electrocardiographically gated intervals throughout the cardiac cycle. Heart rate, mean arterial pressure, preload, and inotropic state did not significantly affect IBR5. FAM increased from 3.5 ± 0.3 dB (mean ± SEM) to 7.0 ± 0.4 dB (p < .01) at a heart rate of 120 beats/min, and decreased to 3.9 ± 0.4 at a heart rate of 160 beats/min. No change in FAM was noted with a rise (70 ± 12 to 45 ± 10 mm Hg) in mean arterial pressure or preload (an increase or decrease in diastolic segment length of ± 10% from the baseline). Dobutamine produced a significant increase in left ventricular dP/dt (2600 ± 200 to 3475 ± 275 mm Hg) and FAM (3.4 ± 0.1 to 6.4; p < .01). Esmolol significantly reduced left ventricular dP/dt (2600 ± 200 to 2000 ± 175 mm Hg, p < .05) and FAM (3.4 ± 0.1 to 6.4 ± 0.1; p < .01). We conclude that IBR5 is independent of heart rate, mean arterial pressure, preload, and inotropic state. Cardiac cycle–dependent amplitude modulation follows changes in cardiac contraction.


ULTRASONIC TISSUE CHARACTERIZATION is intended to quantitatively define the physical state of cardiac muscle, and to differentiate functionally and structurally normal from impaired myocardium. Recent investigations have shown that morphologic alterations accompanying myocardial infarction or cardiomyopathy are associated with elevations in integrated backscatter.1–6 Furthermore, it has also been demonstrated that contraction and relaxation of myocardium are associated with a parallel, cyclical variation of integrated backscatter.7 The cardiac cycle–dependent variation of integrated backscatter is dependent on global and intramural differences in myocardial contraction6, 8 and the magnitude of variation is significantly reduced during coronary occlusion and recovers after reperfusion.6, 9, 10 We have postulated that cardiac contraction and relaxation alter the reflectivity of the ultrasonic scattering elements within myocardium by changing their size, shape, and/or orientation from systole to diastole. Therefore, since myocardial contractile performance is sensitive to alterations in heart rate, preload, afterload, and inotropic state, cardiac cycle–dependent variation in integrated backscatter may also be sensitive to such changes.

Accordingly, this study was designed to systematically determine effects of changes in heart rate, preload, afterload, and inotropic state on integrated backscatter and its cardiac cycle–dependent variation.

Methods

General preparation. Adult mongrel dogs of either sex weighing 15 to 25 kg were anesthetized with sodium pentobar-
hital (30 mg/kg supplemented with 5 mg/kg/hr iv) and ventilated with a respirator (Harvard Model 607). Atelactasis was prevented by maintaining an end-expiratory pressure of 5 to 7 cm of water. In six experiments, induction was accomplished with sodium thiopental (10 mg/kg iv) and anesthesia was maintained with halothane (2.0% in oxygen (2 liters/min) via a ventilator (Monaghan Model 300 D/M). Throughout the experimental procedure, $\text{P}O_2$, $\text{P}CO_2$, and pH were maintained at physiologic levels. Body temperature was controlled at 38°C with a heating pad and servomechanical controller.

Left ventricular pressures were monitored by inserting a pressure transducer-tipped catheter (Millar PC 380;8F) into the left ventricle via the left carotid artery. The left ventricular pressure pulse was electronically differentiated to obtain peak positive left ventricular $dP/dt$. The differentiator was calibrated by means of a triangular waveform of known slope. Phasic and mean aortic blood pressures were recorded via a catheter inserted into the right femoral artery, advanced to the ascending thoracic aorta, and connected to a strain-gauge pressure transducer (Statham P50). The right femoral vein was cannulated for drug administration.

A thoracotomy was performed in the left fifth intercostal space, and the lungs were gently retracted. The heart was suspended in a pericardial cradle. The electrocardiogram (limb lead II) was monitored and all hemodynamic variables were continuously recorded on a Grass (Model 7) polygraph.

Regional myocardial contractile function (segment shortening) was measured in the perfusion territory of the left anterior descending coronary artery by a pair of piezoelectric crystals. The crystals were inserted approximately 10 to 15 mm apart and 7 to 10 mm deep within the left ventricular free wall. They were placed in the circumferential plane parallel to the expected orientation of the subendocardial muscle fiber. Subsequently, the crystals were secured with a single suture and the depth of each was verified at the completion of the experiment. The average depth of the segment length transducers was 8.8 ± 1.0 mm. The leads of each crystal were connected to an ultrasonic amplifier that transformed the sound pulse transmitted between the two crystals into an electronic signal proportional to the distance between the crystals. The tracings were monitored on a Soltec oscilloscope (Model 520). Diastolic segmental length was determined as the distance between the two crystals at the beginning of the rising phase of positive $dP/dt$ (the onset of isovolumetric contraction), and systolic segment length was measured at peak negative $dP/dt$. The diastolic and systolic segment lengths were normalized to a control value of 10 for the initial diastolic segment length by the method of Theroux et al.\textsuperscript{11} Percent segment shortening (%SS) was calculated with the equation: %SS = \( \frac{\text{DL} - \text{SL}}{\text{DL}} \times 100 \), where DL is diastolic and SL is systolic segment length. Piezoelectric crystals were turned off during acquisition of ultrasonic backscatter data to avoid any interference.

**Ultrasonic backscatter instrumentation and data analysis.** Ultrasonic backscatter was measured with a portable research instrument (Marquette Electronic Computed Tissue Characterization System [CTC-II]), a prototype commercial system based on our previous measurement systems.\textsuperscript{6, 12-14} The CTC-II consists of a transmitter-receiver, high-resolution display, control panel, and microprocessor circuitry constructed in a mobile cart. The transmitter drives 2 μsec duration carrier bursts into the transducer, which has a calibrated frequency response. The receiver amplifies and demodulates the returned echoes for analog-to-digital conversion. The data-taking procedures were preprogrammed and called up from the control panel so that the microprocessor directed the data collection, signal processing, and archival storage on floppy disk.

The CTC-II was programmed to perform frequency scans consisting of separate pulse-echo transmissions at frequencies between 4.0 and 6.8 MHz, in 0.1 MHz steps. An electrocardiographic (ECG) module in the CTC-II was used to synchronize the data acquisition with the QRS complex. Six frequency scans, each taking approximately 15 msec, were performed at evenly spaced intervals over the cardiac cycle. The computer automatically annotated the phase of each frequency scan relative to the electrical cycle of the heart, with zero phase being the midpoint of the QRS complex. The transducer was a 6 mm diameter, unfocused disk with a one-quarter wavelength layer on the radiating face and an impedance-matching transformer connecting to the electrical transmission line. The transducer's bandwidth (at the −6 dB points) exceeded the 5 to 7 MHz band used in frequency scanning and is corrected for by self-reciprocity calibration methods involving a perfectly reflecting plane, as described previously.\textsuperscript{14} The diffraction (or radiation field response) from the transducer to the myocardium was calibrated with the use of a suspension of microspheres.\textsuperscript{15}

The transducer was fitted with a 2 cm water-filled fixture, closed by a finger cot, and filled with saline. The fixture maintained the transducer approximately 18 mm from the epicardium, which positioned the myocardium at a calibrated portion of the radiation field of the transducer. While echo patterns on the A mode display were observed, a range gate was positioned proximal to the large epicardial echo and extending some 15 mm to encompass the entire myocardial wall. Frequency scans were performed and the digitized echoes within the range gate, together with the ECG waveform, automatic phase annotations, transmitter level and receiver gain, were recorded on floppy disks. Ultrasonic sampling extended over 16 cardiac cycles at each sampling site.

The ECG waveform stored on magnetic disk also contained marking signals coincident with each frequency scan. The electrocardiogram and automatic phase annotation were overread and corrected before further analysis.

The disks containing frequency scan echoes, transmitter level, gain setting, and ECG waveform were analyzed with the use of a computer (IBM PC). The magnitude of the echo signal was scaled by adjusting for: (1) transmitter level, (2) receiver gain setting, (3) transducer frequency calibration, (4) the diffraction calibration, (5) bulk absorption (1.0 dB/cm MHz), and (6) the Rayleigh scattering spectrum of the tissue.\textsuperscript{15} Next, five of the echo signals from each frequency scan, each of which had a resolution of 2 μsec (0.5 MHz bandwidth), were coherently combined to form a composite echo signal having 0.5 μsec resolution (greater than 2 MHz bandwidth). The corrected echoes resulting from this process had an absolute magnitude, and a perfectly flat frequency content (whitened spectrum) over the frequency range from 4.0 to 7.0 MHz. The integrated backscatter, Rayleigh 5 MHz (IBR5), was constructed by sampling the corrected echoes at selected ranges and averaging the squared magnitudes. The magnitude was expressed (after averaging) in decibels as an absolute measure of the backscatter in square centimeters of reflecting material per cubic centimeter of volume.\textsuperscript{15, 16}

For each frequency scan, the subendocardial region was analyzed by averaging two successive data points spaced 1 μsec apart (approximately 0.77 mm/μsec time of flight). Taking into account the 0.5 μsec resolution of the echoes, this represented two samples, each 0.39 μsec in duration, which were spaced 0.77 mm apart. The large epicardial wall echo was automatically tracked and positioned the subendocardial region to begin 5.4 mm from the epicardial surface. At each data site, 16 heartbeats were recorded with six frequency scans per beat.

The mean IBR5 for a given experiment was determined by averaging together the data from all dogs in the experiment. The magnitude and phase of the amplitude modulation of IBR5 were...
determined by independently averaging the IBR5 (of all dogs for a given experiment) at six evenly spaced phases of the cardiac cycle, expressed as percent of the full cycle starting from the midpoint of the QRS complex. The computer was used to calculate the Fourier coefficient by correlating the IBR5 at six cardiac phases with a sinusoid whose period matched the cardiac cycle (i.e., the fundamental component) and that best matched the amplitude modulation in both magnitude excursions and the phase relative to the cardiac cycle. As an index of the amplitude modulation, twice the magnitude of the Fourier coefficient (FAM), which represented the peak-to-peak excursion of the backscatter, was used. Also, the phase of the Fourier coefficient relative to the cardiac cycle expressed as the percent of the cardiac cycle at which the sinusoid passes from negative to positive was used. A normal heart presents backscatter that is weak (negative part of sinusoid) in systole, and strong (positive part of sinusoid) in diastole, with the transition near the fifty percent point of the cardiac cycle.

**Experimental design.** Experiments were performed in five groups of dogs. In group 1 (n = 6) the effect of heart rate on integrated backscatter was determined. Animals in this group were anesthetized with halothane and treated with ULFS-49 (2.0 mg/kg iv; a specific bradycardic agent) to induce a low baseline heart rate (<80 beats/min). Heart rate was varied by pacing with a Grass electrical stimulator (Model D9) via electrodes attached to the left atrial appendage. Hemodynamics, segmental shortening, and integrated backscatter were measured at heart rates of 80, 100, 125, and 160 beats/min.

All remaining animals were anesthetized with sodium pentobarbital. In group 2 (n = 6), the effects of changes in blood pressure on integrated backscatter were determined. Animals were continuously paced at 130 beats/min. Measurements of hemodynamics, segmental shortening, and integrated backscatter were made during control conditions, after mean arterial pressure was increased 25 mm Hg via a snare around the descending thoracic aorta, and after intravenous infusion of sodium nitroprusside to decrease mean arterial pressure 25 mm Hg.

In groups 3 and 4 (n = 6 and n = 5, respectively), the effects of decreased and increased preload on integrated backscatter were examined during a constant heart rate (130 beats/min) accomplished by atrial pacing. Intravenous nitroglycerin was used to decrease end-diastolic segment length by 10 ± 1%. Rapid intravenous infusion of 150 to 200 ml normal saline was used to increase diastolic segment length by 10 ± 2%. Hemodynamics, segmental shortening, and integrated backscatter measurements were made during control and after the increase or decrease in preload.

In group 5 (n = 6) the effects of inotropic state on integrated backscatter were assessed. Hemodynamics, segmental shortening, and integrated backscatter were measured during control, after administration of the short-acting β-adrenoceptor antagonist esmolol (500 μg/kg), and after intravenous infusions of dobutamine (10 μg/kg/min).

**Statistical analysis.** All hemodynamic values are reported as the mean ± SD. IBR5 and FAM are reported as mean ± SEM. Statistical analysis of the results was completed by analysis of variance and the least significant difference multiple comparisons procedure. Comparisons between control and altered hemodynamic states were considered significant when the probability value was less than .05.

**Results**

The effects of heart rate (group 1) on IBR5, FAM, and hemodynamic variables are illustrated in figure 1. No significant change in IBR5 was observed with rates between 80 to 160 beats/min. FAM showed a small but significant increase, from 3.0 ± 0.4 to 5.8 ± 0.3 dB (p < .01), during an increase in heart rate from 80 to 100 beats/min, it returned toward baseline (4.0 ± 0.4) at a heart rate of 125 beats/min, and ultimately decreased to 1.5 ± 0.3 at 160 beats/min. Peak positive left ventricular dP/dt increased from 1500 ± 175 to 1825 ± 75 mm Hg/sec with an increase in heart rate from 80 to 100 beats/min and returned to baseline at 80 beats/min.

**TABLE 1**

| Effect of Change in MAP on IBR5 and FAM |
|----------------|----------------|----------------|
| Control | Increased | Decreased |
| Heart rate (bpm) | 132 ± 5 | 130 ± 5 | 133 ± 6 |
| MAP (mm Hg) | 70 ± 12 | 95 ± 6 A | 45 ± 6 A |
| LVSP (mm Hg) | 104 ± 7 | 120 ± 5 A | 74 ± 3 A |
| LVEDP (mm Hg) | 8 ± 3 | 10 ± 3 | 12 ± 3 |
| LV dP/dt (mm Hg/sec) | 1700 ± 125 | 1825 ± 125 | 1530 ± 175 |
| Mean LAP (mm Hg) | 7 ± 3 | 8 ± 2 | 9 ± 2 |
| SS (%) | 24 ± 2 | 23 ± 2 | 25 ± 5 |
| IBR5 (dB) | -43.6 ± 0.3 | -42.9 ± 0.2 | -44.5 ± 0.2 |
| FAM (dB) | 4.0 ± 0.4 | 3.5 ± 0.4 | 3.1 ± 0.3 |

LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; other abbreviations are as in figure 1.

A p < .05 vs control.
TABLE 2
Effects of change in preload on IBR5 and FAM

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>138 ± 12</td>
<td>145 ± 10</td>
<td>129 ± 8</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>107 ± 7</td>
<td>107 ± 8</td>
<td>93 ± 7</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>135 ± 9</td>
<td>136 ± 11</td>
<td>130 ± 14</td>
</tr>
<tr>
<td>LVESP (mm Hg)</td>
<td>9 ± 1</td>
<td>12 ± 2A</td>
<td>4 ± 2A</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>1950 ± 250</td>
<td>1700 ± 200</td>
<td>1750 ± 300</td>
</tr>
<tr>
<td>Mean LAP (mm Hg)</td>
<td>7 ± 2</td>
<td>9 ± 1.5</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>DL (mm)</td>
<td>18 ± 1.2</td>
<td>20 ± 1A</td>
<td>15.5 ± 1.1A</td>
</tr>
<tr>
<td>SS (%)</td>
<td>2.1 ± 5</td>
<td>3.1 ± 2</td>
<td>12 ± 5.2</td>
</tr>
<tr>
<td>IBR5 (dB)</td>
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<td>-44.1 ± 0.2</td>
<td>-45 ± 0.2</td>
</tr>
<tr>
<td>FAM (dB)</td>
<td>4.1 ± 0.2</td>
<td>3.8 ± 0.3</td>
<td>3.4 ± 0.2</td>
</tr>
</tbody>
</table>

Abbreviations are as in figure 1 and table 1.

higher rates. No change in mean arterial pressure and left atrial pressure occurred during atrial pacing.

Tables 1 and 2 outline the effects of changes in mean arterial pressure and preload respectively on IBR5 and FAM. Neither an increase or decrease in mean arterial pressure or preload produced any significant change in IBR5 or FAM.

Figure 2 depicts the relationship between contractility and integrated backscatter. Neither esmolol or dobutamine produced a significant change in IBR5. In contrast, FAM increased from a control of 4.0 ± 0.2 to 6.5 ± 0.3 dB (p < .01) during the infusion of dobutamine, and decreased to 1.8 ± 0.2 (p < .01) after esmolol. These changes in FAM closely paralleled alterations in peak positive left ventricular dP/dt which increased from a control of 2325 ± 350 to 3450 ± 250 mm Hg/sec (p < .01) during infusion of dobutamine, and decreased to 1250 ± 200 mm Hg/sec with esmolol. Mean arterial pressure and diastolic segment length did not change significantly during either intervention.

Discussion

Although increasing the frequency of cardiac contraction exerts a positive inotropic effect through the strength-interval relationship, this effect is less prominent in the conscious state than in the anesthetized animal, the depressed heart, or isolated cardiac muscle. In normal conscious subjects at rest, artificially varying the heart rate between 60 and 160 beats/min has little effect on cardiac output, despite altered cardiac contractility. In the present investigation, an initial increase in heart rate, from 80 to 100 beats/min, resulted in an increased left ventricular dP/dt and FAM. At higher rates, no change in dP/dt or FAM was observed. These results contrast with those of Higgins et al., who observed a significant increase in peak positive left ventricular dP/dt in anesthetized dogs. In the latter study, however, control heart rates were substantially higher (120 beats/min); maximum rate achieved was also higher (220 beats/min) and sodium pentobarbital was used as the anesthetic agent. In the present investigation, the baseline heart rate was 80 beats/min, while maximum rate was 160 beats/min, and the anesthetic agent used was halothane (2%). Ross et al. also did not note an increase in cardiac output at heart rates of 60 to 160 beats/min in normal conscious subjects.

FAM was directly related to changes in the inotropic state as reflected by left ventricular dP/dt and segmental shortening. This indirectly supports our hypothesis that cardiac contraction and relaxation may produce changes in the effective area and orientation of the ultrasonic scatterers within the myocardium. In support of this hypothesis, Wickline et al. demonstrated that cardiac cycle-dependent variation in integrated backscatter was dependent on the contractile state of the myocardium. These investigators induced changes in the inotropic state of the myocardium via paired pacing and propranolol and reported that the maximum...

FIGURE 2. Effects of change in the inotropic state of the myocardium on the IBR5 and FAM. FAM follows changes in the contractile state of the myocardium, while no correlation is present for IBR5. *Significant (p < .01) difference. DL = diastolic segment length; SS = segmental shortening; other abbreviations as in figure 1.
rate of change in integrated backscatter waveforms during isovolumetric contraction was faster with paired pacing and slower with propranolol than under control conditions. In contrast, Wickline et al. did not find a significant change in cardiac cycle–dependent variation in integrated backscatter. The principal factor responsible for this apparent paradox involves the method of gating the backscatters of the signal.

In the present study afterload and preload did not alter FAM or maximum left ventricular dP/dt or segmental shortening. Mean arterial pressure was used as an index of afterload, while mean left atrial pressure, diastolic segment length, and left ventricular end-diastolic pressure were used as indexes of preload. Preload alterations in the present study were minor, and this may be responsible for the lack of changes in IBR5 or FAM. Theoretically, an increase in preload should cause an increase in IBR5 concomitant with an increase in sarcomere length. This was not observed, suggesting that larger changes in the size of the ultrasonic scatter is required to produce significant changes in IBR5.

The exact mechanism(s) of this variation in integrated backscatter with cardiac cycle is not clearly understood. Wickline et al. argue that the change in acoustic impedance (which in turn is related to changes in “passive elasstance”) with contraction is responsible for the modulation of the integrated backscatter. Wear et al., in studies of isolated papillary muscle, have shown that modulation in integrated backscatter occurs only in isotonically contracting muscles and not in isometrically contracting muscle. The precise identity of the scattering elements, which give rise to the myocardial backscatter, is not known at this time. Our initial studies based on Fourier analysis of the backscatter and its statistical properties demonstrated that the scatterers could not be resolved at standard diagnostic frequencies (2 to 7 MHz, corresponding to wavelengths of 770 to 220 μm, respectively), and that a “Rayleigh scattering” law applies in which the backscatter arises from multiple reflecting structures, or Rayleigh scatterers, much smaller than these wavelengths. We have postulated that cardiac contraction and relaxation alter the reflectivity of these Rayleigh scatterers by changing their effective area, shape, and/or orientation from systole to diastole. Madaras et al. have reported that the magnitude of ultrasonic backscatter from the myocardium is dependent on the angle between the sound beam and the orientation of the muscle fibers.

In previous studies, time average backscatter, the backscattered energy averaged over the cardiac cycle, has been used as a quantitative index of tissue characterization. In this study a new index of backscatter, IBR5, has been introduced. It is an absolute measurement of the myocardial backscatter independent of operator adjustment and instrumentation. It is similar to time-averaged backscatter, but also corrects for bulk tissue loss, diffraction, and spectral shape. Theoretically it is the optimal measure of backscatter because it uses Rayleigh spectrum and statistics to integrate all the usable backscatter frequency components.

The present study does not directly address the mechanism of cyclic variation in ultrasonic backscatter. The results demonstrate that IBR5 is independent of heart rate, preload, afterload, and inotropic state of the myocardium. FAM, an index of cardiac cycle–dependent variations in integrated backscatter, however, is dependent on cardiac contraction and relaxation, and therefore is sensitive to changes in the contractile state of the myocardium.

We thank Barbara Coons for preparation of the manuscript and Jean Howard and Dan Welsh for technical assistance.

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Influence of heart rate, preload, afterload, and inotropic state on myocardial ultrasonic backscatter.
K B Sagar, L E Pelc, T L Rhyne, L S Wann and D C Waltier

Circulation. 1988;77:478-483
doi: 10.1161/01.CIR.77.2.478

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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