Dependence of Instantaneous Transfer Function on Regional Ischemic Myocardial Volume

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To obtain the instantaneous left ventricular transfer function curve (instantaneous TFC) under conditions of regional ischemia, sinusoidal accelerations ranging from 30 to 150 Hz were applied to a small area of the epicardium of cross-circulated isovolumic canine left ventricle, and the contralateral acceleration was measured under control and during regional coronary occlusion (n=11). The TFC is the ratio of the output to input acceleration amplitudes. The instantaneous TFC was characterized as a single-peaked configuration under control coronary perfusion. However, TFCs progressively changed from a single-peaked to a double-peaked configuration during regional ischemia. To quantify this change in instantaneous TFC, we defined an index D as the mean squared difference of TFC during ischemia from TFC during control. Index D was linearly related to the percent mass of the ischemic region at 40 minutes after onset of ischemia. We conclude that 1) transfer function curves are sensitive measures of myocardial heterogeneity and 2) the fractional ischemic weight of the ventricle is a major factor in determination of the deformation in instantaneous TFC at the later stages of regional ischemia. (Circulation Research 1988;63:1003-1011)

With the recent development of new methods to measure left ventricular viscous and elastic stiffness,1-4 these properties have been examined in both normal and in various pathological states. Templeton et al4 used a forcing function method to investigate the changing aspects of viscous and elastic stiffness during the cardiac cycle. In addition, they found an increase in ventricular viscous stiffness with ligation of the left anterior descending coronary artery.3 Hunter et al,1 using the flow pulse response method, and Shroff et al,3 using the flow clamp method, stressed the importance of chamber resistance in measuring the end-systolic pressure volume relation as an index of contractility.

In contrast to these conventional methods, the transfer function method2 (incorrectly referred to in that report as an impedance method) can provide other information on the physical properties of the regionally ischemic left ventricle. In addition, this method can reveal changes of the instantaneous physical properties of both the normal and ischemic myocardium moment by moment during the cardiac cycle. When we consider the clinical importance of regional myocardial ischemia, it would be of value to add new information on the pathophysiology of regional ischemia that has been gained by this transfer function method. In our previous report,2 we examined the instantaneous transfer function curve (instantaneous TFC) under homogeneous physiological coronary perfusion but did not investigate its behavior under regional ischemia.

Therefore, our aim was to characterize the basic features of left ventricular instantaneous TFC during regional ischemia and to examine the relation between changes in the configuration of the ventricular instantaneous TFC and the fractional weight of ischemic myocardium, using an isolated, cross-circulated left ventricular preparation.

Materials and Methods

Surgical Procedure

The experimental setup is illustrated in Figure 1. We used 11 pairs of mongrel dogs anesthetized with 30 mg/kg sodium pentobarbital. One was used as a source of the isolated heart (source dog) and another

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was for the support of the coronary circulation of the isolated heart (support dog). The heart of the source dog was exposed via a thoracotomy and was isolated under artificial respiration. We maintained coronary perfusion of the isolated heart by cross-circulation. The extracorporeal coronary line for this cross-circulation included the glass cannula inserted into the left main coronary artery (main LCA), the thermister, the buffer system, the air trap, the microfilter (SQ-40, Marusho Sangyo, Tokyo), the peristaltic pump (type 1210, Harvard Apparatus, South Natick, Massachusetts), and the cannula inserted into a femoral artery of the support dog. Coronary venous efflux from the isolated heart was gathered and returned to a femoral vein of the support dog. After isolation of the heart, coronary circulation was maintained at a physiological level via the extracorporeal coronary line while bilateral atria and the right ventricular free wall of the isolated heart were excised, and the edges were sutured to prevent bleeding. Mitral leaflets and chordae tendineae were cut and removed, and the mitral orifice was closed with a rigid rubber mitral plug. This mitral plug was equipped with a latex balloon in the intraventricular lumen. We controlled the left ventricular volume with warmed physiological saline in the balloon. We set another extracorporeal coronary line by inserting the tip of a cannula into the left anterior descending coronary artery (LAD) or left circumflex coronary artery (LCX) to control regional perfusion independently of the perfusion of the main LCA. To induce regional ischemia, the perfusion through this LAD or LCX line was stopped. The size of the ischemic region was varied by changing the catheter tip position in each isolated heart.

The isolated left ventricle was suspended on a stiff, firm supporting apparatus. The tip of a vibrator (EMIC 511B, Shin Nippon Sokki, Tokyo) was fixed to a miniature acceleration sensor (EMIC 540M, Shin Nippon Sokki, Tokyo) and firmly attached to the anterior wall of the ventricular epicardium to provide a measured sinusoidal input. A second identical accelerometer was firmly attached to the contralateral epicardial surface to detect the output oscillation. Left ventricular pressure (LVP) was measured with a catheter-tip micromanometer (PC481, Millar Instruments, Houston, Texas) that was calibrated by a fluid-filled pressure transducer system through the lumen of the catheter.

Heart rate (HR) was fixed by junctional pacing, and bipolar surface ECG was recorded by silver-tipped electrodes adhered to the left ventricular epicardial surface.

Protocol

The left ventricle was perfused by the two independent coronary arterial lines (i.e., main LCA and LAD [or LCX] lines) under a mean perfusion pressure of 80 mm Hg. The blood temperature was maintained at approximately 34°C and PaO₂ at approximately 90 mm Hg. Junctional pacing rate and left ventricular volume were set to make the heart produce appropriate pressure development (greater than 70 mm Hg) without arrhythmias. All measurements were performed after steady cardiac contraction had been attained.

The periods of occlusion were divided into three groups. First, in two experiments, the LAD coronary arterial line was stopped for 120 minutes to examine the sequential change in the instantaneous TFC during a prolonged period of regional ischemia. Second, in one experiment, the LAD coronary arterial line was stopped for 20 minutes and reperfused for 30 minutes. This was done to gain insight into the possible reversibility of changes in the instantaneous TFC. Third, in eight experiments where the regional catheter tip placement was varied, the LAD (five) or LCX (three) coronary arterial line was stopped for 40 minutes for estimation of the relation between the configuration of the instantaneous TFC and the ischemic myocardial mass. We measured instantaneous TFC, as described below, every 10 minutes during each of the above protocols.
When all measurements were completed, black China ink diluted in 22% BaSO₄ was injected through the catheter into the LAD (or LCX), and unstained 22% BaSO₄ was injected through the catheter into the main LCA artery under a common mean coronary perfusion pressure of 80 mm Hg. After fixation with 5% formaldehyde, we sliced the ventricle into 10-mm thick sections perpendicular to the long axis (from base to apex). We measured the weight of the ischemic region stained black. We confirmed that the black-stained region was indeed the region of ischemia by serial reconstruction of the arterial tree serving it and by noting that the stained tree’s common origin was at the site of catheter insertion. This evaluation of regional myocardial mass was performed by one of us (T. Ohyama) without knowledge of the measured instantaneous TFC.

**Measurement of Transfer Function Curve**

The sinusoidal input acceleration was kept at a constant amplitude during the cardiac cycle. The frequency was swept automatically by driving a voltage-controlled oscillator with a function generator (model FG330, Iwatsu Electric Co. Ltd., Tokyo) whose output was step increases in voltage every 4 seconds. The range of frequency was nominally 30 to 150 Hz, and the frequency increment was 4 Hz. Due to drift in the function generator and voltage-controlled oscillator, this increment was occasionally 3 or 5 Hz, so that the frequency sequence was not always exactly 30, 34, 38, . . . Hz. However, the actual frequencies used were measured and are shown in the accompanying figures.

Measurements of ECG, LVP, input signal, and output signal were recorded on a direct-printout light beam oscillograph and an analog tape recorder (type FE-3907W Magnescale, Sony, Tokyo). The signals were subsequently processed by an analog-to-digital converter (12 bit resolution, sampling rate 2 kHz for each channel) and stored on a digital computer (model 990, Texas Instruments, Dallas, Texas). The output acceleration signal was filtered as follows. First, the signal was converted to the frequency domain using the fast Fourier transform algorithm. Second, the spectrum was bandpass filtered with a rectangular window (uniform weighting over the driving frequency ±20 Hz range). Finally, the inverse fast Fourier transform algorithm was applied to yield the filtered output signal. This procedure was used to eliminate distortions resulting from cardiac motion or other vibrations. The frequency response of the entire system, including accelerometers, amplifiers (Emic 505D, Shin Nippon Sokki, Tokyo), and direct-printout light beam oscillograph, was essentially flat between 10 and 500 Hz and 3 dB down in amplitude at 1.5 and 1,100 Hz.

The method of obtaining the instantaneous TFC has been detailed elsewhere, but we give a brief description, illustrated in Figure 2. In this figure, the input sinusoidal acceleration (constant amplitude), $X_{in}$, and the output sinusoidal acceleration from the contralateral sensor, $X_{out}$, are shown at three different driving frequencies ($f_1$, $f_2$, and $f_3$). Peak-to-peak amplitudes of these signals at equivalent times, denoted $t_n$, are $A_1$, $A_2$, and $A_3$ respectively. (Note that all input amplitudes A are the same, as described above.) The instantaneous TFC is a plot of the ratio of output to input amplitude versus frequency. The shape of the curve in the figure is typical of our measurements in control conditions and has two common characteristics. First, at low frequencies there is a gradually falling shape, which we interpret as the lumped response of the cardiac mass against the local stiffness presented by the punch-like deformation of the myocardium at the driving site. Second, there is
Calculation of Index D

We used the mean squared difference of the transfer function from control to quantify the progressive changes in TFC during regional myocardial ischemia. Specifically, we define an index D by the following equation:

$$D = \frac{1}{N} \sum_{k=1}^{N} (T_{\text{isch}}(k) - T_{c}(k))^2$$

where N is the number of data points (typically 31 for our range of frequency and frequency interval), and $T_{\text{isch}}(k)$ and $T_{c}(k)$ are the transfer functions under ischemic and control conditions, respectively, at the k\textsuperscript{th} frequency point. This is shown diagrammatically in Figure 3.

Because the instantaneous TFC changes as a function of instantaneous left ventricular pressure (LVP), the instantaneous TFC in control and ischemic states must be compared at the same instantaneous LVP. In four of eight experiments, the peak LVP was only slightly above 30 mm Hg. We therefore measured D at times corresponding to instantaneous LVP 30 mm Hg in all eight studies, and used the changes in TFC, as given by D, to compare with the estimated values of ischemic myocardial mass. All measurements were made in five sequential cardiac cycles and averaged.

Statistics

Paired Student’s t tests were used for comparing the hemodynamic changes between control and after 40 minutes of ischemia.

Results

The first experiments involved a prolonged (120-minute) period of LAD occlusion. When we examined the sequential change of the instantaneous TFC under the regional ischemia thus induced (Figure 4), a marked and rapid deformation occurred during the early stage of ischemia (0–30 minutes). In contrast, the configuration of instantaneous TFC was relatively unchanged at later stages (30–120 minutes).

The second experiment was 30 minutes of reperfusion after a 20-minute period of LAD flow cessation. The change in the instantaneous TFCs is shown in Figure 5. Data were taken up to 150 Hz in all studies, but to emphasize the configurational changes taking place, we show only data up to 100 Hz in this figure. The control instantaneous TFCs at three different instantaneous LVPs show a single peak, but deformed to a double-peaked configuration after 20 minutes of LAD flow cessation, and returned to a single-peaked shape after 30 minutes of reperfusion. There was, however, a slight difference in these single-peaked TFCs after reperfusion compared with control. Specifically, the frequency and magnitude of the transfer function peaks at both 15 and 20 mm Hg instantaneous LVP were slightly higher after 30 minutes of reperfusion compared with control at corresponding LVPs. This implies a continued but minor change in myocardial viscoelasticity even after 30 minutes of reperfusion. The essential point of these observations, however, is the return of the instantaneous TFC to a single-peaked configuration.

The third series of experiments correlated the change in the TFC curve, as measured by the index D, with regional ischemic mass. Table 1 shows, in the eight experiments, the heart weight, left ventricular volume, heart rate, maximum LVP ($LVP_{\text{max}}$) and left ventricular end-diastolic pressure (LVEDP) during control and 40 minutes after the onset of ischemia, which artery was occluded, weight of ischemic myocardium as percentage of total myocardial weight, and the index D. $LVP_{\text{max}}$ significantly decreased after ischemia, but LVEDP did not.

Figure 6 shows instantaneous TFCs in control state (upper panel) and 40 minutes after LAD flow cessation (lower panel). As in Figure 5, we show data only up to 100 Hz, but it should be noted that all data through 150 Hz were used in computation of index D. The control instantaneous TFCs at 82, 61, 48, 29, and 15 mm Hg of instantaneous LVP are displayed to show the dynamic change during the cardiac cycle. The basic feature of these curves is that they are characterized by a single peak, whose frequency, amplitude, and sharpness increase with...
Figure 4. The change of the instantaneous TFC during 120 minutes of LAD coronary occlusion. The instantaneous TFC changed rapidly from single- to double-peaked configuration within 30 minutes of regional ischemia. However, the configuration was relatively unchanged from 30 to 120 minutes. Details in the text.

The deformation of the instantaneous TFC increased as ischemia progressed. However, as shown in Figure 4, the instantaneous TFC became essentially constant after 40 minutes of ischemia. Therefore, we measured index D at that stage of ischemia. Figure 7 shows the instantaneous TFCs from 30 to 100 Hz at 30 mm Hg instantaneous LVP in the control state and after 40 minutes of ischemia. From top to bottom, instantaneous TFCs from three experiments with increasing ischemic sizes are shown. Corresponding to this, the magnitude of the deformation in instantaneous TFC from the control state also increased. Figure 8 shows the highly significant relation between index D and percentage of ischemia (r=0.980, p<0.005).

Discussion

"Transfer function" is a widely used technical term. When a sinusoidal input is applied to a linear system, the output is also sinusoidal. If \( X(\omega) \) and \( Y(\omega) \) are the (complex) Fourier transforms of the input and output, respectively, at angular frequency \( \omega \), then the ratio \( Y(\omega)/X(\omega) \) is the (complex) transfer function at that frequency. The important feature is that in the frequency domain, the input and output of a linear system are multiplicatively related via the transfer function. A full description of the transfer function includes both its magnitude and phase; in this report, however, we restrict our attention only to the magnitude, \( T \). The transfer function completely characterizes the system and includes the viscoelastic properties of the myocardium. An important point in use of the transfer function is that the linearity of the system should be assured over both the amplitude and frequency range used. In our method, we confirmed that the left ventricle could be taken as linear if the magnitude of acceleration in input oscillation was kept constant and small (below 1g) throughout the frequency range from 50 to 200 Hz. This procedure means that the displacement of the input signal decreases rapidly, as the square of the frequency.

The transfer function curve method differs in several ways from other more conventional methods of measuring myocardial physical properties. First, the TFC method possesses higher temporal resolution. The forcing function method of Templeton et al. estimates viscoelastic parameters every 50 msec. However, this interval seems too long to examine in detail the dynamic changes of the myocardial physical properties during an isovolumic contraction or relaxation, as these periods last only about 40 msec. Therefore, this method would be inappropriate to describe the instantaneous, dynamic changes of the myocardial physical properties during cardiac contraction. Second, the TFC method can be used in the ejecting heart preparation, even though additional signal processing is required to eliminate the effects of heart sounds. This application is possible because the TFC method only depends on signals from epicardial sensors, whereas other methods are restricted to the isovolumic beating left ventricle. Third, the TFC method can be applied to the heart with heterogeneous myocardial properties such as are induced by regional ischemia, with clear differences in the curve characteristics, whereas the...
interpretation of more classical methods in the heterogeneous setting is more difficult.

In this study, the instantaneous TFC during regional ischemia was characterized as a double-peaked configuration, in sharp contrast to the single peak configuration seen in the physiological state of homogeneous myocardial perfusion. In a previous study, we investigated the effect of global ischemia. In that condition, a double-peaked configuration did not appear, but rather a depressed single peak was observed. The double-peaked configuration seen here in regional ischemia must therefore be attributable to the heterogeneous character of this lesion.

The recovery of the TFC with reperfusion after 20 minutes of ischemia, as shown in Figure 5, is consistent with the results reported by Jennings et al. They showed that no irreversible myocardial injury (i.e., myocardial necrosis) developed when the coronary artery flow was reperfused within the first 15 minutes after coronary occlusion.

For purposes of comparing TFCs in different states, we chose to compare them at corresponding LVPs, although of course different choices (such as time in the cardiac cycle) are possible. We reasoned as follows. First, we characterize the myocardium in control conditions by its instantaneous TFC, considering it to be a viscoelastic medium. Second, we investigate departures from the control TFC due to induced perturbations in the medium, which in this study is regional ischemia. To the extent that our primary focus is on the myocardium as a viscoelastic medium and that the perturbations affect those properties, we ought therefore to compare control and ischemic conditions under circum-

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**Figure 5.** Top panel: Instantaneous TFCs at three different values of instantaneous left ventricular pressure (LVP) during the cardiac cycle in the control state. Middle panel: Instantaneous TFCs at these same pressures following 20 minutes of LAD occlusion. All curves assumed a double-peaked configuration. Bottom panel: Instantaneous TFCs at these same pressures following 30 minutes of LAD reperfusion. All curves returned to a single-peaked configuration.

**Figure 6.** Top panel: Instantaneous TFCs over a range of instantaneous LVP in the control state. Note that all curves display a single peak, and that the frequency of the peak and the peak amplitude increase with increasing LVP. Bottom panel: TFCs in the same heart after 40 minutes of LAD occlusion, where we attempted to match the LVP in control. LVP 82 mm Hg was unattainable. All curves showed the characteristic double peak.
stances wherein the viscoelastic properties are closely matched. This implies, in our case, comparing studies under matched LVP. Other studies are possible, considering the heart as primarily a force generating organ, wherein the timing is of obvious importance. But here, under matched LVP conditions, we can investigate the effect of regional ischemia on the purely viscoelastic properties of the myocardium, regardless of whether or not the timing of the force generation was common to the various states. Evidence for the validity of this reasoning is apparent in the close relation we found between index D, computed at equivalent LVPs, and mass of the ischemic region. Given the wide variability of LVP over time in the ischemic case, such a relation would be obscured if other criteria were used in selecting TFCs to compare. We describe below our current hypothesis regarding the origin of the splitting of the control TFC configuration into a double-peaked one, and note that such an interpretation requires comparison at matched LVP, the protocol adopted in this study.

To what extent might our results be traceable to a fall in the "garden hose" effect, that is, to a decrease of the erectile force by the coronary arteries? Two arguments suggest that this does not play a major role in the observed phenomenon. First, the coronary perfusion was abruptly stopped at the onset of ischemia. Nevertheless, the TFC changed its configuration gradually, albeit most rapidly at the beginning. A virtually instantaneous change in the TFC would be expected if the garden hose effect were the dominant mechanism. Second, the second peak in the TFC appeared at a higher frequency than the single control peak. This strongly suggests that the ischemic region is stiffer in its elastic properties than the nonischemic region, which is in direct contrast to the notion that the ischemic region might become more compliant due to the loss of the garden hose effect.

A more likely explanation for our results is that the myocardium, in its ischemic state, behaves like a multiply coupled oscillator system. In a simplified model possibly appropriate to the control state, we demonstrated that the myocardial physical properties of elastance and resistance are related directly to the transfer function, specifically to changes in the peak amplitude, frequency, and sharpness. These parameters are not sufficient, of course, to describe the double-peaked TFCs observed in this study. Indeed, a model description of the double-peaked curves is problematic; in terms of lumped models, it is not at all clear what model would be most appropriate. We chose therefore to describe the change in the TFC by the empirical quantity given by index D, the mean squared difference. The usefulness of this index is suggested by the very strong correlation seen between D and the size of the ischemic region (Figure 8). While index D is at this stage of our understanding wholly empirical, it nevertheless has the desirable property of being model independent. On the other hand, we do not know why the correlation of D with myocardial ischemic size should be so strongly linear.

APPENDIX

A multiply coupled oscillator system is a lumped version of the vibrations of an elastic continuum, which may be valid over a limited frequency range. But some results from the theory of elastic vibrations of a continuous medium may also help in our interpretations of these results. Specifically, we refer to the breaking of degenerate modes of oscillation as a mechanism for generating double-peaked TFCs. In this view, we explicitly do not envision the motion of the heart to be a phenomenon describable in lumped terms. Rather, we consider modes of oscillation of a continuous medium. An appropriate approximation to the myocardium might be a thick-walled incompressible elastic sphere, with an incompressible fluid interior. Since we measure displacements normal to the myocardial surface, we may safely ignore those modes of

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**Table 1. Hemodynamic Data, Fractional Ischemic Weight, and Index D in Eight Experiments**

<table>
<thead>
<tr>
<th>Exp No.</th>
<th>Heart weight (g)</th>
<th>LVV (ml)</th>
<th>HR (beats/min)</th>
<th>LVP&lt;sub&gt;max&lt;/sub&gt;/LVEDP Control</th>
<th>LVP&lt;sub&gt;max&lt;/sub&gt;/LVEDP Ischemia, 40'</th>
<th>Region</th>
<th>Fractional ischemic weight (%)</th>
<th>Index D (10&lt;sup&gt;-4&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>123</td>
<td>15</td>
<td>80</td>
<td>74/4</td>
<td>34/6</td>
<td>LAD</td>
<td>30</td>
<td>6.64</td>
</tr>
<tr>
<td>2</td>
<td>106</td>
<td>18</td>
<td>80</td>
<td>72/8</td>
<td>64/8</td>
<td>LCX</td>
<td>9</td>
<td>0.62</td>
</tr>
<tr>
<td>3</td>
<td>103</td>
<td>20</td>
<td>70</td>
<td>104/4</td>
<td>30/17</td>
<td>LCX</td>
<td>51</td>
<td>12.51</td>
</tr>
<tr>
<td>4</td>
<td>99</td>
<td>16</td>
<td>70</td>
<td>76/6</td>
<td>30/6</td>
<td>LAD</td>
<td>27</td>
<td>4.89</td>
</tr>
<tr>
<td>5</td>
<td>92</td>
<td>12</td>
<td>80</td>
<td>84/12</td>
<td>64/12</td>
<td>LAD</td>
<td>11</td>
<td>1.79</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>12</td>
<td>70</td>
<td>75/5</td>
<td>40/3</td>
<td>LAD</td>
<td>42</td>
<td>9.44</td>
</tr>
<tr>
<td>7</td>
<td>71</td>
<td>8</td>
<td>90</td>
<td>100/6</td>
<td>34/6</td>
<td>LAD</td>
<td>27</td>
<td>5.43</td>
</tr>
<tr>
<td>8</td>
<td>140</td>
<td>15</td>
<td>80</td>
<td>93/3</td>
<td>43/3</td>
<td>LCX</td>
<td>37</td>
<td>10.54</td>
</tr>
</tbody>
</table>

| Mean   | 103.0           | 14.5    | 77.5           | 85.0/6.0                        | 42.4*7.6*                        |         | 29.2                         | 6.48                     |
| ±SD    | ±21.0           | ±3.5    | ±6.6           | ±12.0±2.4                       | ±14.1±4.7                        | ±13.4   | ±3.89                        |

**LVP**, left ventricular volume; **HR**, heart rate; **LVP<sub>max</sub>**, maximum left ventricular pressure; **LVEDP**, left ventricular end diastolic pressure.

*Significantly different from control (p < 0.01); *Not significantly different.
oscillation where the displacements are tangential to the surface. These purely torsional modes may indeed be excited at these frequencies, but do not contribute to the observed TFC. In the case of radial modes (with sufficient tangential components to accommodate the boundary conditions of no stress at the outer myocardial surface, and continuity of normal displacement at zero shear at the inner surface), it is clear that the lowest pure mode is one wherein the myocardial "sphere" distorts from an oblate sphere to a prolate sphere in an oscillatory fashion. This mode is pure in the sense that it does not involve any interaction with the external measurement or excitatory devices. This would correspond to the peak observed in the TFC. (There is a very low frequency peak, arising probably from the simple mass of the heart oscillating in a lumped fashion against the local stiffness presented by the heart to the driving shaft. We do not consider this peak in this argument.)

What are the characteristics of this lowest oscillatory mode? Since there is a single axis that determines the oblate/prolate distortion, it is clear that there is minimally a threefold symmetry, and therefore at least a threefold degeneracy, in the mode. That is, there are three independent modes (and of course any linear combination of these) with linearly independent axes of deformation, but with exactly the same frequency of free oscillation. Now in our preparation, one axis is in fact favored, since there is the predetermined axis of excitation. This may in part break the symmetry, but quantifying this would be difficult; in particular, we hypothesize that a linear combination of the three independent degenerate modes is itself an adequate description of the observed peak. If, under these circumstances, any perturbation of the myocardium from its standard state occurs, then a breaking of the degeneracy can occur. Thus, in the case of myocardial ischemia, one suspects that the appropriate local stiffness in the vicinity of the ischemic region may have changed. (It is unlikely that a mass perturbation occurs.) Such a change in stiffness means that the local velocity of elastic wave propagation changes and that the model, which before was symmetric and therefore had identical oscillatory frequencies, now is no longer symmetric, and the natural oscillatory frequencies may break into at least a pair. The extent of the splitting ought to be proportional to the extent of the perturbation, in this case represented by the size of the ischemic region.

This explanation of the breaking of degenerate modes may be illustrated in any number of ways. Perhaps the simplest is to consider the natural vibrations of a drum head. One pair of modes (not the lowest in frequency) is characterized by a single nodal line across the drum, a line of no displacement. It is clear that another, independent mode is.

This is an argument based on dipole symmetry. There are reasons to believe that the dipole mode does not exist in an incompressible medium and that the quadrupole mode is the lowest. In that case, the order of degeneracy would be five. However, the arguments presented below do not depend on the precise value of the order of the degeneracy, merely that there be multiple independent modes with the same free vibration frequency.
equivalent to a 90° rotation of this mode and that there is a twofold degeneracy. It is also clear, by symmetry, that the two modes have the same frequency. If a small point-like mass is affixed to the surface of the drum, a splitting occurs. The mode that had its nodal line coincident with the perturbing mass is unaffected since its displacement is already zero, whereas the mode with its nodal line 90° off (perpendicular to the radius vector to the point mass) now has an effective mass that is increased relative to the unperturbed state. It therefore has a lower frequency of vibration. In short, in any circumstance where there is a degeneracy of modes of oscillation (usually due to an underlying symmetry in the geometry), a perturbation in the mass or stiffness of the medium that breaks the symmetry will also break the commonality of the frequencies. In such a case, a double-peaked (at least) characteristic of the TFC would be expected.

This study has focused on describing the basic pattern of the left ventricular TFC under regional ischemia and exploring possible underlying mechanisms for the double-peaked configuration. It is of course premature to apply these results to the clinical field, but we are encouraged by two observations. First, the size of the ischemic region correlated well with changes in the TFC, which can be measured with epicardial sensors only. Second, the recovery of the TFC with reperfusion is consistent with the known time course of induction of irreversible myocardial injury. Third, it is well established that left ventricular function, exercise tolerance, and prognosis are correlated with the mass of ischemic region.16-18 This is consistent with the results of this study, where we determined the degree of functional depression of LVP, estimated by \( \Delta LVP = LVP_{\text{max}} \text{at control} - LVP_{\text{max}} \text{after 40 minutes of regional ischemia} \). We compared \( \Delta LVP \) with index D, and found a significant correlation:

\[
\Delta LVP = 3.9 \times D + 16.8, \quad r = 0.75, \quad p < 0.05
\]

This implies that this technique has the potential to address functional questions quantitatively through use of the index D, which we emphasize is only transfer function dependent. These suggest the possibility of future use of this technique in the clinical setting, such as real-time monitoring of the expansion of an ischemic region during open chest surgery under hypothermic cardioplegia. In case of coronary artery sclerosis or left ventricular hypertrophy, myocardial protection during surgery might be nonuniform. Real-time evaluation of the extent of regional damage is therefore important to assess for future use in diagnosis and treatment of functional loss.

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