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Electromechanical Association in Regionally Stunned Swine Myocardium

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Background: **Postischemic myocardial dysfunction ("stunned" myocardium) is a common problem after cardiac surgery and cardiac transplantation. A "low-voltage" QRS complex in the electrocardiogram is also often seen in patients with severe cardiac dysfunction. The authors investigated the relationship between mechanical function and electrographic characteristics in postischemic swine myocardium, and determined whether inotropic stimulation with dobutamine alters the electrogram while improving mechanical function.**

Methods: **Regional wall thickening and regional electrogram from electrodes in the endo- and epicardium were measured in 12 pigs during intravenous infusion of several doses of dobutamine (1–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) before and after 10 or 15 min of ischemia followed by 1 h of reperfusion.**

Results: **Wall thickening was abolished after ischemia and reperfusion, and QRS amplitude decreased 25% in the endocardium and 29% in the epicardium. Dobutamine infusion restored both wall thickening and myocardial QRS amplitude to baseline values. The correlation between myocardial QRS amplitude and systolic wall thickening was significant in each animal ($r = 0.88 \pm 0.02$ (mean ± 1 SEM, $n = 12$); median $r = 0.89$; range 0.74–0.95, $P < 0.01$, for all relations).**

Conclusions: **This study showed a close association between local electrical and mechanical events in postischemic swine myocardium. (Key words: Heart, ischemia: contractility; electrophysiology; left ventricular function. Pharmacology: dobutamine.)**

IMPAIRED myocardial contraction after ischemia is a common problem during cardiac surgery and cardiac transplantation. During reperfusion after nonlethal ischemia, coronary blood flow and ST-segment changes are restored to normal within several minutes, but myocardial dysfunction persists for hours or days.[1–4] This condition has been called "stunned" myocardium.[5] Several causes of myocardial stunning have been postulated, but the details are not yet clearly understood.[6–12]

In the clinical setting, a "low-voltage" QRS complex in the electrocardiogram is also often seen in severe heart failure. One study has reported serious defects in the generation and conduction of electrical signals in postischemic myocardium.[13] However, the relationship between mechanical function and electrophysiology has not been determined. The first goal of this study was to define the relationship between regional mechanical function and the local electrogram changes in postischemic myocardium. The second goal was to determine how inotropic stimulation with dobutamine alters mechanical and electrical function in postischemic myocardium.

Materials and Methods

General Preparation

The protocol was approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. Fifteen farm-bred pigs (20–25 kg) of either sex were given ketamine (10 mg/kg intramuscularly) and atropine (0.1 mg intramuscularly) and then anesthetized with halothane (0.5–2.5% end-tidal). After tracheal intubation with a cuffed endotracheal tube through a tracheostomy, the pigs' lungs were ventilated with a positive pressure respirator (Harvard ventilator, South Natrick, MA) with 5 cmH_2O positive end-expiratory pressure. The inspiratory gas composition consisted of oxygen and air. The partial pressure of oxygen in arterial blood (Pa_{O_2}) was kept at at least 200 mmHg by controlling the flow of oxygen. Tidal volume was fixed at 15 ml/kg, and respiratory rate was adjusted to

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keep the level of the partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) within the normal range (35–40 mmHg). Arterial blood was sampled for determination of Pa_{O_2}, Pa_{CO_2}, and *p*H (Radiometer, Copenhagen, NV, Denmark). Blood *p*H was kept within normal range by using a sodium bicarbonate solution. Arterial blood pressure was measured with a saline-filled transducer (Gould, Cleveland, OH) through a polyethylene catheter placed into the thoracic aorta *via* the right subclavian artery. Left ventricular (LV) pressure was measured with a Millar micromanometer catheter (Millar, Houston, TX) inserted through the right carotid artery. The heart was exposed *via* a median sternotomy and suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected free from the epicardium just distal to the first diagonal branch and encircled by a 2-0 silk tie with a red-rubber snare. Wires were sutured to the right atrium for pacing (Metronic 5880A; Medtronic, Minneapolis, MN) to keep the heart rate constant at approximately 175 beats/min. After instrumentation, the pericardium was left open but the sternum was loosely approximated. Halothane was discontinued after instrumentation, and anesthesia was maintained with morphine (3 mg/kg subcutaneously) and pentobarbital (25 mg/kg intravenously plus 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$ intravenously).

Dimension Measurements

Regional mechanical function was measured in the area supplied by the LAD with a pair of ultrasonic crystals (fig. 1) and a sonomicrometer (Triton model 120, 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 lensed crystal 2 to 3 mm in diameter was sewn to the epicardium at the location that minimized the distance between crystals. The pair of crystals measured wall thickness. A temporary (10–15 s) occlusion of the LAD, once the crystal pair was in place, confirmed that the set was located in the ischemic area.

The short axis of the LV was measured at the papillary muscle level, as a reflection of LV cavity size, with a second ultrasonic crystal pair (fig. 1). A wide-angle crystal was implanted into the middle of septum, and a lensed crystal 2 to 3 mm in diameter was sutured onto the LV free wall.

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

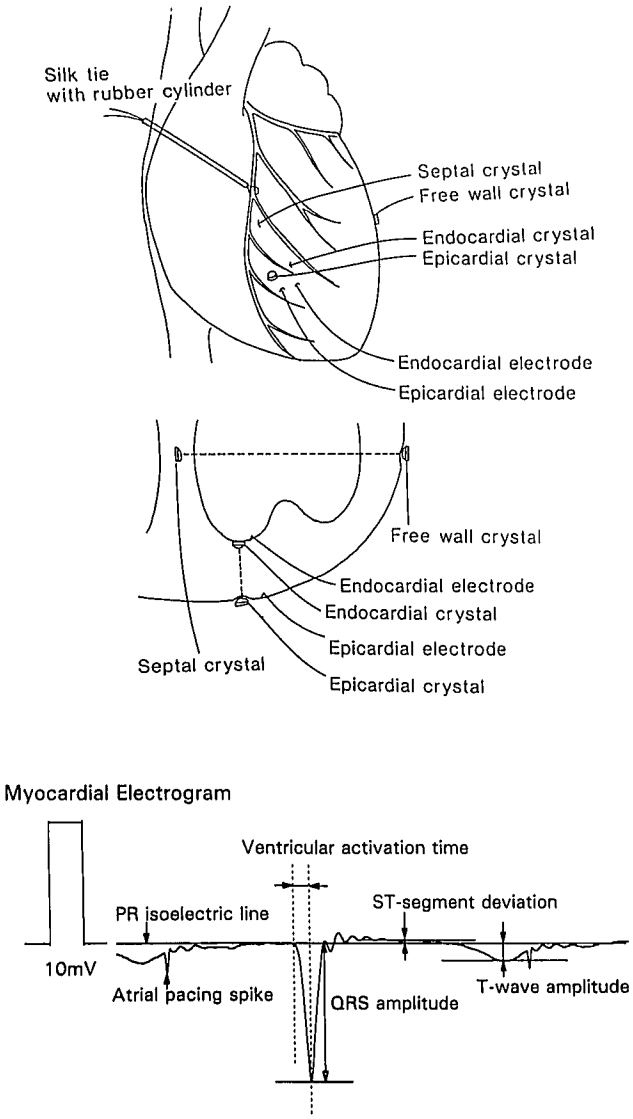

Fig. 1. Diagram of the experimental preparation; both a frontal and a cross-sectional view are shown. A pair of piezoelectric crystals was used to measure wall thickness in the myocardium supplied by the left anterior descending coronary (LAD) artery. A wide-angle crystal of the second pair of crystals was implanted into the middle of the septum, and a lensed crystal, 2 to 3 mm in diameter, was sutured to the left ventricular free wall for measurement of ventricular short axis. Teflon-coated stainless steel wires, bare only at the tip (approximately 2 mm), were inserted into both subendocardium and subepicardium to serve as intramyocardial electrodes. A section of the LAD measuring 2 cm in length distal to the first diagonal branch was dissected from the epicardium, and a silk suture allowed temporary coronary occlusion. Also shown is a representative myocardial electrogram recorded from an electrode located in the endocardium referenced to an electrode on the animal's back. Ventricular depolarization produces a downgoing deflection ("QRS"). See text for details about how specific measurements of the complex were made.

of the crystal sets was checked to be certain that the set was perpendicular to the epicardium. All crystals in the septum were located at the midpapillary muscle level.

Electrographic Measurements

Stainless steel wires (Teflon Medwire; Sigmund Cohn, Mount Vernon, NY), coated with Teflon except for the distal 2 mm, were inserted into both subendocardium and subepicardium to serve as intramyocardial electrodes (fig. 1). A hooked endocardial electrode was plunged through myocardium and into the LV cavity, then withdrawn until the hook engaged the muscle. Myocardial electrograms were recorded from endocardium and epicardium (Gould Universal Amplifier Model 13-4615-58, Cleveland, OH) with a reference electrode on the animal's back. The amplifier of the myocardial electrogram had a low-frequency cutoff of 0.1 Hz and upper-frequency cutoff of 3 kHz, and a notch filter at 60 Hz.

Experimental Protocol

Heart rate was controlled by atrial pacing during the experiment. Blood pressure was not controlled. After a baseline measurement, dobutamine was infused intravenously in doses of 1, 2.5, 5, 10, and 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 5 min. Once a steady state was reached at each dose, ventilation was stopped at the end of expiration, and all measurements were obtained. When hemodynamics had returned to baseline after the dobutamine infusion, lidocaine (1 mg/kg intravenously) was given, and acute regional myocardial ischemia was produced by complete occlusion of the LAD for either 10 or 15 min. Occlusion time was varied to produce a range of stunning. Then, reperfusion was allowed in a gradual manner over 1–2 min by slowly loosening the silk ligature. After 60 min of reperfusion, a second baseline measurement was obtained; each dose of dobutamine was infused again for 5 min, and measurements were made at each dose.

Myocardial Electrogram Versus *Surface ECG*

In five separate animals, myocardial electrodes and the coronary occluder were installed, and then the pericardium and chest were closed tightly. A pleural drainage tube was inserted into the pleural space to evacuate air. A baseline measurement was obtained, and myocardial electrograms and surface ECG were recorded for 90 s after complete coronary occlusion. The body-surface ECG was recorded from subcutaneous needle electrodes placed in the standard configuration. The surface ECG signal from the V_3 lead overlying the ischemic area was recorded. The amplifier used for the body-surface ECG had a lower cutoff frequency of 0.3 Hz and an upper-cutoff frequency of 50 Hz (Gould Isolated ECG Amplifier Model 13-4615-64A).

Data Collection and Analysis

Aortic pressure, LV pressure, LV short axis dimension, 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 LV ratio of change of ventricular pressure to change in time (dP/dt) was obtained with an analog circuit (Gould Differentiator Amplifier Model 13-4615-71). To allow accurate timing of the start and end of systole, a paper speed of 100 mm/min was used. The beginning of systole was taken as the time when LV dP/dt first left the baseline before peak-positive LV dP/dt. The end of systole was assumed to occur 25 ms before peak-negative LV dP/dt. The absolute change in wall thickness during systole was calculated as end-systolic wall thickness minus end-diastolic wall thickness. The absolute change in LV short axis length during systole was calculated as end-diastolic short axis length minus end-systolic short axis length.

The myocardial electrogram showed a complex that resembled surface electrocardiogram (ECG) lead V_3 (rS pattern). The amplitude of the first large wave was called the "myocardial QRS" wave, and its amplitude relative to baseline was determined (fig. 1). The elevation or depression of the ST-segment of the myocardial electrogram was measured relative to the PR isoelectric line 80 ms after the J-point of the surface ECG. T-wave amplitude was measured as the peak positive or negative wave after the ST-segment with the PR-segment as baseline. Ventricular activation time was measured as the interval between the beginning of the QRS complex and the peak deflection. These waves were measured and stored with a visual waveform editorial software (Wave Master II, Canopus).

Statistical Analysis

The distribution of each variable was examined by a plot of the cumulative frequency on the normal probability scale *versus* each variable on a linear scale, and was found to be reasonably normal.[14] Statistical significance for each dependent variable was calculated by

two-way ANOVA with time period (before and after stunning) and dobutamine as independent variables (SPSS/PC, Release 1.1, 1984). Linear regression techniques were used to test the relationship between variables. Because the relations between QRS amplitude and systolic thickening during dobutamine were similar in the 10- and 15-min occlusion animals, the data were pooled. The level of statistical significance was taken as $P < 0.05$. The data are presented as mean ± 1 SEM.

Results

Myocardial ischemia during LAD occlusion was confirmed by a prompt reduction in wall thickening and by ST-segment elevation in the surface ECG and myocardial electrogram. Three pigs died of ventricular fibrillation (VF) caused by myocardial ischemia. One pig was salvaged from VF by a single DC shock. Epicardial electrogram data from two animals were excluded from the statistical analysis, because of chronic pericarditis in one and because of a faulty electrical connection in the other. The final analysis was based on data from 12 pigs for endocardial electrogram, and from 10 pigs for epicardial electrogram.

Results from the ANOVA for each dependent variable are presented in table 1. Heart rate and systolic arterial pressure (table 2) were not affected by ischemia and reperfusion, or by dobutamine infusion, but diastolic arterial pressure was decreased slightly by ischemia and reperfusion ($P < 0.05$) and by dobutamine ($P < 0.05$). Left ventricular end-diastolic pressure decreased with dobutamine ($P < 0.05$), but was not changed by ischemia and reperfusion. Left ventricular dP/dt increased with dobutamine ($P < 0.001$), but decreased with ischemia and reperfusion ($P < 0.001$). End-diastolic short-axis dimension was not affected by ischemia and reperfusion, nor by dobutamine (table 3). The change during systole in short axis dimension decreased with ischemia and reperfusion ($P < 0.05$), and increased with dobutamine ($P < 0.001$). End-diastolic wall thickness was reduced by ischemia and reperfusion ($P < 0.001$), and increased by dobutamine ($P < 0.05$). The relationship between end-diastolic wall thickness and LV end-diastolic pressure (fig. 2) changed after ischemia and reperfusion ($P < 0.002$). Wall thickening during systole was abolished by ischemia and reperfusion ($P < 0.001$), but restored to preischemic baseline value by dobutamine infusion after ischemia and reperfusion (table 4).

Table 1. Analysis of Variance

	Significance	
	Ischemia and Reperfusion	Dobutamine
Hemodynamics (table 2)		
Heart rate	NS	NS
Systolic arterial blood pressure	NS	NS
Diastolic arterial blood pressure	<0.05	<0.05
Left ventricular end-diastolic pressure	NS	<0.05
Ratio of change of left ventricular pressure to change in time	<0.001	<0.001
Dimensions (tables 3 and 4)		
End-diastolic wall thickness	<0.001	<0.05
Absolute change of wall thickness	<0.001	<0.001
End-diastolic short-axis length	NS	NS
Absolute change of short-axis length	<0.05	<0.001
Endocardial electrogram (table 5)		
QRS amplitude	<0.001	<0.02
ST segment	<0.001	NS
T-wave amplitude	<0.01	NS
Ventricular activation time	<0.05	<0.05
Epicardial electrogram (table 6)		
QRS amplitude	<0.01	NS
ST segment deviation	<0.001	NS
T-wave amplitude	<0.05	NS

Significance was calculated by two-way analysis of variance.

Ischemia and reperfusion = changes caused by ischemia and reperfusion; dobutamine = the effects of inotropic stimulation.

None of the interaction terms was significant.

With ischemia and reperfusion, the QRS amplitude of the endocardial electrogram decreased (table 5), and ST-segment elevation actually resolved (decreased toward baseline). Endocardial QRS increased with dobutamine ($P < 0.02$). Similarly, epicardial QRS amplitude decreased, and ST-segment elevation resolved after ischemia and reperfusion (table 6). Dobutamine had no effect on epicardial QRS amplitude, ST-segment, or T-wave amplitude.

Ventricular activation time was prolonged after ischemia and reperfusion only in the endocardium ($P < 0.05$). With dobutamine infusion, ventricular activation time decreased to baseline values in the endocardium ($P < 0.05$).

Regression analysis between endocardial QRS amplitude and wall thickening during systole in individual pigs showed positive correlations in all pigs (r = 0.88 ± 0.02 (mean ± 1 SEM, n = 12); median r = 0.89; range 0.74–0.95, $P < 0.01$, for all relations; fig. 3).

Table 2. Hemodynamic Effects of Myocardial Stunning and Dobutamine

Hemodynamic Variable	Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					
	0.0	1.0	2.5	5.0	10.0	25.0
Preischemia						
HR (beats · min^{-1})	176.3 ± 0.8	176.2 ± 0.8	176.3 ± 0.8	176.2 ± 0.8	177.0 ± 1.4	178.5 ± 3.0
SBP (mmHg)	92.2 ± 4.3	91.0 ± 4.5	97.4 ± 4.2	101.3 ± 4.1	99.4 ± 4.1	100.3 ± 4.1
DBP (mmHg)	64.6 ± 4.3	64.5 ± 4.9	69.8 ± 4.7	71.3 ± 4.4	67.7 ± 4.5	59.0 ± 3.9
LVEDP (mmHg)	5.3 ± 0.6	5.5 ± 0.5	4.6 ± 0.7	4.6 ± 0.7	3.7 ± 0.8	4.3 ± 0.8
dP/dt (mmHg · s^{-1})	1,414 ± 144	1,452 ± 110	1,693 ± 88	2,339 ± 123	3,142 ± 172	4,801 ± 289
Postischemia						
HR (beats · min^{-1})	176.6 ± 0.8	175.9 ± 0.9	176.1 ± 0.8	176.1 ± 0.8	175.9 ± 2.1	182.8 ± 3.7
SBP (mmHg)	90.9 ± 3.5	93.0 ± 3.4	93.6 ± 3.0	97.5 ± 2.8	97.4 ± 3.2	99.7 ± 2.9
DBP (mmHg)	63.5 ± 3.6	65.1 ± 3.3	63.4 ± 3.2	63.6 ± 3.2	59.3 ± 3.7	51.5 ± 3.6
LVEDP (mmHg)	6.6 ± 0.8	5.7 ± 0.9	4.9 ± 0.8	4.5 ± 0.7	4.0 ± 0.7	3.7 ± 0.7
dP/dt (mmHg · s^{-1})	1,117 ± 59	1,202 ± 80	1,345 ± 83	1,788 ± 74	2,447 ± 108	4,088 ± 165

Data are presented as means ± SEM (n = 12).

HR = heart rate; SBP = systolic arterial blood pressure; DBP = diastolic arterial blood pressure; LVEDP = left ventricular end-diastolic pressure; dP/dt = the ratio of change of ventricular pressure to change in time.

See table 1 for statistical significance.

Regression analysis between epicardial QRS amplitude and wall thickening during systole in individual pigs also showed direct relations in all pigs (r = 0.84 ± 0.04 (mean ± 1 SEM, n = 10); median = 0.84; range 0.56–0.96; $P < 0.02$, for all other relations except VF case; fig. 4). The animal with VF during the coronary occlusion showed especially low QRS amplitude in the epicardium, in spite of the improvement of wall thickening by dobutamine. Linear regression for end-diastolic wall thickness (as opposed to "thickening") *versus* endocardial QRS amplitude in each pig showed direct relations in all pigs (r = 0.86 ± 0.04 (mean ± 1 SEM, n = 12); median r = 0.89; range 0.43–0.98, $P < 0.02$, for all relations except one).

The myocardial electrogram wave corresponded in time to the S-wave of V_3, the surface ECG. We compared the changes in amplitude of the respective waves after total coronary occlusion for 90 s (fig. 5). After coronary occlusion, the amplitude changes occurred simultaneously. The endocardial QRS amplitude correlated

Table 3. Left Ventricular Dimensional Effects of Myocardial Stunning and Dobutamine

Left Ventricular Short Axis	Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					
	0.0	1.0	2.5	5.0	10.0	25.0
Preischemia						
EDSA (mm)	42.6 ± 1.3	42.4 ± 1.3	42.4 ± 1.3	41.9 ± 1.3	41.3 ± 1.3	40.8 ± 1.3
ESSA (mm)	40.2 ± 1.3	39.8 ± 1.3	39.5 ± 1.3	38.5 ± 1.3	37.4 ± 1.4	36.2 ± 1.4
D-SA (mm)	2.4 ± 0.2	2.6 ± 0.2	2.9 ± 0.2	3.4 ± 0.3	3.8 ± 0.3	4.6 ± 0.4
Postischemia						
EDSA (mm)	43.9 ± 1.3	43.6 ± 1.3	43.1 ± 1.3	42.4 ± 1.3	41.9 ± 1.3	41.1 ± 1.4
ESSA (mm)	41.6 ± 1.2	41.3 ± 1.2	40.6 ± 1.2	39.5 ± 1.2	38.3 ± 1.3	36.7 ± 1.3
D-SA (mm)	2.3 ± 0.2	2.2 ± 0.2	2.5 ± 0.2	2.9 ± 0.2	3.6 ± 0.3	4.4 ± 0.3

Data are presented as means ± SEM (n = 12).

EDSA = end-diastolic short axis; ESSA = end-systolic short axis; D-SA = absolute short-axis shortening during systole.

See table 1 for statistical significance.

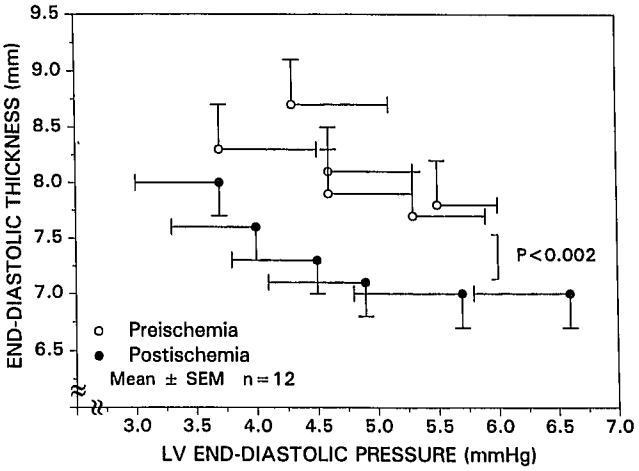

Fig. 2. Regional end-diastolic wall thickness decreased after infusion and reperfusion at each dose of dobutamine. This finding is consistent with previous studies showing local expansion of postischemic myocardium, a phenomenon known as creep. The points represent average data at each dose of dobutamine before and after ischemia and reperfusion.

significantly with both R- and S-wave amplitudes of the surface ECG (table 7), and the highest correlation was with the S-wave ($r = 0.98 \pm 0.01$ (mean ± 1 SEM, $n = 5$); median $r = 0.98$; range 0.95–0.99, $P < 0.0001$, for all relations). These data indicate a clear correspondence between the myocardial electrogram and the electrical events measured on the body surface.

Discussion

The data indicate a clear correlation between local electrical and mechanical forces in postischemic myocardium. In addition, intravenous dobutamine infusion increased both regional systolic contraction and the amplitude of the local electrogram.

Assumptions

The interpretation of these results depends, in large measure, on the correctness of the assumptions inherent in our experimental design. We assumed that postischemic myocardial dysfunction was caused by myocardial stunning, rather than continuing ischemia or infarction, and that this dysfunction remained constant during the experiment. After reperfusion, systolic wall thickening rapidly returned to normal, but then gradually declined over the next 30 min. The ST segment of the regional electrograms returned to baseline within several minutes. These dynamic events probably result, in part, from coronary hyperemia during early reperfusion.[15] According to experiments done in dogs, less than 20 min of coronary occlusion does not induce myocardial necrosis.[16,17] In our pig, we shortened the occlusion time to less than 15 min, because pigs have less collateral flow than dogs.[18] We did not confirm the absence of necrosis by histology, but we doubt that irreversible damage occurred, because dobutamine infusion increased postischemic contraction. We also infer that postischemic mechanical dysfunction was not caused by residual myocardial ischemia, because the ST-segment elevation that occurred during coronary occlusion rapidly improved after release of the coronary snare.

We assumed that regional wall thickening during systole was an accurate estimate of regional myocardial contractility. Wall thickening is determined by regional contractility, heart rate, preload, and afterload.[19] Heart

Table 4. Local Dimensional Effects of Myocardial Stunning and Dobutamine

Regional Wall Thickness	Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					
	0.0	1.0	2.5	5.0	10.0	25.0
Preischemia						
EDWT (mm)	7.7 ± 0.4	7.8 ± 0.4	7.9 ± 0.4	8.1 ± 0.4	8.3 ± 0.4	8.7 ± 0.4
ESWT (mm)	9.1 ± 0.5	9.2 ± 0.5	9.5 ± 0.5	10.2 ± 0.6	10.8 ± 0.6	11.6 ± 0.6
D-WT (mm)	1.3 ± 0.2	1.4 ± 0.2	1.6 ± 0.2	2.1 ± 0.3	2.5 ± 0.4	2.9 ± 0.4
Postischemia						
EDWT (mm)	7.0 ± 0.3	7.0 ± 0.3	7.1 ± 0.3	7.3 ± 0.3	7.6 ± 0.3	8.0 ± 0.3
ESWT (mm)	7.0 ± 0.3	7.2 ± 0.3	7.5 ± 0.4	8.1 ± 0.4	8.9 ± 0.4	10.2 ± 0.5
D-WT (mm)	0.1 ± 0.1	0.1 ± 0.1	0.4 ± 0.2	0.8 ± 0.2	1.3 ± 0.3	2.1 ± 0.3

Data are presented as means ± SEM (n = 12). Data have been rounded after averaging.

EDWT = end-diastolic wall thickness; ESWT = end-systolic wall thickness; D-WT = absolute wall thickening during systole.

See table 1 for statistical significance.

Table 5. Electrical Effects of Myocardial Stunning and Dobutamine

Endocardial Electrogram	Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					
	0.0	1.0	2.5	5.0	10.0	25.0
Preischemia						
QRS (mV)	12.0 ± 0.7	12.1 ± 0.7	12.1 ± 0.8	12.6 ± 0.8	13.0 ± 0.9	13.8 ± 0.9
ST (mV)	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.5 ± 0.2
TWA (mV)	−1.7 ± 0.5 (n = 10)	−1.8 ± 0.5 (n = 9)	−1.8 ± 0.5 (n = 10)	−1.6 ± 0.4 (n = 11)	−1.7 ± 0.5 (n = 11)	−2.1 ± 0.5 (n = 11)
VAT (ms)	13.2 ± 0.7	13.5 ± 0.7	12.8 ± 0.8	12.5 ± 0.8	12.0 ± 0.8	11.7 ± 0.8
Postischemia						
QRS (mV)	9.0 ± 0.8	9.0 ± 0.8	9.4 ± 0.8	10.0 ± 0.8	10.9 ± 0.8	12.2 ± 0.8
ST (mV)	0.6 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.2
TWA (mV)	0.5 ± 0.6 (n = 10)	0.3 ± 0.6 (n = 11)	0.0 ± 0.6	−0.6 ± 0.6	−1.0 ± 0.5	−2.0 ± 0.5
VAT (ms)	14.1 ± 0.5	14.3 ± 0.5	13.7 ± 0.6	13.2 ± 0.5	12.9 ± 0.5	12.3 ± 0.6

Data are presented as means ± SEM (n = 12). Data have been rounded after averaging.

QRS = QRS amplitude; ST = ST-segment deviation; TWA = T-wave amplitude; VAT = ventricular activation time.

See table 1 for statistical significance.

rate was controlled by atrial pacing, and changes in arterial blood pressure were small. Left ventricular end-diastolic pressure decreased with dobutamine, but this effect should have decreased regional contraction by a Frank-Starling mechanism, and cannot account for the increase in regional contraction that we observed with dobutamine.

We assumed that changes in the short axis dimension of the LV reflect changes in LV volume. Left ventricular volume may be underestimated by this measurement after ischemia, because the stunned area was affected by creep (local expansion).[20] The data indicate that neither ischemia and reperfusion nor dobutamine affected LV volume, as estimated by our short-axis measurement of LV cavity size. This finding is important, because ECG amplitude is affected by heart size. Other experiments have shown that the R-wave amplitude of the surface ECG increases with increasing ventricular volume.[21,22] We used a relatively high pacing rate to avoid increases in heart rate and resultant changes in end-diastolic LV volume with dobutamine infusion.

We used the voltage of the PQ interval as the baseline against which myocardial QRS amplitude was measured, because a slight ST-segment elevation was present before ischemia. The myocardial QRS amplitude measured at this period was, in fact, about 8% less than it would have been if the ST segments had been strictly isoelectric. These considerations do not change the conclusions of the study, however, because they indicate that our measurements actually underestimated the difference between control and postischemic myocardial QRS amplitude.

Interpretation

The results of the current study are of interest for two reasons. First, the covariance of electrical potentials and mechanical function postischemia indicates some common underlying defect in the myocardial cell that may provide insight into the mechanism of myocardial stunning. Although many mechanisms have been proposed, none is currently accepted by all investigators. Previous studies have demonstrated widespread, rather nonspecific damage after sublethal ischemia and uncontrolled reperfusion,[23] and it may be that a summation of small injuries, rather than one critical defect, is responsible for contractile dysfunction. The current results show that any proposed critical defect will need to explain electrical, as well as mechanical, stunning.

The second reason that the covariance of electrical and mechanical events is of interest is the possibility that ECG morphology could be used to predict ventricular function. A "low-voltage ECG" is often observed in patients with heart failure after cardiopulmonary bypass, and has been suggested as a predictor of survival in a recent clinical report.[24] The current results provide some grounding in fact for this observation, and extend the concept by showing that recovery of mechanical function during inotropic stimulation coincides with recovery of ECG amplitude.

Table 6. Electrical Effects of Myocardial Stunning and Dobutamine

Epicardial Electrogram	Dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$) 0.0	1.0	2.5	5.0	10.0	25.0
Preischemia						
QRS (mV)	13.6 ± 1.4	13.7 ± 1.5	13.7 ± 1.5	14.1 ± 1.5	14.7 ± 1.5	15.1 ± 1.6
ST (mV)	1.0 ± 0.2	1.1 ± 0.2	0.9 ± 0.3	0.7 ± 0.2	1.0 ± 0.2	1.2 ± 0.4
TWA (mV)	−1.2 ± 0.7 (n = 9)	−0.9 ± 0.7 (n = 7)	0.0 ± 0.8 (n = 9)	0.0 ± 1.0 (n = 9)	−0.8 ± 1.0 (n = 9)	−0.7 ± 1.0 (n = 9)
VAT (ms)	7.8 ± 1.9	7.2 ± 1.8	7.5 ± 1.9	7.2 ± 1.8	7.2 ± 1.8	7.2 ± 1.8
Postischemia						
QRS (mV)	10.1 ± 1.1	10.2 ± 1.2	10.4 ± 1.1	11.1 ± 1.2	11.9 ± 1.2	12.7 ± 1.3
ST (mV)	0.2 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	0.2 ± 0.2	0.5 ± 0.2	0.8 ± 0.1
TWA (mV)	1.9 ± 0.8	1.8 ± 0.7 (n = 9)	1.7 ± 0.9 (n = 9)	−0.7 ± 0.8	−0.1 ± 0.9	−1.4 ± 1.1 (n = 9)
VAT (ms)	7.3 ± 1.8	6.9 ± 1.6	6.7 ± 1.6	6.6 ± 1.5	6.5 ± 1.5	6.1 ± 1.4

Data are presented as means ± SEM (n = 10). Data have been rounded after averaging.

QRS = QRS amplitude; ST = ST-segment deviation; TWA = T-wave amplitude; VAT = ventricular activation time.

See table 1 for statistical significance.

Why should electrical and mechanical function be linked after ischemia? It is possible that the association is only a coincidence, and arises from the widespread damage to cellular components that occurs during sublethal ischemia and subsequent reperfusion. Other studies have demonstrated that a burst of free radicals occurs early after reoxygenation.[25] Previous studies have demonstrated functional defects in a number of enzyme systems and subcellular structures, including the cell membrane.[23] Thus, reduced electrical and mechanical activity could simply be concomitant phe-

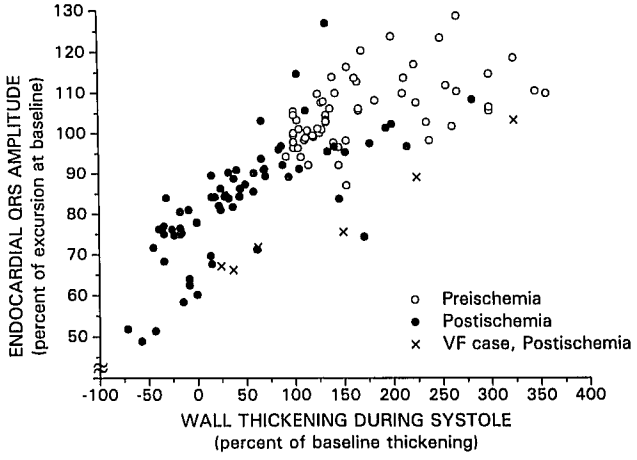

Fig. 3. These data demonstrate a significant direct correlation (r = 0.88 ± 0.02 (mean ± 1 SEM, n = 12); median r = 0.89; range 0.74–0.95 in individual pigs, $P < 0.01$ for all relations) between electrogram QRS amplitude measured in the subendocardium and regional systolic contraction. This finding supports the concept of electromechanical association in postischemic myocardium during inotropic stimulation. A single case in which a DC shock (20 mA) was used to rescue the animal from ventricular fibrillation (VF) is plotted separately (X).

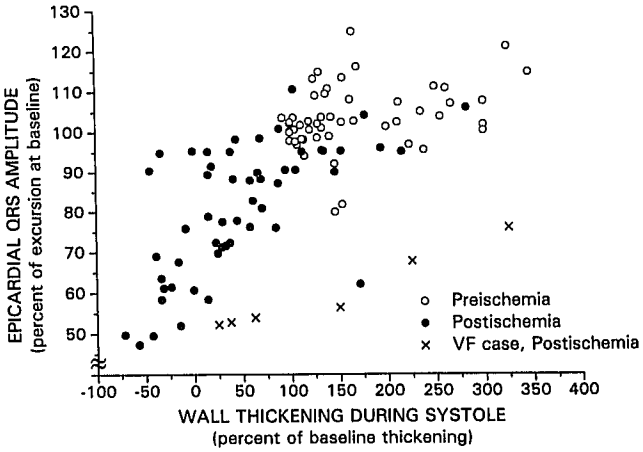

Fig. 4. The recovery of epicardial QRS amplitude was in proportion to the recovery of regional wall thickening with dobutamine after ischemia. The regression line between epicardial QRS amplitude and wall thickening showed a positive correlation, but the correlation coefficient, including the ventricular fibrillation (VF) case (r = 0.84 ± 0.04 (mean ± 1 SEM, n = 10); median r = 0.84; range 0.56–0.96; $P < 0.02$ for all relations except VF case), was lower than that for endocardial QRS amplitude and wall thickening. The VF case showed low electrical amplitude, despite recovery of wall thickening, a phenomenon that may indicate direct damage to the epicardium by the DC shock.

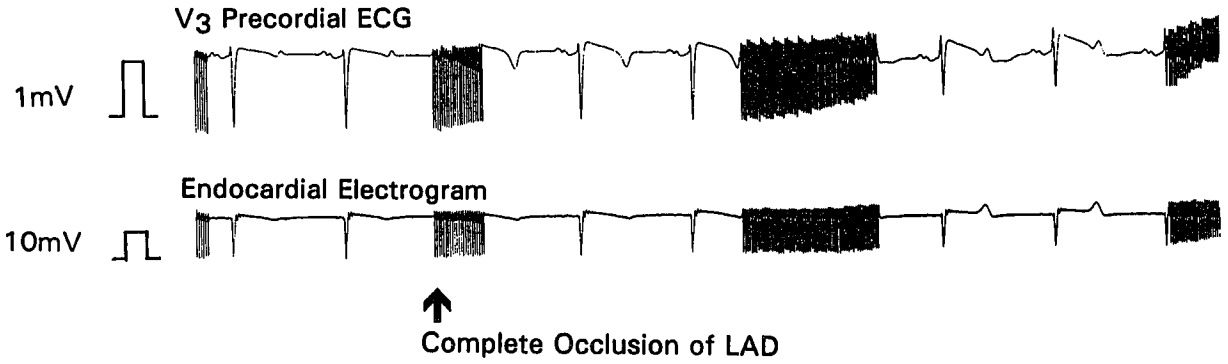

Fig. 5. In five separate closed-chest animals, the changes in myocardial QRS amplitude from an electrode located in the inner layer of myocardium perfused by the left anterior descending coronary artery (LAD) were compared with changes in a body-surface lead overlying the LAD (V_3). After abrupt occlusion of LAD in a representative animal, R-wave amplitude of V_3 increased as S-wave amplitude decreased. A simultaneous decrease in myocardial QRS amplitude occurred. The average correlation coefficient (r) for the beat-to-beat relationship between myocardial QRS and surface electrocardiogram ECG changes was 0.98 ± 0.01 (mean ± 1 SEM, n = 5). These data indicate that the local ECG changes observed in postischemic myocardium should also be observed in ECG complexes recorded from the body surface. (Paper speed: 100 mm/min and 100 mm/s)

nomena. Somewhat against this notion is the response to inotropic stimulation. Simultaneous improvement in both factors during inotropic stimulation implies some common denominator.

A prior study of the electrophysiology of postischemic myocardium provides some insight into the current results. Levine *et al.*[13] occluded the LAD in dogs for 10 min and allowed 20 min of reperfusion. After this, the hearts were rapidly excised and small sections of myocardium were placed in a tissue bath. Careful placement of microelectrodes into cells within the muscle strip allowed recording of monophasic action potentials. Compared with normal cells, the resting membrane potential of postischemic cells was increased (−61 *versus* −81 mV) and the action potential amplitude was reduced (64 *versus* 94 mV). Conduction velocity through the tissue, which was measured with a second electrode, was reduced from 0.78 m/s in normal tissue to 0.31 m/s in postischemic tissue. The efficiency of cell-to-cell electrical conduction was also measured in this preparation. A small electrical current that does not result in depolarization was injected into the tissue during diastole at one electrode, and the distance from this electrode, at which the signal had decreased to 1/e of its initial value, was determined. This distance, termed the "space constant," was 1.05 mm in normal tissue, but only 0.45 mm in postischemic tissue. These findings document serious defects in the generation and conduction of electrical signals within postischemic myocardium.

It seems reasonable that the 30% reduction in the action potential of individual cells noted by Levine *et al.*[13] may account for a portion of the reduction in myocardial QRS amplitude observed in this study. The action potentials are reduced largely because the resting membrane voltage is closer to zero, an effect that may be caused by impaired ion pumping by the sarcolemmal Na^+-K^+ pump. This pump is damaged by free

Table 7. Relationship Between Surface V_3 Electrocardiogram and Myocardial Electrogram

Pig Number	Endocardial QRS *versus* V_3 SWA			Endocardial QRS *versus* V_3 RWA		
	Slope	Intercept	r	Slope	Intercept	r
1	0.21	−1.81	0.98	−0.09	1.51	0.97
2	0.05	−0.45	0.99	−0.02	0.64	0.93
3	0.17	−0.60	0.95	−0.08	1.01	0.98
4	0.06	0.35	0.99	−0.03	0.63	0.99
5	0.12	−0.51	0.97	−0.03	0.62	0.90
Average	0.12	−0.60	0.98	−0.05	0.88	0.96
	Epicardial QRS *versus* V_3 SWA			Epicardial QRS *versus* V_3 RWA		
	Slope	Intercept	r	Slope	Intercept	r
1	0.19	−2.29	0.97	−0.08	1.72	0.97
3	0.20	−0.65	0.98	−0.08	1.00	0.96
4	0.12	−0.21	0.98	−0.07	0.95	0.95
5	0.12	−1.04	0.94	−0.03	0.76	0.87
Average	0.16	−1.05	0.97	−0.07	1.11	0.94

Linear regression analysis.

QRS = QRS amplitude; SWA = S-wave amplitude; RWA = R-wave amplitude

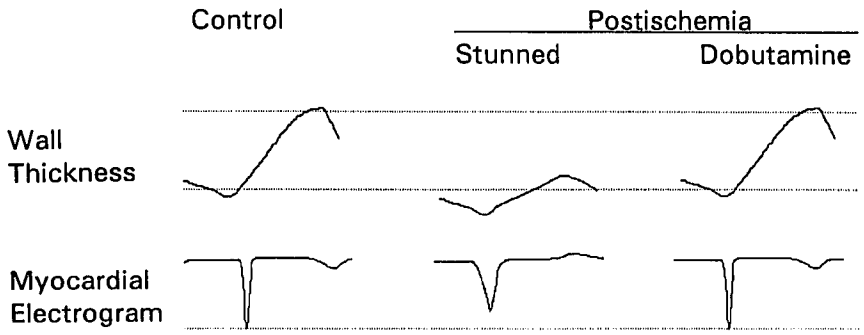

Fig. 6. Stylized drawing showing how the phenomenon of creep may underlie the association of electrical and mechanical events in postischemic myocardium. Stunning produces decreases in end-diastolic thickness (caused by creep) in addition to decreases in systolic thickening (upper trace). Dobutamine restores systolic thickening to control levels and simultaneously reverses creep. The regional myocardial electrogram shows reduced QRS amplitude in stunned myocardium (lower traces) because thinning of the ventricular wall moves the electrical generators in the tissue farther away from the recording electrode. QRS amplitude returns to baseline during dobutamine infusion as end-diastolic thickness increases. Impressive correlations between QRS amplitude and both systolic thickening and end-diastolic thickness were observed in the current study.

radicals in reperfused myocardium.[26] Under normal conditions, administration of a positive inotropic agent stimulates the sodium pump and results in hyperpolarization of the cell.[27] It is plausible that a similar effect in postischemic myocardium could make resting membrane potential more negative and restore the action potential. However, no experimental data concerning the effects of β-receptor stimulation on cell membrane potentials after ischemia are available to support this hypothesis.

Although it is convenient to think of the myocardial QRS amplitude as the summation of action potentials of individual cells, there are temporal components of this summation process that could have affected the myocardial QRS amplitude. For example, myocardial QRS amplitude will be higher if the myocardial cells surrounding the electrode depolarize simultaneously, and lower if depolarization is temporally dispersed. Such dispersion would lead to a "smearing" of the aggregate waveform, with longer duration and lower amplitude. In the current study, ventricular activation time, as reflected in the time necessary for the signal to reach the peak of the endocardial QRS wave, was prolonged in postischemic myocardium by about 7%, and recovered with dobutamine. This finding reflects slowed cell-to-cell conduction of electrical impulses, and is consistent with Levine's results.[13] Cell-to-cell conduction occurs through intercalated discs, and is sensitive to the level of intracellular ionized calcium. Increases in free calcium concentration above that necessary to produce contraction inhibit cell-to-cell conduction.[28] Thus, the calcium overload and increased diastolic calcium levels that occur in postischemic myocardium[29] probably account, in part, for altered conduction properties. Only careful measurements of intracellular calcium can resolve this mechanism.

A third possible link between electrical and mechanical events involves ventricular wall thickness. Thinning of the ventricular wall has been shown to reduce R-wave amplitude of surface ECG complexes in overlying areas, and an inverse relationship between end-diastolic ventricular volume and R-wave amplitude exists in patients with chamber enlargement.[30] In the current study, end-diastolic thickness was reduced by about 10% after ischemia and reperfusion, and restored to baseline levels during dobutamine infusion. End-diastolic thickness decreased with ischemia and reperfusion, in part, because of increased LV diastolic pressure, and, in part, because of a change in the material properties of the myocardium, termed "creep."[20] Data shown in figure 2 illustrate a thinning of the ventricular wall after ischemia and reperfusion caused by creep that becomes less manifest at low end-diastolic pressures during dobutamine infusion. The phenomenon of creep occurs in stunned myocardium, and a linear relationship between reduced systolic contraction and the degree of creep has been observed.[20] It is of interest that creep is reversed by dopamine infusion postischemia.[20]

We propose the following explanation (fig. 6) for our observations: stunned myocardium is characterized

by both reduced systolic thickening and local thinning. Wall thinning reduces local electrical amplitude because the electrical generators move farther from the recording electrode. With dobutamine, systolic contraction improves, diastolic thinning caused by creep decreases, and the local electrogram recovers. An impressive correlation exists in the current data between end-diastolic wall thickness and myocardial QRS amplitude. Thus, the results demonstrate good correlations between endocardial QRS amplitude and both systolic contraction and end-diastolic thickness. These correlations indicate that wall thickness is the intervening variable that mechanistically explains electromechanical association in stunned myocardium.

These concepts appear to be at variance with published reports that the R wave of the surface ECG increases with increasing LV volume (hence decreasing wall thickness).[31] In fact, dilation of the heart reduces the QRS amplitude, as shown in a study of patients undergoing coronary angiography.[30] The original observation can be explained by the fact that radial expansion of the heart during increases in LV volume actually moves the heart closer to the chest wall, and provides a stronger electrical signal for the overlying electrode.[32]

We made both 10- and 15-min coronary occlusions to investigate the effect of occlusion time on myocardial QRS amplitude. The longer occlusion produced more profound effects on both myocardial QRS amplitude and contraction (fig. 7). Epicardial QRS amplitude seemed to be spared, relative to endocardial QRS amplitude, after 10-min occlusion, but was reduced significantly after 15-min occlusion, indicating that the process of myocardial stunning had propagated to the epicardium with the longer period of ischemia.

Limitations

These concepts should be applied in the clinical setting with caution. Although ECG morphology may estimate ventricular function after cardiopulmonary bypass or angioplasty, a number of factors complicate the analysis, and will probably reduce the sensitivity and specificity of the technique. For example, R-wave amplitude of surface ECG leads is influenced by the proximity of the heart to the chest wall, the nature of the conductor between the heart and the electrode, the electrical axis of depolarization, and the size of the heart.

The heart rate used in these studies (175 beats/min) exceeds the values usually encountered in anesthetized

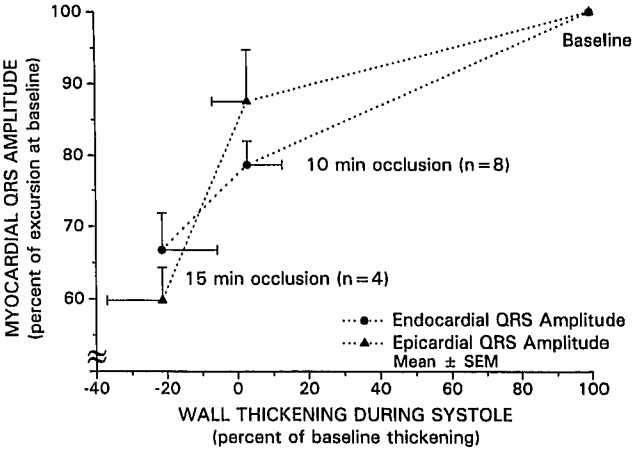

Fig. 7. Effects of 10- and 15-min occlusion time on myocardial QRS amplitude and wall thickening measurements were made after 1 hour of reperfusion in the absence of dobutamine. A graded response in both variables to increased ischemia is evident.

patients. Whether or not the relations we have demonstrated hold at lower heart rates remains to be determined. Further study is also required to determine whether recovery of electrical amplitude follows the same time course as the natural recovery from stunning in the hours and days after ischemic insult.

One pig had VF during ischemia. The animal was salvaged with a single DC shock of 20 mA *via* internal paddles. The epicardial QRS amplitude was much lower than in the other animals after ischemia (fig. 4). This observation indicates that defibrillation may injure the epicardium and alter the relationship between electrical and mechanical forces. If confirmed, this effect would limit the clinical application of these concepts, because defibrillation is commonly used after removal of the aortic cross clamp to restore sinus rhythm.

In conclusion, the impetus for this study was the clinical observation that poor contractile performance of the heart is often associated with reduced R-wave amplitude ("low-voltage ECG"). The study confirmed this clinical impression in a well controlled experimental model: reduced electrical potentials accompany impaired regional contraction after ischemia and reperfusion. The study extends our understanding of this phenomenon by demonstrating that electrical potentials and contractile force improve, hand in hand, during inotropic stimulation of postischemic myocardium. The current study indicates, but does not prove, that the connection between electrical and mechanical

events is thinning of stunned myocardium caused by creep. Electromechanical association occurs in post-ischemic myocardium.

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