Anesthesiology
80:582–594, 1994

Speed and Sensitivity of Mechanical Versus *Electrographic Indicators to Mild or Moderate Myocardial Ischemia in the Pig*

Seiji Watanabe, M.D., Charles W. Buffington, M.D.†*

Background: **Intraoperative myocardial ischemia may be detected and quantified by indexes of myocardial contraction or by electrography. The relative reliability of these two approaches is controversial. Two issues are relevant: the timing of events after the onset of mild to moderate ischemia, and the sensitivity of measures to ischemia at steady state.**

Methods: **In eight pigs, a carotid-to-left anterior descending coronary artery shunt with a flow meter was installed. Flow to the left anterior descending coronary artery was reduced in steps of 10% from baseline values to 50% of baseline. Wall thickness, myocardial QRS amplitude, and ST-segment deviation were measured every 1 min for 6 min at each step. Regional myocardial lactate extraction was measured at 6 min.**

Results: **Linear relations were found between the percentage of baseline coronary flow and all four dependent variables at steady state, indicating equal sensitivity (defined as rate of change with respect to flow reduction) to myocardial ischemia. After flow reduction, decreases in systolic wall thickening occurred first and were followed by a QRS amplitude decrease and then ST-segment elevation. The onset of ischemia was earlier with more severe reductions of coronary flow.**

Conclusions: **Mechanical and electric measures of myocardial ischemia show equal sensitivity at steady state even though regional contraction changed more quickly than did QRS amplitude or the ST-segment after an abrupt reduction in coronary flow. (Key words: Animals: swine. Complications: myocardial ischemia. Heart: coronary stenosis; electrophysiology; myocardial contractility; myocardial oxygen consumption. Metabolism: lactate. Monitoring: electrocardiography.)**

* Assistant, Kurume University; Research Fellow, University of Pittsburgh.

† Professor of Anesthesiology.

Received from the Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania and the Department of Anesthesiology, Kurume University, Fukuoka, Japan. Accepted for publication November 3, 1993. Supported by an intramural award from the Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh, and in part (to SW) by the Foundation of Kurume University.

Address reprint requests to Dr. Watanabe: Department of Anesthesiology, Kurume University, 67 Asahimachi, Kurume Fukuoka 830, Japan.

DETECTION of myocardial ischemia is important during anesthesia in patients with coronary artery disease. Perioperative ischemia has been linked to morbid outcomes such as myocardial infarction, cardiac failure, and death.[1–3] Presumably, early detection and prompt treatment of perioperative ischemia would decrease the incidence and severity of such events.

The relative reliability of measures of myocardial contraction, such as those provided by transesophageal echocardiography (TEE), and measures of myocardial electric activity obtained from the electrocardiogram (ECG), is a matter of controversy. Two questions have been raised: which technique provides the earlier indication of ischemia, and which provides the more sensitive response to myocardial ischemia? Numerous studies in both animals and humans have demonstrated that regional myocardial contraction decreases rapidly after total coronary occlusion, and that ECG evidence of ischemia lags contractile failure by seconds to minutes.[4–8] Scant attention has been paid, however, to the rate of change of TEE and ECG variables after the onset of less severe ischemia. This question is important because the ischemia that occurs in a clinical setting is rarely complete. Rather, mild to moderate imbalances in oxygen supply and demand occur as a result of either changes in systemic hemodynamics or partial coronary occlusion by spasm or platelet aggregates.

The issue of sensitivity is controversial in part because the experimental approaches have varied. Some studies have defined sensitivity in terms of "first noticeable change"; some have used an arbitrary criterion to establish a positive response; and others have used statistical tests to define a significant response. Many studies have been performed in dogs, whose relative abundance of intercoronary collateral vessels leads to an unpredictable response to coronary occlusion that further complicates the analysis.

Therefore, the purpose of the current study was to compare the time courses of systolic wall thickening,

ST-segment deviation, and QRS amplitude after graded reductions in coronary flow. We measured myocardial lactate flux as an indicator of ischemia and used the values of other dependent variables corresponding to the transition to lactate production to determine the time when these variables indicated the onset of myocardial ischemia. The results confirm the previous observation that mechanical dysfunction precedes ECG changes after an abrupt decrease in flow and show that this lag time increases with mild flow reduction. The results also demonstrate linear relations among all four dependent variables and percentage reduction of coronary flow at steady state, suggesting equal sensitivity to ischemia.

Materials and Methods

General Preparation

The protocol was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. Eight technically successful experiments were accomplished in 23 farm-bred pigs (20–25 kg) of either sex. Experimental difficulties resulted largely from coronary cannulation. Eleven pigs died after coronary dissection, occlusion of a septal branch, or coronary spasm. In four pigs, reliable samples of regional venous blood could not be obtained.

The pigs were given acetylsalicylic acid (25 $mg \cdot kg^{-1}$ orally) the night before surgery to decrease platelet activation by the external perfusion circuit (see below). Before each experiment, the pigs received ketamine (10 $mg \cdot kg^{-1}$ intramuscular) and then were anesthetized with halothane (0.5–2.5% end-tidal concentration). After tracheal intubation with a cuffed tube through a tracheostomy, the lungs were ventilated with oxygen and air delivered by a positive-pressure respirator (Harvard, South Natick, MA) with 5 cmH_2O positive end-expiratory pressure. The partial pressure of oxygen in arterial blood was kept greater than 200 mmHg by controlling the flow of oxygen. Tidal volume was fixed at 15 $ml \cdot kg^{-1}$ and respiratory rate adjusted to keep the arterial carbon dioxide tension at 35–40 mmHg. Blood gas tensions and *p*H were measured at intervals during the experiment (Radiometer, Copenhagen, Denmark).

Arterial pressure was measured with a saline-filled transducer (Gould, Cleveland, OH) through a polyethylene catheter placed into the thoracic aorta *via* the right brachial artery. Left ventricular (LV) pressure was measured with a micromanometer (Millar, Houston, TX) inserted through a purse-string suture in the left atrial appendage. The heart was exposed by left thoracotomy and suspended in a pericardial cradle. Several ribs were removed to improve access to the heart. Wires were sutured to the left atrium for pacing (Metronic 5880A, Medtronic, Minneapolis, MN). Heart rate was held constant at approximately 140 $beats \cdot min^{-1}$. The pericardium was left open. Halothane was discontinued after instrumentation, and anesthesia was maintained with morphine (3 $mg \cdot kg^{-1}$ subcutaneously) and pentobarbital (25 $mg \cdot kg^{-1}$ intravenously [iv] plus 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$ iv). Metacurine (4 mg iv initial bolus and subsequent 2 mg iv bolus doses as needed) was used for muscle relaxation.

Regional Wall Thickening

Regional myocardial contraction was measured in the area supplied by the left anterior descending coronary artery (LAD) with a pair of ultrasonic crystals and a sonomicrometer (Triton, San Diego, CA). A 1–2-mm–diameter lensed piezoelectric crystal was inserted through a stab wound in the epicardium and tunneled tangentially to a position at the endocardial surface. A 2–3-mm–diameter lensed crystal was sewn to the epicardium at the location that minimized the distance between crystals. The pair of crystals measured wall thickness. A temporary occlusion of the LAD, after the crystal pair was in place, confirmed that the set was located in the ischemic area. At autopsy, the inner crystal of the wall thickness pair was located by blunt dissection. Each inner crystal was within 3 mm of the subendocardium. The orientation of the crystal sets was checked to ensure that the set was perpendicular to the epicardium.

Myocardial Electrographic Measurements

Stainless steel wires (Medwire, Mount Vernon, NY), coated with Teflon except for the distal 2 mm, were inserted into both the subendocardium and the subepicardium to serve as intramyocardial electrodes. The electrode was pushed into the LV cavity and then withdrawn until a hook at the tip engaged the muscle. Electrograms were recorded from endocardium and epicardium (model 13-4615-58, Gould) relative to a reference electrode at the T6 level on the animal's back. The amplifier of the myocardial electrogram had a low-frequency cutoff of 0.1 Hz and high-frequency cutoff of 3 kHz and a notch filter at 60 Hz. The electric circuit was calibrated by applying a 10-mV direct-current sig-

nal to the electrodes (General Resistance, Branford, CT) at the end of each experiment.

Coronary Perfusion

The proximal LAD was dissected free from the epicardium, and papaverine in saline (2.5 mg · ml^{-1}) was poured over the artery to minimize spasm. Lidocaine (30 mg iv) and heparin (750 U · kg^{-1} iv bolus plus 250 U · kg^{-1} · h^{-1}) were given, and a 4-mm–long, thin-walled, 14-G Teflon tube was inserted into the LAD and tied into place. Blood from the left carotid artery was supplied to this cannula by a shunt. After cannulation, the shunt was clamped for 10 s, and release of the clamp elicited a brisk reactive hyperemia with a peak flow 1.5–2.0 times resting flow in all animals. The shunt was made of thick-walled Silastic tubing (3.0 mm ID, Dow Corning, Midland, MI) and incorporated an electromagnetic flow probe and an adjustable screw clamp. The inside of the shunt was coated with a silicone compound (Prosil-28, PCR, Gainesville, FL) and dried before use. A flow meter (Zepeda SWF-4RD, Seattle, WA) was used to measure total coronary flow. The flow meter was calibrated with the pig's blood by timed collection after each experiment.

Regional Lactate Metabolism

A 22-G catheter was inserted retrograde into a small vein in the territory supplied by the LAD. Usually, a vein parallel to the second diagonal branch of the LAD was used for this purpose. Small samples of blood (0.5–0.6 ml) were slowly withdrawn over 20–30 s from this catheter, and a simultaneous blood arterial sample was obtained. The samples were stored on ice for 10–15 min until measurement of oxygen content (OSM3 Hemoximeter, Copenhagen, Denmark), oxygen tension (ABL Radiometer), and lactate concentration (Yellow Springs Instruments, Yellow Springs, OH).

Experimental Protocol

Insertion of the intramyocardial electrodes often produced an injury current characterized by ST-segment elevation. The ST segment returned to within 1 mV of the TQ baseline within 15–60 min. The heart rate was stabilized at 140 beats · min^{-1} by atrial pacing. Arterial blood pressure was not controlled. Hemodynamic, electrographic, and regional wall thickness data were recorded, and coronary flow was measured. Matched arterial and coronary venous blood samples were obtained for analysis of lactate and oxygen content. Then the screw clamp was abruptly tightened to reduce coronary flow by about 10% from the initial baseline value. Flow tended to decrease abruptly and then increase slightly over 10–20 s as autoregulation compensated for the decrease in coronary pressure. A second, small adjustment of the screw clamp was frequently made to offset this compensation and to maintain constant flow. Measurements were recorded every 1 min for 6 min after flow reduction, and then blood samples were obtained. The stenosis was released; a reactive hyperemia occurred; and coronary flow was permitted to return to the baseline value.

In subsequent experimental trials, coronary flow was reduced by approximately 20, 30, 40, and 50% of the initial baseline flow. Flow reductions were not randomized because myocardial stunning can occur after severe flow reduction (see below). The animal was killed with potassium chloride (1 ml · kg^{-1} iv) while deeply anesthetized. *Post mortem* examination revealed that the electrodes and sonomicrometer crystals were located within the central area of the perfused zone in all animals.

Coronary Embolization

To determine whether the experimental procedures induced vascular collapse, we performed an additional experiment in five animals. The LAD was completely occluded for 45 s and regional contraction and distal coronary pressure recorded. The occlusion was released, and after a recovery period, a suspension of 50-μm–diameter glass beads in blood (total volume 2–2.5 ml) was injected into the LAD to stop flow at a capillary level. This approach maintains proximal coronary artery pressure and should prevent vascular collapse. The time course of contractile failure after microembolization was compared with that after coronary occlusion to determine the influence of vascular collapse.

Myocardial Electrogram versus *Surface Electrocardiogram*

In five different animals a median sternotomy was done instead of a left thoracotomy. Myocardial electrodes and an LAD occluder were installed, and then the pericardium and chest were closed tightly. A drainage tube was inserted to evacuate air from the pleural space. After a baseline measurement had been obtained, the LAD was completely occluded, and myocardial electrograms and a surface ECG from a V3 lead overlying the ischemic area were recorded for 90 s. The surface ECG was recorded from subcutaneous needle electrodes placed in the standard configuration using

an amplifier with a low-frequency cutoff of 0.3 Hz and high-frequency cutoff of 50 Hz (model 13-4615-64A, Gould).

Data Collection and Analysis

Aortic pressure, LV pressure, regional wall thickness, and regional electrograms were recorded on a polygraph (Gould). (These signals were also digitized at 2 kHz by a 12-bit analog-to-digital converter [Canopus, Kobe, Japan] and recorded on floppy disk for later computerized analysis [NEC, Tokyo, Japan]). The first derivative of LV pressure with respect to time (LV $dP \cdot dt^{-1}$) was obtained with an analog circuit (model 13-4615-71, Gould). To allow accurate timing of the start and end of systole, a paper speed of 100 $mm \cdot s^{-1}$ was used. The beginning of systole was considered as the time when LV $dP \cdot dt^{-1}$ first left the baseline, before peak positive LV $dP \cdot dt^{-1}$. The end of systole was assumed to occur 25 ms before peak negative LV $dP \cdot dt^{-1}$. The absolute change in wall thickness during systole was calculated as end-systolic wall thickness minus end-diastolic wall thickness and was normalized to end-diastolic thickness.

The myocardial electrogram showed an "rS" complex that resembled the surface ECG lead V3 (fig. 1). The QRS amplitude (primarily a reflection of S-wave amplitude) was measured in millivolts relative to the PR baseline. The elevation or depression of the ST segment was measured relative to the PR isoelectric line 100 ms after the beginning of QRS complex. These waves were measured and stored with a visual waveform editorial software (Wave Master II, Canopus).

Steady-state Data. The flow during each experimental trial was expressed as a percentage of the initial baseline value at the beginning of the experiment. Dependent variables (hemodynamics, wall thickness, and electrogram amplitudes) measured at steady state were plotted against percent flow reduction in each animal. Sequential points were connected by straight lines. Because of experimental variability, the target value for flow reduction was not always precisely achieved. Consequently, values for the dependent variables at uniform percent reductions of coronary flow (*i.e.*, 10, 20, . . . 50%) were obtained by interpolation and averaged. Steady-state values of lactate metabolism were plotted against absolute coronary flow in each animal (fig. 2, top). A best-fit curve was constructed by eye, and the flow value at which lactate extraction changed to production was obtained by interpolation. Similar plots of absolute coronary flow *versus* wall thickening,

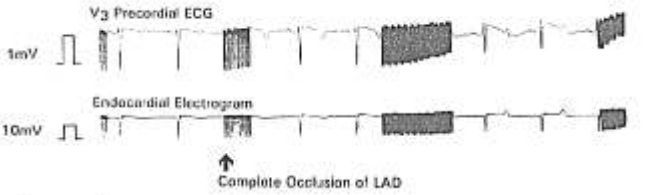

Fig. 1. Lead V3 precordial electrocardiogram and endocardial electrogram tracing from one pig. After abrupt occlusion of the LAD acute ischemia produced synchronous and proportional changes in the amplitude of the QRS complex and ST segment of both leads. These data suggest that the local electrographic changes that were observed in the current study should also be observed in electrocardiogram complexes recorded from the body surface. (Paper speed 100 $\cdot$ mm $\cdot$ min^{-1} and 100 mm $\cdot$ s^{-1}.)

QRS amplitude, and ST deviation (for both endocardial and epicardial electrograms) were constructed. Because of a small residual effect due to myocardial stunning (see below), values for these variables were normalized to the value obtained just before each flow reduction. The value of these normalized dependent variables occurring at the flow value corresponding to the onset of lactate production ("threshold value") was obtained.

Dynamic Events. To demonstrate the time course of the ischemic cascade, the normalized dependent variables (see above) were plotted against time for each trial in each animal (fig. 2, third level). Then the time at which the dependent variable crossed the threshold value corresponding to lactate production was tabulated. These times were considered to represent the "onset of ischemia" for a given dependent variable. The onset times were plotted against corresponding flow reductions in each animal, and interpolations were made for averaging.

Statistical Analysis. Descriptive statistics were calculated (SPSS/PC version 4.0, 1990). The relationships between degree of coronary flow reduction and all dependent variables at 6 min were calculated by linear regression analysis. The onset times corresponding to lactate production for the dependent variables data were compared by regression analysis. The data are presented as the mean ± 1 standard error of the mean.

Results

Most dependent variables were stable throughout the experiment (table 1); however, a small effect of time or preceding ischemia was noted in systolic wall thickening. Thickening decreased from an initial value of

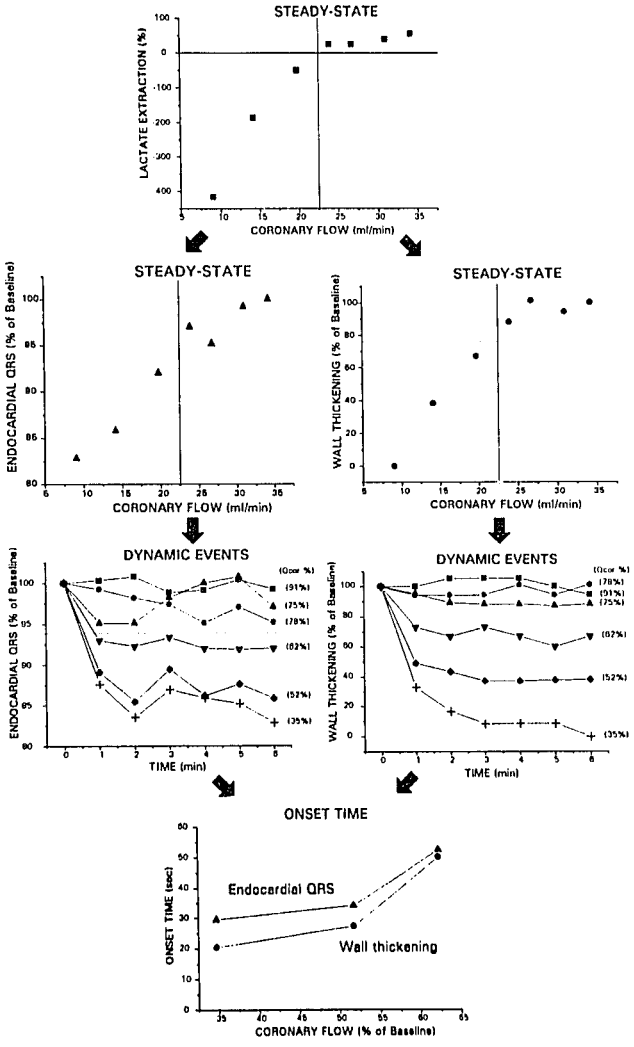

Fig. 2. The process used to calculate onset time of myocardial ischemia as indicated by changes in regional wall thickening and QRS amplitude in each animal. First, steady-state values of lactate metabolism were plotted against absolute coronary flow, and a best-fit curve relating the two variables was constructed by eye (*top*). The flow value at which lactate extraction changed to production was obtained by interpolation. Then, the values of myocardial contraction and electrogram parameters corresponding to this flow value were determined (*second level*). To demonstrate the time course of events after abrupt flow reduction, the dependent variables were plotted for each run against time in each animal (*third level*). Then the time at which the dependent variable crossed the "threshold" value corresponding to lactate production at steady state was tabulated. These times were considered to represent the "onset" of ischemia for a given dependent variable. The onset times were plotted against corresponding coronary flow in each animal and interpolations made for the purpose of averaging (*bottom*).

27% before the first flow reduction to 22% before the final trial, probably because of mild myocardial stunning.

Steady-state Results

Arterial blood pressure and heart rate were stable during the entire experiment (data not shown), as evidenced by values during steady state at 6 min after abrupt reduction in coronary flow (table 2). The rate–pressure product was on the order of 13,000 mmHg · beat · min^{-1}. Regional myocardial oxygen consumption in the LAD perfusion territory was about 2.3 ml · min^{-1} at full flow and decreased to 1.6 ml · min^{-1} at the lowest flow ($P < 0.05$). LV end-diastolic pressure increased with decreasing flow ($P < 0.05$). Change in systolic wall thickening (expressed as a percentage of end-diastolic wall thickness) decreased in a linear fashion with decreases in coronary flow, from 27% at 100% flow to 9% at 50% flow ($P < 0.05$). Myocardial lactate extraction was positive (48%) at 100% flow and became negative at about 80% flow. Proportional increases in lactate production occurred with further decreases in flow ($P < 0.05$). Linear decreases in endocardial QRS amplitude and ST deviation from baseline occurred with decreased flow ($P < 0.05$). In contrast, small decreases in QRS amplitude and even smaller changes in the ST deviation of the epicardial electrogram were noted with decreased flow.

The steady-state correlates of lactate production were determined for each animal (see above) and averaged (table 3). Lactate production occurred when coronary flow was reduced by 20%. This flow corresponded to a 30% decrease in systolic thickening, a 20% decrease in endocardial QRS amplitude, a 1.8-mV deviation of the endocardial ST segment, a 12% decrease in epicardial QRS amplitude, and a 0.5-mV deviation of the epicardial ST segment.

Dynamic Results

The time course of events after the abrupt reduction of coronary flow was consistent among animals. An example is shown in figure 2. Rapid changes occurred in systolic thickening, whereas less rapid changes occurred in the electrograms. All changes were completed well within the 6 min allowed for steady state, with the exception of small progressive changes in QRS amplitude in several animals during the most severe flow reduction (data not shown).

The time after flow reduction necessary for each dependent variable to reach the threshold value corre-

Table 1. Values Before Flow Reduction

Experimental Trial	1	2	3	4	5
Systolic arterial pressure (mmHg)	92.4 ± 2.7	93.1 ± 1.4	91.5 ± 2.3	90.9 ± 2.5	88.7 ± 2.5
Heart rate (beats/min)	141 ± 1.3	141 ± 1.3	141 ± 1.3	141 ± 1.3	141 ± 1.7
End-diastolic wall thickness (mm)	6.7 ± 0.5	6.8 ± 0.5	6.7 ± 0.5	6.8 ± 0.5	6.5 ± 0.5
Systolic wall thickening (%)*	27.6 ± 3.7	28.3 ± 3.9	24.3 ± 4.0	23.5 ± 3.8	22.8 ± 3.5
Endocardial electrogram					
QRS amplitude (mV)	15.7 ± 1.4	15.6 ± 1.3	15.5 ± 1.3	15.5 ± 1.3	15.1 ± 1.4
ST segment deviation (mV)	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
Epicardial electrogram					
QRS amplitude (mV)	14.3 ± 2.1	14.8 ± 1.9	14.5 ± 2.2	14.4 ± 2.3	15.4 ± 2.3
ST segment deviation (mV)	0.3 ± 0.2	0.0 ± 0.1	0.0 ± 0.2	−0.1 ± 0.2	−0.3 ± 0.1
Coronary flow (ml/min)	27.4 ± 1.7	27.0 ± 1.7	26.1 ± 1.3	26.3 ± 1.5	24.9 ± 1.1
Number of animals	8	8	8	8	7†

Data are mean ± SEM.

* (End-systolic wall thickness − end-diastolic wall thickness)/end-diastolic wall thickness × 100.

† One animal missed the 5th trial.

sponding to myocardial lactate production is shown in figure 3. Systolic wall thickening reached threshold value first, usually within 20–40 s. Endocardial QRS amplitude reached threshold value next, usually within 60–90 s, and endocardial ST deviation reached threshold last, often requiring 100–150 s. The onset time for all dependent variables decreased as the severity of flow restriction increased ($P < 0.05$).

Coronary Embolization

A straight-line relation between systolic thickening and time after occlusion of coronary flow was assumed. Individual correlation coefficients averaged 0.93 (range 0.88–0.96) and improved to 0.95 ($P < 0.01$) when treatment (coded for microsphere embolization *vs.* coronary occlusion) was included in the regression model. Although a significant increase in predictive ability was achieved with the addition of the treatment code, the physiologic significance of such a small effect is uncertain. Inspection of the plots of decrease in systolic thickening after coronary occlusion and that occurring after microembolization revealed very similar time courses (fig. 4, left). Proximal coronary pressure was maintained at systemic levels after microembolization, but decreased rapidly after coronary occlusion (fig. 4, right).

Myocardial Electrogram versus *Surface Electrocardiogram*

The major wave of the myocardial electrogram QRS complex corresponded in time to the S wave of the V_5 surface ECG. After total coronary occlusion for 90 s (fig. 1 and table 4), the changes in amplitude of the respective waves occurred simultaneously. Myocardial QRS amplitude correlated directly with S-wave and inversely with R-wave amplitude of the surface ECG ($r^2 = 0.94–0.95$). The ST segment of both the precordial ECG and the endocardial electrogram was elevated. R^2 was 0.79 ± 0.08 for the five animals, and the slope constant was positive.

Discussion

We determined how graded reductions in coronary blood flow affect myocardial contraction, electrograms, and lactate metabolism in a region of the pig heart. Linear relations were found between the degree of flow reduction and the three dependent variables at steady state. Contractile dysfunction occurred earlier than electrogram changes after flow reduction, although the time difference decreased with more severe ischemia. Changes in the amplitude of the electrogram complex occurred earlier than changes in the ST segment.

Assumptions and Characteristics of the Model

We assumed that 6 min was long enough to achieve a steady state for lactate metabolism. This assumption is supported by data from a previous study[9] in which lactate production occurred quickly during mild ischemia: values obtained at 5 min were approximately 90% of the peak values after 10 min of ischemia. We

Table 2. Values at 6 Min After Coronary Flow Reduction

Coronary Flow Reduction (% of Baseline)*	50% Reduction	40% Reduction	30% Reduction	20% Reduction	10% Reduction	Baseline
Systolic arterial pressure (mmHg)	89 ± 3	89 ± 2	91 ± 2	92 ± 2	93 ± 2	92 ± 3
Heart rate (beats/min^{-1})	141 ± 2	141 ± 1	141 ± 1	141 ± 1	141 ± 1	141 ± 1
RPP ($\times 10^{-3}$)	12.5 ± 0.4	12.5 ± 0.3	12.8 ± 0.4	13.0 ± 0.4	13.0 ± 0.4	13.0 ± 0.4
MV_{O_2} (ml O_2/min^{-1})‡	1.65 ± 0.13	1.81 ± 0.13	2.06 ± 0.16	2.31 ± 0.15	2.37 ± 0.17	2.34 ± 0.19
LVEDP (mmHg)§	8.5 ± 1.1	7.7 ± 1.0	7.2 ± 0.8	6.4 ± 0.9	5.7 ± 1.1	5.4 ± 1.1
Systolic wall thickening (%)†‡	9.2 ± 3.9	13.5 ± 3.9	16.7 ± 4.2	20.1 ± 4.1	23.9 ± 3.7	27.8 ± 3.7
EDWT (mm)	6.3 ± 0.5	6.4 ± 0.5	6.6 ± 0.5	6.7 ± 0.5	6.8 ± 0.5	6.7 ± 0.5
ΔWTsys (mm)‡	0.6 ± 0.2	0.9 ± 0.2	1.1 ± 0.3	1.3 ± 0.3	1.6 ± 0.2	1.8 ± 0.2
Myocardial lactate extraction (%)‡	−133 ± 24	−87 ± 21	−41 ± 18	−1 ± 8	33 ± 4	48 ± 5
Myocardial lactate flux (mM)‡	−14.3 ± 1.8	−10.3 ± 2.2	−6.6 ± 3.2	0.4 ± 1.7	8.0 ± 1.2	13.6 ± 2.0
Endocardial electrogram						
QRS amplitude (mV)‡	6.6 ± 2.2	8.7 ± 2.0	10.3 ± 2.0	12.1 ± 1.8	14.5 ± 1.5	15.7 ± 1.4
ST segment deviation (mV)§	5.1 ± 1.2	4.3 ± 0.9	3.4 ± 0.7	2.5 ± 0.6	1.6 ± 0.5	0.6 ± 0.2
Epicardial electrogram						
QRS Amplitude (mV)‡	9.8 ± 2.7	11.2 ± 2.6	12.3 ± 2.6	13.1 ± 2.4	13.8 ± 2.2	14.3 ± 2.1
ST segment deviation (mV)§	1.7 ± 0.8	1.0 ± 0.8	0.8 ± 0.6	0.7 ± 0.5	0.4 ± 0.3	0.3 ± 0.2

Data are mean ± SEM (n = 8).

RPP = rate pressure product; MV_{O_2} = myocardial oxygen consumption; LVEDP = left ventricular end-diastolic pressure; EDWT = end-diastolic wall thickness; ΔWTsys = change in wall thickness during systole.

* Baseline is flow value at start of experiment.

† (End-systolic wall thickness − end-diastolic wall thickness)/end-diastolic wall thickness × 100.

Data have been rounded after averaging.

‡ 95% of confidence area of slope of linear regression did not include zero, and its value was positive ($P < 0.05$).

§ 95% of confidence area of slope of linear regression did not include zero, and its value was negative ($P < 0.05$).

intentionally limited the period of ischemia to minimize long-lasting effects such as stunning. Lactate production is a well-accepted standard indicating myocardial ischemia.[9-11] Factors that confound interpretation of lactate data tend to give false-negative results. For example, venous samples may be an admixture of

Table 3. Steady-State Correlates of Lactate Production

Animal	Coronary Flow (ml/min^{-1})	Systolic Wall Thickening (%)*	Endocardial Electrogram		Epicardial Electrogram	
			QRS Amplitude (mV)	ST Segment Deviation (mV)	QRS Amplitude (mV)	ST Segment Deviation (mV)
1	25 (82)	20 (84)	15 (84)	0.9	21 (95)	−1.1
2	24 (88)	13 (56)	8 (63)	2.0	5 (68)	1.5
3	15 (70)	36 (78)	16 (75)	1.4	20 (97)	0.3
4	26 (85)	19 (78)	7 (70)	3.5	10 (90)	0.1
5	22 (65)	16 (74)	12 (98)	0.3	14 (91)	0.8
6	22 (72)	18 (69)	8 (72)	1.7	10 (81)	1.3
7	17 (92)	5 (40)	15 (88)	2.1	10 (81)	0.7
8	19 (79)	30 (75)	18 (85)	2.1	13 (94)	0.5
Mean	21.3 (79.1)	19.5 (69.4)	12.2 (79.3)	1.8	12.8 (87.1)	0.5
SEM	1.3	3.5	1.5	0.4	1.9	0.3

* (End-systolic wall thickness − end-diastolic wall thickness)/end-diastolic wall thickness × 100.

† Numbers in parentheses are percentage of baseline values.

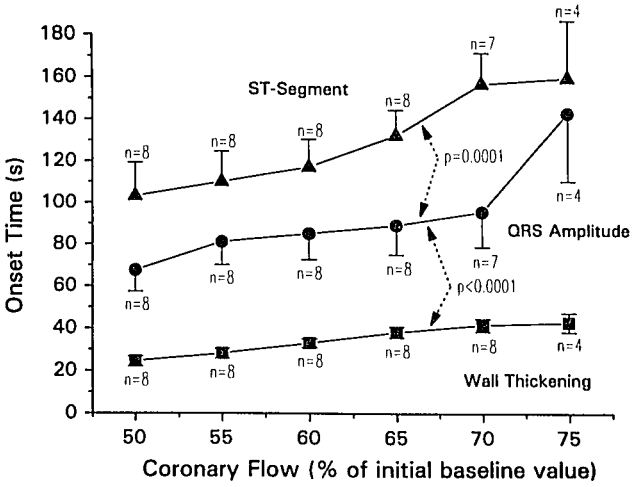

Fig. 3. The time after coronary flow reduction at which each dependent variable reached the threshold value corresponding to myocardial lactate production is plotted as a function of flow level. Regression analysis using dummy variables determined that the onset time indicated by reduced systolic wall thickening (squares) was shorter than the onset time determined by endocardial QRS amplitude (circles), which was shorter than that of endocardial ST-segment deviation (triangles). The onset time of each variable decreased in proportion to the severity in reduction of coronary flow ($P < 0.05$, slopes not equal to zero).

blood draining from ischemic and nonischemic myocardium, and lactate extraction by the nonischemic region may obscure lactate production by the ischemic zone.[12] Thus, net lactate production by the myocardium is a reliable and conservative indicator of myocardial ischemia.

We used consecutive 10% decrements in flow instead of random flow reductions. This was done to minimize any carryover effects from myocardial stunning and (possible) cellular necrosis resulting from the most severe ischemia. A small reduction in baseline myocardial contraction was present in several animals after recovery from the next-to-last trial, a finding that is consistent with mild stunning. Although we did not test for cellular necrosis and thus cannot conclusively rule it out, such a result is unlikely, given the short duration of ischemia. Nicklas *et al.* found no histochemical or ultrastructural evidence of myocardial necrosis even after 16 5-min total coronary occlusions in dogs,[13] but that conclusion may or may not apply to pigs.

A second carryover effect of some concern is the possibility that early ischemia influenced the response to later flow reduction through the phenomenon of preconditioning.[14] The concept is based on the observation that myocardial *p*H and high-energy compounds are reduced at a slower rate during a second episode of coronary occlusion than during the initial episode. Such an effect seems unlikely in the current experiment because of the short duration and mild degree of ischemia produced by the first three to four flow reductions.

Another assumption about the model is that little arterial blood reached the LAD zone *via* collateral vessels. We did not measure collateral flow in our animals and thus cannot exclude the possibility. In general, coronary pressure (measured in the perfusion circuit) decreased to only 3–6 mmHg more than left atrial pressure within 15 s when the perfusion circuit was clamped. This finding suggests little collateral flow. In comparison, a similar maneuver in dogs results in pressures 12–20 mmHg higher than left atrial pressure (data not shown). A previous study of normal pig hearts using the Schlesinger technique of injection found no evidence of interarterial coronary communications in 44 of 45 animals.[15] A study of collateral flow in pigs during complete coronary occlusion also showed very low levels.[16] Therefore, it seems unlikely that our measurements of LAD inflow seriously underestimated distal myocardial flow.

We assumed that the myocardial electrogram measured local electric events and was not greatly influenced by electric activity in other areas of the heart. If we had used a monopolar electrode to measure intracellular potentials, then this assumption would certainly be correct; we wanted to obtain a signal from more than just one cell, however, and used a bipolar electrode system to measure the difference in potential between the intramyocardial electrode and a reference

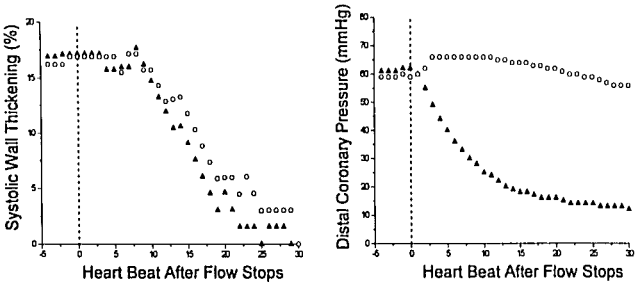

Fig. 4. In five pigs, loss of contractile function was observed after total coronary occlusion (triangles) and then after microembolization with 50-μm glass beads (circles). The results from one pig (*left*) illustrate the similar time courses. This similarity occurred despite considerable differences in proximal coronary pressure (*right*), suggesting that vascular collapse was not an important influence in contractile dysfunction in our model.

Table 4. Relation Between Surface V_3 Electrocardiogram and Myocardial Electrogram

Dependent Variable	Slope		Independent Variable	Constant	Coefficient
Surface V_3 SWA	0.12 (0.06)	×	END-QRS	−0.60 (0.77)	r^2 = 0.95 (0.02)
	0.15 (0.04)	×	EPI-QRS	−1.04 (0.89)	r^2 = 0.94 (0.03)
Surface V_3 ST	0.07 (0.03)	×	END-ST	+0.10 (0.19)	r^2 = 0.79 (0.08)
	0.07 (0.04)	×	EPI-ST	+0.02 (0.03)	r^2 = 0.88 (0.05)

Linear regression analysis mean (SD).

Surface V_3 SWA = S wave amplitude of surface V_3 electrocardiogram (ECG); END-QRS = endocardial QRS amplitude (n = 5); EPI-QRS = epicardial QRS amplitude (n = 4); Surface V_3 ST = ST segment deviation from isoelectric line of surface V_3 ECG; END-ST = endocardial ST segment deviation from isoelectric line (n = 5); EPI-ST = epicardial ST segment deviation from isoelectric line (n = 4).

electrode on the pig's back. Electric activity in nonischemic regions of the heart could have influenced the measurement. We assumed that the electric activity of normal myocardium was relatively constant and that these far-field effects would be small.

Interpretation

The current study confirms the results of several previous investigations and extends our understanding of experimental ischemia. For decades, students of cardiovascular physiology have investigated myocardial ischemia and its manifestations. Early studies demonstrated a rapid loss of contractile function,[17] ECG ST-segment changes,[18] and myocardial lactate production[19] after myocardial ischemia. Subsequent studies refined these concepts in different models and under various conditions. The stimulus for these efforts has been the need to diagnose and quantify myocardial ischemia in patients with coronary disease and to assess the impact of therapy on ischemia both in experimental animals and in patients.

The current study differs in important ways from prior work. First, partial coronary occlusion was used to produce mild to moderate ischemia rather than total coronary occlusion, which produces intense ischemia. Second, electric, biochemical, and mechanical measures of ischemia were measured at the same time. Third, and most important, an accepted standard of ischemia (the onset of lactate production), rather than an arbitrary criterion, was used to define the moment that electric and mechanical factors indicated ischemia. As a result, we can draw valid conclusions about the timing of events during ischemia.

Steady-state Data. Myocardial lactate extraction changed to production with about a 20% decrease in LAD flow. That ischemia occurred with such seemingly minor reductions in flow suggests that coronary autoregulation was intact and that the "100%" baseline flow values were close to the ischemic threshold. Sympathetic coronary constriction may have been present in these open-chest animals, an effect that would restrict coronary flow at baseline but should not effect the severity of ischemia during flow reduction.[20] If autoregulation was not intact, or if some exogenous vasodilator had been present at baseline, then a curvilinear relation between percent flow reduction and the dependent variables might have been observed. The myocardium would initially compensate for reduced flow by increasing oxygen extraction, and little ischemia would result until this compensatory mechanism had been exhausted. Curvilinear relations of this sort have been observed between coronary flow and contraction[11,21,22] as well as lactate metabolism.[11,19,23] In these studies, reasonably linear relations were observed between coronary flow and the dependent variable at lower flow ranges. The slope of these relations appears to depend on the species studied, being steeper in pigs (which lack collateral vessels) than in dogs. Previous studies have found a reasonably linear relation between decreasing flow and ST-segment elevation measured from electrodes in the endocardium,[24] but subepicardial leads have shown ST-segment depression with mild flow reduction and demonstrate elevation only when ischemia becomes transmural.[25] These linear relations are unlikely to hold true for greater degrees of ischemia in which substrate depletion limits lactate production and abolishes regional contraction.

The term "sensitive" has been used by other authors in their comparison of electric, mechanical, and metabolic measures of myocardial ischemia. The implicit definition of "sensitive" has varied between studies. Some authors have used the term in a statistical sense, defining sensitivity as "positivity in the presence of disease." This analysis requires a criterion value sep-

arating positive from negative results (as well as criteria separating ischemia from nonischemia). Such definite thresholds are difficult to establish for continuous variables. Particularly in clinical studies,[4,26] arbitrary criteria for positivity are used, and no accepted standard measure of ischemia is available. A less precise definition of sensitivity is related to the magnitude of changes observed: variables that change a great deal during ischemia are considered more sensitive than variables that change only slightly. Of course, the size of the response signal can be electronically amplified, so a cogent approach is to consider the response as a fraction of the maximum change elicited. In this scheme, a "sensitive" response variable has a large rate of change with respect to the change of the measured quantity. When this strategy is applied to the current data at steady state (fig. 5), roughly linear response rates in all variables are noted as flow is reduced. This finding argues strongly that mechanical, electric, and metabolic effects of ischemia provide equally sensitive measures of the cellular consequences of flow deprivation. Finally, the term "sensitivity" is often used when the rate of change of a measured variable with respect to time is discussed. We believe that "onset time" is a more precise description of this concept.

Dynamic Events. Analysis of the time dependence of events after abrupt flow reduction demonstrated that regional wall thickening reached the threshold of myocardial ischemia in 20–40 s, faster than either endocardial QRS amplitude (60–90 s) or ST-segment deviation (100–150 s). The time differences were greater after mild coronary flow reduction and decreased with more severe reductions. Battler and colleagues have published similar results in dogs,[5] although they documented time to onset at only two levels of coronary stenosis and did not actually measure coronary flow. Their results demonstrate statistically significant changes in wall thickening at 1 min after imposition of both "mild" and "moderate" coronary stenoses, with significant elevation in endocardial ST segments at 2 min and epicardial ST segments at 3–4 min. No universally accepted standard establishing ischemia was used in their study, and no analysis of QRS amplitude was reported. The faster onset times in the current study likely result from a higher heart rate (140 *vs.* 70 beats · min^{-1}) and the species difference.

Why does contractile dysfunction precede electric changes during the onset of ischemia? The answer likely relates to the subcellular events that occur when oxygen supply is restricted. The decrease in contractile

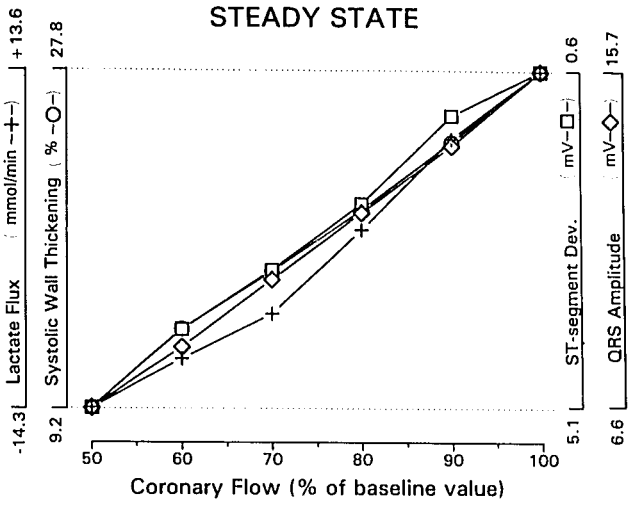

Fig. 5. Plots of myocardial lactate flux (plus signs), systolic thickening (circles), endocardial ST-segment deviation (squares), and endocardial QRS amplitude (diamonds) against coronary flow at steady state reveal linear relations indicating equal sensitivity of all variables to myocardial ischemia. Average data from eight animals are shown (error bars are omitted to enhance comparison). Relations were scaled to eliminate the "gain factor." A variable with greater sensitivity to ischemia would change more with small decreases in flow. Lactate production occurred at about 80% of baseline flow. These data do not reflect the *speed* with which variables change after an abrupt decrease in coronary flow, but rather the steady values seen after 6 min.

force is closely correlated with a decrease in the ratio of phosphocreatinine to inorganic phosphate, a measure of the energy reserve of the myocardium.[27] A second factor that may play a role in some models is loss of muscle turgor due to decompression of coronary arteries.[28] We tested the effects of "vascular collapse" on early contractile dysfunction after total coronary occlusion in our model, reasoning that such an effect would most likely be seen with the largest decrease in coronary pressure. We found a statistically significant difference in time course between the two methods of flow reduction, but the absolute magnitude of the effect was small (1–4 s; fig. 4). These results are similar to those obtained by Schultz and colleagues in a model of acute regional ischemia[29] and suggest that the primary origin of regional dysfunction in our model is ischemia and not vascular collapse.

The reason myocardial electrogram changes lag behind contractile dysfunction early in ischemia is unknown. In fact, the mechanism linking ischemia to ST-segment changes is only partially understood. ST-segment "elevation" actually results from depression of

the TQ baseline, an event linked to increased extracellular potassium ion concentration.[30] During early ischemia, the diffusion of inorganic phosphate and lactate across the cell membrane requires efflux of positively charged ions (predominantly potassium) to maintain electroneutrality.[31] It is tempting to speculate that increase in extracellular potassium ion concentration (and thus ST-segment change) is delayed because equilibration in the extracellular space is not instantaneous and washout of potassium ion and lactate occurs during partial (low-flow) ischemia.

One of the principal findings of the current study was that QRS amplitude decreased as the severity of ischemia increased, and that this event occurred more rapidly than did change in the ST segment. A previous study has demonstrated decreased action potential amplitude in ischemic myocardium.[32] Ischemia alters resting membrane potential (by potassium ion efflux) without altering the active-phase potential, which depends on sodium and calcium gradients and the conductance of these ions. Thus, a smaller change in potential occurs in each cell during activation. Ischemia also alters conduction velocity between cells,[33] leading to "smearing" of the aggregate potential derived from a group of cells. QRS amplitude also depends on the thickness of the ventricular wall near the electrode. Thinning, such as occurs during ischemia,[34] moves individual generators farther away from the electrode and results in a smaller compound action potential. This last mechanism probably accounts for the increased speed with which QRS amplitude changes after the onset of flow reduction. Thus, the amplitude of the complex is probably affected by a fast component (ventricular thinning caused by ischemia) and a slower component related to changes is resting membrane potential. In support of this notion, we found a direct relation between endocardial QRS amplitude and end-diastolic thickness (average $r = 0.81 \pm 0.08$ in eight animals) in the current study. Ours is not the first investigation of QRS complex changes with ischemia.[35] Bashour *et al.* noted a transient transformation of R waves into Q waves caused by reversible ischemia.[36] Ribiero *et al.* investigated the decrease in QRS amplitude of the epicardial electrogram with ischemia.[37]

Clinical Implications

Previous clinical studies have demonstrated that TEE ischemia occurs more frequently than ECG ischemia in patients with coronary artery disease undergoing anesthesia and surgery. For example, Haagmark *et al.* detected regional wall motion and abnormalities twice as frequently as ECG ischemia in their patients,[26] and Leung *et al.* found that 82% of such abnormalities after cardiopulmonary bypass during coronary artery bypass surgery were not accompanied by ECG changes.[2] These observations have led to the assertion that TEE monitoring provides the most sensitive and specific approach to intraoperative ischemia detection.[4,38] The current results do not entirely support this notion, however, because they demonstrate equal sensitivity for regional contraction and ECG parameters at steady state. Equal sensitivity to ischemia for these modalities implies that some episodes of "TEE ischemia" are not actually caused by ischemia.

The current study confirms the impression that ECG changes, particularly ST-segment changes, lag regional contraction abnormalities after the onset of ischemia. The results suggest that QRS amplitude decreases quickly, however, opening the possibility that the QRS complex may be a better criterion for ECG-based ischemia detection than the ST segment. We found that decreases in myocardial contraction were always accompanied by changes in QRS amplitude and ST segment at steady state. This finding contrasts with the often-quoted concept put forward by Battler and colleagues that regional contraction abnormalities can occur in the absence of ECG changes.[5]

Limitations

As with all laboratory studies, caution should be exercised when extrapolating these results to the clinical setting. We made special efforts to reduce confounding influences, such as altered hemodynamics, that may be present in the operating room and intensive care unit. In particular, acute increases in preload that result in changes in ventricular volume will likely decrease R wave amplitude[39] and could lead to a mistaken diagnosis of ischemia. Changes in body position that affect the distance from the heart to the recording electrode also will influence R-wave amplitude.[40] Of course, monitoring of regional wall motion as an indicator of myocardial ischemia is not without problems.[41] Regional contraction is known to be sensitive to changes in preload and afterload,[42] and stunning can produce wall motion abnormalities in the absence of ischemia. Although TEE permits continuous monitoring of regional wall motion during anesthesia, problems defining end systole and the correct reference point make computerized detection of regional abnormalities difficult.[43] Direct observation of echocardiographic im-

ages can provide an impression of regional contraction, but this approach is less accurate than experimental techniques such as crystal implantation, which allows precise measurement of regional dimensions. Valid samples of regional venous blood are even more difficult to obtain in the clinical setting than in a laboratory, and the time lag between sampling and analysis decreases the efficiency of myocardial metabolism as an on-line monitor for ischemia. Finally, changes in body position, ventilation, plasma ion concentration, and ventricular volume alter the ECG in ways that either accentuate or mask the changes caused by ischemia.

This study confirms a close correlation among mechanical, electric, and metabolic consequences of myocardial ischemia. Regional wall thickening, ST-segment elevation, and QRS amplitude changed in a linear fashion with decreases in coronary flow. When relative (rather than absolute) changes were considered, mechanical and electric measures were equally sensitive to ischemia. After an abrupt decrease in coronary flow, regional wall thickening declined to values correlated with myocardial lactate production more quickly than ST-segment changes. QRS amplitude changed before the ST segment, and therefore may be a better criterion for ECG-based detection of intraoperative ischemia.

The project could not have been done without the expert technical assistance of David Lentz, Marc Wallace, and Susan Dase. The authors thank Carolyn Cuba for expert secretarial assistance and Lisa Cohn for editorial comments.

References

1. Slogoff S, Keats AS: Does perioperative myocardial ischemia lead to postoperative myocardial infarction? ANESTHESIOLOGY 62:107–114, 1985

2. Leung JM, O'Kelly B, Browner WS, Tubau J, Hollenberg M, Mangano DT, the SPI Research Group: Prognostic importance of postbypass regional wall-motion abnormalities in patients undergoing coronary artery bypass graft surgery. ANESTHESIOLOGY 71:16–25, 1989

3. Mangano DT: Perioperative cardiac morbidity. ANESTHESIOLOGY 72:153–184, 1990

4. Smith JS, Cahalan MK, Benefiel DJ, Byrd BF, Lurz FW, Shapiro WA, Roizen MF, Bouchard A, Schiller NB: Intraoperative detection of myocardial ischemia in high-risk patients: Electrocardiography versus two-dimensional transesophageal echocardiography. Circulation 72:1015–1021, 1985

5. Battler A, Froelicher VF, Gallagher KP, Kemper WS, Ross JJ Jr: Dissociation between regional myocardial dysfunction and ECG changes during ischemia in the conscious dog. Circulation 62:735–744, 1980

6. Nesto RW, Kowalchuk GJ: The ischemic cascade: Temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 57:23C–30C, 1987

7. Sugishita Y, Koseki S, Matsuda M, Tamura T, Yamaguchi I, Ito I: Dissociation between regional myocardial dysfunction and ECG changes during myocardial ischemia induced by exercise in patients with angina pectoris. Am Heart J 106:1–8, 1983

8. Smith HJ, Kent KM, Epstein SE: Relationship between regional contractile function and S-T segment elevation after experimental coronary artery occlusion in the dog. Cardiovasc Res 12:444–448, 1978

9. Apstein CS, Gravino F, Hood WB Jr: Limitations of lactate production as an index of myocardial ischemia. Circulation 60:877–887, 1979

10. Waters DD, Da Luz P, Wyatt HL, Swan HJC, Forrester JS: Early changes in regional and global left ventricular function induced by graded reductions in regional coronary perfusion. Am J Cardiol 39: 537–543, 1977

11. Stowe DF, Mathey DG, Moores WY, Glantz SA, Townsend RM, Kabra P, Chatterjee K, Parmley WW, Tyberg JV: Segment stroke work and metabolism depend on coronary blood flow in the pig. Am J Physiol 234:H597–H607, 1978

12. Guth BD, Wisneski JA, Nesse RA, White FC, Heusch G, Mazer D, Gertz EW: Myocardial lactate release during ischemia in swine: Relation to regional blood flow. Circulation 81:1948–1958, 1990

13. Nicklas JM, Becker LC, Bulkley BH: Effects of repeated brief coronary occlusion on regional left ventricular function and dimension in dogs. Am J Cardiol 56:473–478, 1985

14. Schott RJ, Rohmann S, Braun ER, Schaper W: Ischemic preconditioning reduces infarct size in swine myocardium. Circ Res 66: 1133–1142, 1990

15. Blumgart HL, Zoll PM, Freedberg AS, Gilligan DR: The experimental production of intercoronary arterial anastomoses and their functional significance. Circulation 1:10–27, 1950

16. Fedor JM, McIntosh DM, Rembert JC, Greenfield JC Jr: Coronary and transmural myocardial blood flow responses in awake domestic pigs. Am J Physiol 235:H435–H444, 1978

17. Tennant R, Wiggers CJ: Effect of coronary occlusion of myocardial contraction. Am J Physiol 112:351–361, 1935

18. Barnes AR, Mann FC: Electrocardiographic changes following ligation of the coronary arteries of the dog. Am Heart J 7:477–497, 1931

19. Shea TM, Watson RM, Piotrowski SF, Dermksian G, Case RB: Anaerobic myocardial metabolism. Am J Physiol 203:463–469, 1962

20. Buffington CW, Feigl EO: Adrenergic coronary vasoconstriction in the presence of coronary stenosis in the dog. Circ Res 48:416–423, 1981

21. Gallagher KP, Matsuzaki M, Koziol JA, Kemper WC, Ross J Jr: Regional myocardial perfusion and wall thickening during ischemia in conscious dogs. Am J Physiol 247:H727–H738, 1984

22. Heusch G: The relationship between regional blood flow and contractile function in normal, ischemic and reperfused myocardium. Basic Res Cardiol 86:197–218, 1991

23. Case RB, Nasser MG, Crampton RS: Biochemical aspects of early myocardial ischemia. Am J Cardiol 24:766–775, 1969

24. Lekven J, Ilebekk A, Fonstelien, Kiil F: Relationship between ST-segment elevation and local tissue flow during myocardial ischaemia in dogs. Circ Res 9:627–633, 1975

25. Guyton RA, McClenathan JH, Newman GE, Michaelis LL: Significance of subendocardial S-T segment elevation caused by coronary stenosis in the dog. Am J Cardiol 40:373–379, 1977

26. Haggmark S, Hohner P, Ostman M, Friedman A, Diamond G, Lowenstein E, Reiz S: Comparison of hemodynamic, electrocardio-

graphic, mechanical, and metabolic indicators of intraoperative myocardial ischemia in vascular surgical patients with coronary artery disease. ANESTHESIOLOGY 70:19–25, 1989

27. Schwartz GG, Schaefer S, Meyerhoff DJ, Gober J, Fochler P, Massie B, Weiner MW: Dynamic relation between myocardial contractility and energy metabolism during and following brief coronary occlusion in the pig. Circ Res 67:490–500, 1990

28. Koretsune Y, Corretti MC, Kusuoka H, Marban E: Mechanism of early ischemic contractile failure: Inexcitability, metabolite accumulation, or vascular collapse? Circ Res 68:255–262, 1991

29. Schulz R, Guth BD, Heusch G: No effect of coronary perfusion on regional myocardial function within the autoregulatory range in pigs: Evidence against the Gregg Phenomenon. Circulation 83:1390–1403, 1991

30. Watanabe I, Johnson TA, Buchanan J, Engle CL, Gettes LS: Effect of graded coronary flow reduction on ionic, electrical, and mechanical indexes of ischemia in the pig. Circulation 76:1127–1134, 1987

31. Kleber AG: Resting membrane potential, extracellular potassium activity, and intracellular sodium activity during acute global ischemia in isolated perfused guinea pig hearts. Circ Res 52:442–450, 1983

32. Kimura S, Bassett AL, Kohya T, Kozlovskis PL, Myerburg RJ: Simultaneous recording of action potentials from endocardium and epicardium during ischemia in the isolated cat ventricle: Relation of temporal electrophysiologic heterogeneities to arrhythmias. Circulation 74:401–409, 1986

33. De Mello WC: Intercellular communication in cardiac muscle. Circ Res 51:1–9, 1982

34. Edwards CH II, Rankin JS, McHale PA, Ling D, Anderson RW: Effects of ischemia on left ventricular regional function in the conscious dog. Am J Physiol 240:H413–H420, 1981

35. London MJ: Monitoring for myocardial ischemia, Vascular Anesthesia. Edited by Kaplan TA. New York, Churchill Livingstone, 1991, pp 249–287

36. Bashour TT, Kabbani SS, Brewster HP, Wald SH, Hanna ES, Cheng TO: Transient Q waves and reversible cardiac failure during myocardial ischemia: Electrical and mechanical stunning of the heart. Am Heart J 106:780–783, 1983

37. Ribeiro LGT, Louie EK, Hillis LD, Davis MA, Maroko PR: Early augmentation of R wave voltage after coronary artery occlusion: A useful index of myocardial injury. J Electrocardiology 12:89–95, 1979

38. Gewertz BL, Kremser PC, Zarins CK, Smith JS, Ellis JE, Feinstein SB, Roizen MF: Transesophageal echocardiographic monitoring of myocardial ischemia during vascular surgery. J Vasc Surg 5:607–613, 1987

39. Lekven J, Chatterjee K, Tyberg JV, Parmley WW: Influence of left ventricular dimensions on endocardial and epicardial QRS amplitude and ST-segment elevations during acute myocardial ischemia. Circulation 61:679–689, 1980

40. Feldman T, Childers RW, Borow KM, Lang RM, Neumann A: Change in ventricular cavity size: Differential effects on QRS and T wave amplitude. Circulation 72:495–501, 1985

41. Lowenstein E, Haering JM, Douglas PS: Acute ventricular wall motion heterogeneity: A valuable but imperfect index of myocardial ischemia. ANESTHESIOLOGY 75:385–387, 1991

42. Buffington CW, Coyle RJ: Altered load dependence of postischemic myocardium. ANESTHESIOLOGY 75:464–474, 1991

43. Thys DM: The intraoperative assessment of regional myocardial performance: Is the cart before the horse? J Cardiothorac Anesth 1:273–275, 1987