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EXPERIMENTAL STUDIES

Myocardial Dysfunction After Resuscitation From Cardiac Arrest: An Example of Global Myocardial Stunning

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Objectives. **This study investigated the effect of prolonged cardiac arrest and subsequent cardiopulmonary resuscitation on left ventricular systolic and diastolic function.**

Background. **Cardiac arrest from ventricular fibrillation results in cessation of forward blood flow, including myocardial blood flow. During cardiopulmonary resuscitation, myocardial blood flow remains suboptimal. Once the heart is defibrillated and successful resuscitation achieved, reversible myocardial dysfunction, or "stunning," may occur. The magnitude and time course of myocardial stunning from cardiac arrest is unknown.**

Methods. **Twenty-eight domestic swine (26 ± 1 kg) were studied with both invasive and noninvasive measurements of ventricular function before and after 10 or 15 min of untreated cardiac arrest. Contrast left ventriculograms, ventricular pressures, cardiac output, isovolumetric relaxation time (tau) and transthoracic Doppler-echocardiographic studies were obtained.**

Results. **Twenty-three of 28 animals were successfully resuscitated and postresuscitation data obtained. Left ventricular ejection fraction showed a significant reduction 30 min after resuscitation ($p < 0.05$). Regional wall motion analysis revealed diffuse, global left ventricular systolic dysfunction. Left ventricular end-diastolic pressure increased significantly in the postresuscitation period ($p < 0.05$). Isovolumetric relaxation time (tau) was significantly increased over baseline by 2 h after resuscitation ($p < 0.05$). Similar findings were noted with the Doppler-echocardiographic analysis, including a reduction in fractional shortening ($p < 0.05$), a reduction in mitral valve deceleration time ($p < 0.05$) and an increase in left ventricular isovolumetric relaxation time at 2 h after resuscitation ($p < 0.05$). By 24 h, these invasive and noninvasive variables of systolic and diastolic left ventricular function had begun to improve. At 48 h, all measures of left ventricular function had returned to baseline levels.**

Conclusions. **Myocardial systolic and diastolic dysfunction is severe after 10 to 15 min of untreated cardiac arrest and successful resuscitation. Full recovery of this postresuscitation myocardial stunning is seen by 48 h in this experimental model of ventricular fibrillation cardiac arrest.**

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Cardiac arrest remains a major cause of morbidity and early mortality in the United States today. Successful treatment of cardiac arrest includes the rapid initiation of basic life support measures, including cardiopulmonary resuscitation (CPR). Immediate institution of such efforts can result in resuscitation rates as high as 30% to 40% (1). Unfortunately, >50% of all patients initially resuscitated will subsequently die before leaving the hospital (2–4). The vast majority of such deaths are secondary to either central nervous system or myocardial failure (5). There has been substantial work investigating the treatment or prevention of cerebral damage associated with cardiac arrest and CPR (6–10), but minimal data are available concerning the effect of cardiac arrest and resuscitation on subsequent myocardial function.

A cardiovascular postresuscitation syndrome has been described (11) in which cardiac filling pressures, including both central venous and pulmonary artery occlusive pressures, temporarily increase after resuscitation. Cardiac index declines after cardiac arrest and resuscitation, with its recovery dependent on the period of untreated cardiac arrest (11). In a study using an isolated heart preparation, both systolic and diastolic myocardial dysfunction were observed during the first 20 min after successful cardiac resuscitation (12).

The aim of the present study was to define the nature, extent and duration of postresuscitation myocardial dysfunction in an in vivo porcine model of ventricular fibrillation cardiac arrest.

Methods

All animal experiments conformed to the "Position of the American Heart Association on Research Animal Use" adopted by the Association in November 198- and with the approval of the University of Arizona Institutional Animal Care and Use Committee.

Animal preparation. Twenty-eight male and female domestic swine (26 ± 1 kg) were anesthetized with isoflurane in oxygen using an adapted face/snout mask. An endotracheal

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catheter was placed through the oropharynx, and anesthesia was maintained with isoflurane, delivered with a volume-limited and rate-cycled ventilator (Harvard Instruments) to maintain the end-expiratory partial pressure of carbon dioxide (Pco_2) between 35 and 45 mm Hg. Muscle fasciculations were eliminated with intravenous Metocurine (1 mg/h). Electrocardiographic (ECG) leads were placed, and vascular access was obtained by placement of 8F vascular sheaths in the bilateral carotid arteries and external jugular veins. A 7F solid-state micromanometer pigtail catheter containing a central lumen for injection (Millar Instruments) was placed in the left ventricle through the right carotid access. An 8F pulmonary artery balloon catheter (Edwards) was inserted through the right external jugular vein and advanced to the right pulmonary artery. Through the left external jugular vein, a 5F solid-state micromanometer pressure transducer catheter (Millar) was inserted into the right atrium for pressure monitoring. A similar catheter was inserted into the ascending aorta through the left carotid artery for monitoring aortic pressure. End-tidal carbon dioxide concentration was monitored using a capnometer system (Hewlett-Packard, model 47210A) attached to the external end of the endotracheal tube.

Left ventricular systolic variables. Systolic function of the left ventricular myocardium was evaluated, using both invasive and noninvasive techniques. Single-plane ventricular contours were obtained at a 45° right anterior oblique projection, using 12 ml of contrast medium (Omnipaque, Sanofi Winthrop Pharmaceuticals) injected through the left ventricular Millar pigtail catheter over 3 s. These ventricular silhouettes were recorded on tape for subsequent analyses and digitized in end-systole and end-diastole. Left ventricular ejection fraction and volumes were calculated using standard techniques (13). A Vanguard XR-55 LV analyzer was used to quantitate regional wall motion according to the centerline radial cord technique of Sheehan et al. (14). Left ventricular pressures, as well as positive and negative dP/dt, were recorded with micromanometer pressure tranducer catheters and a Gould four-channel physiologic recorder (Gould Inc.). A fluid-filled pulmonary artery balloon catheter was placed for determination of pulmonary artery pressures, including pulmonary artery occlusive pressures and cardiac outputs, by thermodilution. Transthoracic Doppler-echocardiographic examinations (Interspec, model XL) were performed for measuring fractional shortening as well as global and segmental wall motion abnormalities.

Left ventricular diastolic variables. Diastolic function was measured with both invasive and noninvasive techniques. Isovolumetric relaxation time was measured with a unique computer-enhanced process, as previously described (15). Briefly, left ventricular pressure data were measured continually with a solid-state micromanometer pressure transducer catheter. These data were transferred using an analog/digital converter at 1,000 Hz directly in the memory of an IBM AT personal computer. After screening and eliminating any premature beats, the left ventricular pressure waveforms were digitized and averaged over 20 to 50 complete cardiac cycles. Using these composite data, left ventricular dP/dt (positive and negative) and end-diastolic pressure were calculated. Isovolumetric relaxation time (tau) was determined as the time (in ms) during isovolumetric relaxation required for the left ventricular pressure to decline from the point of maximal negative left ventricular dP/dt to the pressure point equal to the end-diastolic pressure. This portion of the left ventricular pressure curve was fitted to an exponential equation. $P = P_o e^{-At}$ (where P_o = pressure at dP/dt min), such that when the natural logarithm of the pressure was plotted against time, the resulting curve was linear with slope A. Transthoracic Doppler-echocardiography was also used to assess left ventricular diastolic function by measuring mitral valve deceleration time and left ventricular isovolumetric relaxation times.

Echocardiographic variables. Echocardiographic data were obtained at baseline and at 5 and 24 or 48 h. M-mode tracings, acquired from the parasternal long-axis plane, were used to measure systolic and diastolic left ventricular chamber diameter and posterior wall and interventricular septal thickness. Pulsed wave Doppler echocardiography was used to obtain isovolumetric relaxation and deceleration times from a sample volume located at the tips of the mitral leaflets. Deceleration time was determined as the interval from peak mitral velocity to extrapolated or actual baseline crossing. Isovolumetric relaxation time was identified as the interval between closure of the aortic valve and opening of the mitral valve. Aortic leaflet motion could be recorded simultaneously with the mitral velocity. Measurements were obtained at a video sweep speed of 100 mm/s, using electronic calipers, with a time resolution of 10 ms. The mean of three measurements from the same video screen was reported for both isovolumetric relaxation and deceleration times. An ECG tracing was recorded simultaneously with the echocardiogram.

Experimental protocol. Since all volatile anesthetic agents suppress myocardial function, efforts were made to maintain the concentration of inhaled isoflurane at the minimum required for adequate anesthesia. Ventricular fibrillation was electrically induced by pacing the right ventricle at rates of 400 to 600 beats/min and confirmed by the ECG and loss of the aortic pressure pulsations. Anesthesia and ventilation were discontinued during the arrest period.

Cardiopulmonary resuscitation efforts were begun after 15 min (n = 10) or 10 min (n = 18) of untreated ventricular fibrillation. Twenty-three of 28 swine were successfully resuscitated and survived >1 h. All data analysis is based on these 23 animals. Resuscitation efforts included standard American Heart Association Basic Life Support, consisting of external chest compressions and positive pressure ventilations (16). Sternal chest compressions were manually performed at 100/min, using a 50% compression cycle and a 2- to 3-in. (5 to 7.5 cm) compression depth. Ventilation was volume controlled (15 to 18 ml/kg), using a Harvard volume-limited ventilator delivering 15 breaths/min. Epinephrine was given as a 1-mg intravenous bolus 1 min after initiation of CPR. After 3 min of CPR, external defibrillation was attempted with 5 or 6 J/kg. Additional defibrillation shocks were delivered, if needed,

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following the American Heart Association Guidelines for Advanced Cardiac Life Support (17).

Successful defibrillation and resuscitation were defined as a perfusing rhythm, resulting in an aortic systolic blood pressure >50 mm Hg for ≥1 min. During the immediate postdefibrillation stage, dopamine, lidocaine or atropine were used according to the Advanced Cardiac Life Support Guidelines, if necessary (17). All such drugs were terminated before the collection of the 30-min data in the four swine that needed such immediate postresuscitation support. When the animals stabilized, isoflurane was titrated, as necessary, to maintain adequate analgesia and anesthesia. Animals remained instrumented for measurements of systolic and diastolic function until ~6 h after induced cardiac arrest. Left ventricular function data were acquired at 30 min and 2 and 5 h after resuscitation. All catheters were then removed, and the animals were weaned from anesthesia and ventilation, placed in a postoperative observation facility and given intramuscular Butorphanol (Aveco Co.) for discomfort as needed. Twenty-four or 48 h after resuscitation, surviving animals were reanesthetized and reinstrumented for collection of similar systolic and diastolic left ventricular function data. Complete echocardiographic examinations were performed in 14 swine, all of which had 10 min of untreated ventricular fibrillation before resuscitation. Studies were completed at baseline, 5 h and at either 24 h (n = 9) or 48 h (n = 5). After final data collection was complete, the animals were euthanized by intravenous solution (Beuthansia-D, Schering-Plough). Necropsy studies were performed by a veterinarian.

Four additional animals were studied post hoc to further elucidate the mechanism of postresuscitation myocardial stunning. Two swine underwent the same experimental protocol with 10 min of untreated ventricular fibrillation before successful resuscitation. Each had myocardial blood flow measured using nonradioactive colored microspheres and standard microsphere techniques, as previously done in our laboratory (18–20). Nonradioactive colored microspheres measuring 12 ± 4 μm (Interactive Medical Technology, Ltd.) were injected into the left ventricle over 15 s as a bolus containing ~5 million spheres. Reference blood samples were withdrawn at 5 ml/min for 155 s, commencing 5 s before each microsphere injection. At the completion of the study, each subject was killed, and tissue samples were collected from the anterior, lateral and inferior walls of the myocardium. Myocardial wall samples were surgically divided into halves, the outer 50% designated as the epicardium and the inner 50% representing the endocardium. Using sequential collagenase and sodium hydroxide digestion, the spheres were extracted from the reference (blood) and organ of interest (myocardium) samples. Extracted spheres were then counted by color using a hemocytometer. When the number of tissue microspheres and the number of reference microspheres are known, regional blood flow can be calculated using a standard formula, whereby the tissue sample blood flow (ml/min) divided by the number of microspheres in the tissue sample equals the reference blood flow (5 ml/min) divided by the number of microspheres in the reference blood sample.

An additional two swine were studied after high energy shocks were administered without inducing ventricular fibrillation cardiac arrest. These animals were then examined for evidence of similar systolic or diastolic abnormalities due to the shocks alone. The two animals were given ~20% more joules than the highest amount received by any previous animal. These animals received five shocks for a total of 886 J. Systolic and diastolic ventricular function were studied exactly as previously reported.

Data analysis. Left ventricular measurements of systolic and diastolic function were performed at five time intervals: baseline, 30 min, 2 h, 5 h and 24 or 48 h after resuscitation. Three distinct subgroups were studied: 1) group A = 15 min of untreated cardiac arrest before resuscitation (n = 8); 2) group B = 10 min of untreated ventricular fibrillation before resuscitation and restudy at 24 h (n = 10); 3) Group C = 10 min of untreated ventricular fibrillation before resuscitation and restudy at 48 h (n = 5). No animal was studied at both 24 and 48 h secondary to vascular access limitations. Repeated measures analysis of variance was used to compare the mean values of all left ventricular function variables within each group over time from a prearrest baseline and at 30 min, 2 h and 5 h after resuscitation and, when available, at 24 or 48 h after resuscitation. A Newman-Keuls multiple comparisons procedure was performed to further identify specific differences between the different time intervals. A significant difference was assumed when a p value ≤0.05 was reached.

Some comparisons were made between two subgroups: animals undergoing 15 min of untreated cardiac arrest versus those undergoing 10 min of untreated ventricular fibrillation before resuscitation. Such analyses utilized a Student *t* test for unpaired values. A similar limit of $p < 0.05$ was utilized to identify statistically significant differences.

Echocardiographic data were obtained only for animals undergoing 10 min of untreated cardiac arrest and at only three intervals: baseline, 5 h and either 24 h (n = 9) or 48 h (n = 5). Therefore, 24- and 48-h data were combined, and a repeated measures analysis of variance was performed to assess changes in left ventricular echocardiographic variables over time. Again, a Newman-Keuls multiple comparisons test was utilized to identify specific differences among the three time intervals.

All data analysis was performed utilizing the commercially available software program, TRUE EPISTAT, 5.2 edition. All results are mean value ± SE.

Results

Outcome data. The initial study group received 15 min of untreated ventricular fibrillation before any attempt at resuscitation. Initial return of spontaneous circulation was achieved in 8 of 10 swine, however, no animal survived 24 h. Therefore, the period of untreated ventricular fibrillation was shortened to 10 min. After this period of cardiac arrest, 16 of 17 animals

Table 1. Comparison of Duration of Cardiac Arrest

	Ventricular Fibrillation		
	15 min (mean ± SE)	10 min (mean ± SE)	p Value
CPP (mm Hg)			
1 min of CPR	41 ± 6	45 ± 5	0.7
3 min of CPR	38 ± 4	44 ± 9	0.6
EF (%) at 5 h post-CPR	25 ± 3	32 ± 2	< 0.05
PA at 30 min post-CPR	24 ± 3	15 ± 2	< 0.05
PAOP at 30 min post-CPR	8 ± 10	4 ± 1	< 0.05

CPP = coronary perfusion pressure during cardiopulmonary resuscitation (CPR); EF = Left ventricular ejection fraction; PA = mean pulmonary artery pressure; PAOP = mean pulmonary artery occlusive pressure.

were successfully resuscitated, 15 of 16 survived for 24 h. Ten of these 24-h survivors were euthanized as per protocol; however, the final five were observed for another 24 h. All five animals survived the full 48 h.

There were no differences in coronary perfusion pressures during cardiopulmonary resuscitation between the 15- and 10-min ventricular fibrillation groups to explain the difference in outcome (Table 1). However, several variables of left ventricular function indicated that 15 min of untreated cardiac arrest produced significantly more left ventricular dysfunction than did 10 min of untreated cardiac arrest. Left ventricular ejection fraction was significantly lower 5 h after resuscitation in the swine undergoing 15 min of untreated ventricular fibrillation than in those undergoing only 10 min (Table 1). Decreased ventricular function was also indicated by increases in pulmonary artery pressures and pulmonary artery occlusive pressures at 30 min after resuscitation in the animals undergoing the 15 min of ventricular fibrillation (Table 1).

Surviving animals underwent complete necropsy by a board-certified veterinarian (R.W.H.). Utilizing a previously published trauma score (21), attention was paid to CPR-produced injury and trauma. Seven of the 16 animals undergoing necropsy studies had some degree of mild cardiac contusion; however, none of these contusions was large or transmural. Typically, they were seen over the anterior portion of the right ventricle. The most common injury was pulmonary atatelectasis, with 12 (75%) of 16 animals having some degree of such injury. The next most common was rib fracture; 9 (56%) of 16 animals had at least two rib fractures or more. A mean trauma score of 6.6 ± 0.7 was found for the 16 animals (21). Three animals were studied post hoc to examine whether myocardial infarction resulted from the lengthy period of untreated ventricular fibrillation before successful resuscitation. Each of these animals received 15 min of untreated ventricular fibrillation cardiac arrest. At 24 h, the animals were euthanized, and their myocardium was stained with triphenyl tetrazolium chloride (TTC), according to standard methodology previously utilized in our laboratory (22). No evidence of myocardial infarction was seen; rather, each sample of left ventricular myocardium exhibited consistent beefy red staining indicative of viable myocardium.

Angiographic data. No differences in left ventricular ejection fraction were seen among the three different subgroups at baseline. However, left ventricular ejection fraction decreased significantly by the 30-min postresuscitation time period in each group and continued to be significantly depressed for the

Table 2. Left Ventricular Angiographic Data Before and After Cardiac Arrest (mean ± SE)

	Baseline	30 min	2 h	5 h	24 h	48 h
LVEF (%)						
Group A	58 ± 3	—	33 ± 3*	25 ± 3*	—	—
Group B	55 ± 2	30 ± 3*†	30 ± 2*†	33 ± 2*†	42 ± 2*	—
Group C	54 ± 2	26 ± 3*‡	27 ± 3*‡	30 ± 4*‡	—	54 ± 3
PSP/ESV						
Group A	11 ± 2	8 ± 2*	7 ± 2*	6 ± 1*	—	—
Group B	7 ± 1	5 ± 1*	5 ± 1*	5 ± 1*	5 ± 1*	—
Group C	7 ± 1	5 ± 1*‡	5 ± 0*‡	5 ± 1*‡	—	10 ± 1*
EDV (ml)						
Group A	28 ± 6	30 ± 6	30 ± 7	28 ± 5	—	—
Group B	34 ± 4	35 ± 6	34 ± 4	37 ± 5	35 ± 4	—
Group C	31 ± 5	32 ± 5	29 ± 2	32 ± 5	—	31 ± 6
ESV (ml)						
Group A	12 ± 3	20 ± 4*	22 ± 5*	21 ± 3*	—	—
Group B	15 ± 2	26 ± 5*	27 ± 4*	25 ± 3*	19 ± 2	—
Group C	15 ± 2	24 ± 4*‡	22 ± 2*‡	22 ± 3*‡	—	13 ± 3
SV (ml)						
Group A	17 ± 3	10 ± 3*	9 ± 2*	7 ± 2*	—	—
Group B	18 ± 2	9 ± 2*†	10 ± 1*†	12 ± 2*†	16 ± 2	—
Group C	17 ± 3	9 ± 2*‡	7 ± 1*‡	10 ± 2*‡	—	18 ± 4

*$p < 0.05$ versus baseline. †$p < 0.05$ versus 24 h. ‡$p < 0.05$ versus 48 h. EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; Group A = 15 min of untreated ventricular fibrillation; Group B = 10 min of untreated ventricular fibrillation/24-h data; Group C = 10 min of untreated ventricular fibrillation/48-h data; PSP/ESV = peak systolic pressure/end-systolic volume ratio; SV = stroke volume; — = ventricular fibrillation.

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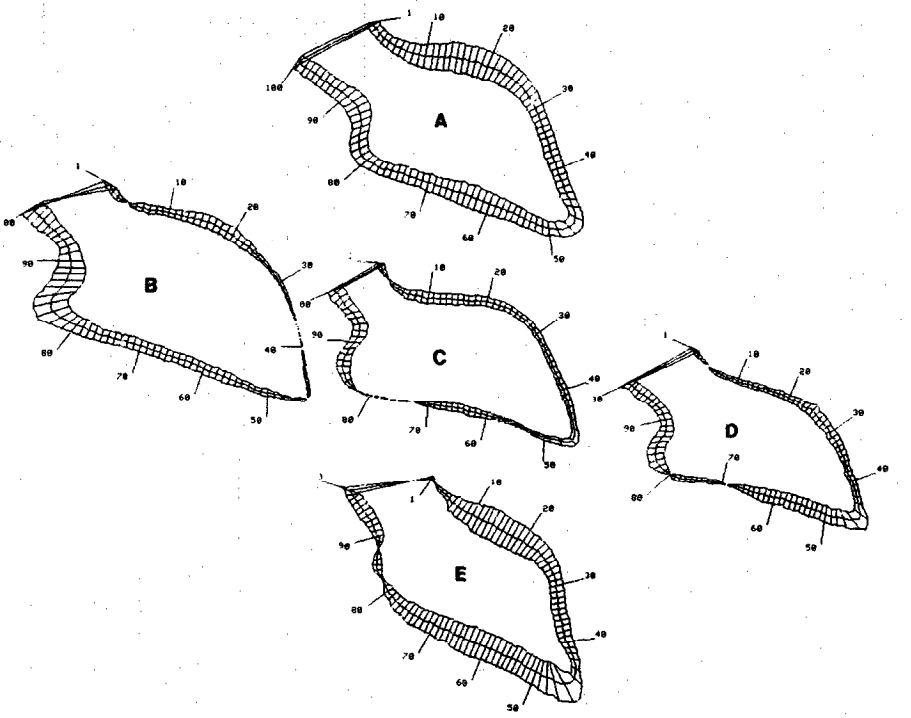

Figure 1. Contrast left ventriculograms from one swine showing the progressive systolic dysfunction and illustrating the diffuse global involvement. **A,** Prearrest baseline. **B to E,** 30 min and 2, 5 and 48 h after resuscitation, respectively.

first 5 h after resuscitation (Table 2). Partial recovery was seen by 24 h, and full recovery was observed by 48 h (Table 2). The systolic dysfunction was a diffuse process. Global left ventricular systolic dysfunction was observed in all ventricular walls, including the anterior, apical and inferior walls (by contrast ventriculography) and the lateral wall (by echocardiography), as opposed to the focal wall motion abnormalities seen with myocardial infarction and subsequent reperfusion. Figure 1 shows the changes in left ventricular ejection fraction in one animal over the first 48 h after resuscitation and illustrates the diffuse nature of this left ventricular systolic dysfunction.

End-systolic and end-diastolic left ventricular volumes were calculated from the contrast ventriculograms. No change in end-diastolic volume was seen after resuscitation, but end-systolic volume increased consistently when measured at 30 min, 2 h and 5 h after resuscitation (Table 2). Similarly, stroke volume was also compromised at 30 min, 2 h and 5 h after resuscitation in all groups (Table 2).

Peak left ventricular systolic pressure divided by end-systolic volume is a commonly calculated ratio for measurement of global myocardial contraction (23,24). This ratio decreased significantly in all groups during the first 5 h after resuscitation and continued to be depressed at 24 h but made a full recovery by 48 h (Table 2).

Hemodynamic data. The major hemodynamic changes seen from baseline through 48 h after resuscitation are presented in Table 3. Right heart pressures, including right atrial pressure, mean pulmonary artery pressure, and mean pulmonary artery occlusive pressure, increased insignificantly after successful resuscitation within each subgroup.

Cardiac output measured by thermodilution technique decreased after resuscitation in each subgroup but was significantly lower only in group B. Partial recovery was observed by 24 h and full recovery by 48 h. Peak systolic left ventricular pressure was generally unchanged throughout the 48-h study period among all groups. Left ventricular end-diastolic pressure increased significantly in all subgroups during the first 5 h after resuscitation before returning to baseline levels by 48 h (Table 3).

Measurement of tau documented temporarily impaired relaxation of the left ventricle after resuscitation. The increase in isovolumetric relaxation time, from baseline to 5 h and the subsequent decline toward baseline level from 5 to 48 h, was significant in group B (Table 3).

Echocardiographic data. Standard diameters and variables of fractional shortening, mitral valve deceleration time and left

Table 3. Hemodynamic Data Before and After Successful Resuscitation (mean ± SE)

	Baseline	30 min	2 h	5 h	24 h	48 h
HR (beats/min)						
Group A	123 ± 7	134 ± 8	152 ± 7*	161 ± 9*	—	—
Group B	118 ± 5	159 ± 6*†	127 ± 4	122 ± 4	119 ± 6	—
Group C	143 ± 18	177 ± 11	172 ± 22	154 ± 13	—	152 ± 11
RA (mm Hg)						
Group A	8 ± 1	7 ± 2	4 ± 2	5 ± 1	—	—
Group B	5 ± 1	7 ± 1	5 ± 1	4 ± 1	4 ± 1	—
Group C	0 ± 0	4 ± 2	2 ± 1	2 ± 2	—	−1 ± 1
PA (mm Hg)						
Group A	16 ± 4	24 ± 3	18 ± 1	18 ± 4	—	—
Group B	11 ± 1	15 ± 2	14 ± 2	14 ± 2	14 ± 1	—
Group C	14 ± 2	17 ± 2	16 ± 1	16 ± 2	—	11 ± 1
PAOP (mm Hg)						
Group A	3 ± 2	8 ± 1	6 ± 1	7 ± 2	—	—
Group B	3 ± 2	4 ± 1	5 ± 2	3 ± 2	3 ± 2	—
Group C	2 ± 2	3 ± 1	4 ± 1	4 ± 1	—	2 ± 1
CO (ml/min per kg)						
Group A	14 ± 1	10 ± 1	12 ± 2	11 ± 1	—	—
Group B	18 ± 1	16 ± 1	13 ± 1*	13 ± 0*	14 ± 1*	—
Group C	19 ± 1	18 ± 1	16 ± 1	15 ± 2	—	19 ± 1
PSP (mm Hg)						
Group A	101 ± 8	120 ± 6	113 ± 4	105 ± 6	—	—
Group B	94 ± 5	119 ± 5*†	104 ± 4	98 ± 7	95 ± 4	—
Group C	97 ± 8	110 ± 1	103 ± 7	92 ± 3	—	118 ± 9
LVEDP (mm Hg)						
Group A	11 ± 1	18 ± 3*	21 ± 3*	20 ± 3*	—	—
Group B	11 ± 1‡	18 ± 2*	22 ± 3*†	21 ± 3*†	14 ± 2	—
Group C	12 ± 2	19 ± 3‡	13 ± 3	13 ± 4	—	7 ± 1
LV +dP/dt						
Group A	980 ± 124	1,344 ± 98	1,224 ± 138	1,075 ± 141	—	—
Group B	914 ± 143	1,111 ± 188	894 ± 81	778 ± 62	830 ± 84	—
Group C	1,460 ± 112‡	1,450 ± 235‡	1,266 ± 180‡	1,084 ± 156‡	—	1,880 ± 132
LV −dP/dt						
Group A	−973 ± 116	−1,096 ± 99	−1,148 ± 122	−960 ± 109	—	—
Group B	−966 ± 157	−989 ± 108	−910 ± 76	−829 ± 62	−925 ± 88	—
Group C	−1,540 ± 121‡	−1,534 ± 232‡	−1,356 ± 202‡	−1,204 ± 178‡	—	−1,950 ± 126
Tau (ms)						
Group A	—	—	—	—	—	
Group B	29 ± 1	38 ± 4	46 ± 3*	41 ± 3	34 ± 2	—
Group C	28 ± 3	34 ± 2	41 ± 9	34 ± 3	—	26 ± 1

*$p < 0.05$ versus baseline. †$p < 0.05$ versus 24 h. ‡$p < 0.05$ versus 48 h. CO = cardiac output; HR = heart rate; LV +dP/dt = left ventricular positive dP/dt; LV −dP/dt = left ventricular negative dP/dt; LVEDP = left ventricular end-diastolic pressure; RA = mean right atrial pressure; Tau = isovolumetric relaxation time; other abbreviations as in Tables 1 and 2.

ventricular isovolumetric relaxation time were measured (Table 4). Echocardiographic analysis showed diminished systolic ventricular function as a decreased fractional shortening. Diminished diastolic ventricular function was also shown by a decreased mitral valve deceleration time and an increased isovolumetric relaxation time at 5 h after resuscitation. Restoration to baseline of these variables occurred by 24 to 48 h after resuscitation.

Post hoc studies. *Myocardial blood flow data.* From the several animals studied in which regional blood flow was measured before cardiac arrest and at 5 h after resuscitation, no significant decline in myocardial blood flow was seen, whereas left ventricular ejection fraction declined significantly. Myocardial blood flow averaged 119 ± 10 ml/min per 100 g at baseline and was 123 ± 9 ml/min per 100 g at 5 h after resuscitation. Left ventricular ejection fraction was 50 ± 7% at baseline but was markedly depressed, averaging only 19 ± 5% ($p < 0.02$) during the first 5 h after resuscitation. Figure 2 illustrates this relation.

Defibrillation data. To assess whether the defibrillation shocks contributed to the degree of left ventricular dysfunction found after resuscitation, the number of shocks and total joules received were tabulated. The number of shocks ranged from one to four, with 18 of 23 animals receiving only one shock and no animal receiving more than four shocks (mean 1.4 ± 0.2). The mean total joules was 303 ± 38 J (range 190 to 760). The

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Table 4. Echocardiographic Data (mean ± SE)

	Baseline	5 h	24/48 h
Fractional shortening (%)	29 ± 1	23 ± 1*†	28 ± 2
Mitral valve deceleration time (ms)	98 ± 5	61 ± 3*†	88 ± 4*
LV isovolumetric relaxation time (ms)	72 ± 3	91 ± 3*†	73 ± 4
LV diastolic diameter (mm)	41 ± 1	42 ± 1	40 ± 2
LV systolic diameter (mm)	29 ± 1	32 ± 1	29 ± 2
LV posterior wall (mm)	7 ± 0	6 ± 0	6 ± 0
LV septum (mm)	7 ± 9	6 ± 0	6 ± 0

*$p < 0.05$ versus baseline. †$p < 0.05$ versus 24/48 h. LV = left ventricular.

animal receiving the most shocks (four) for a total amount of 760 J did not have the lowest ejection fraction during the study, nor was it evident that other left ventricular function variables indicated a correlation between total joules and left ventricular dysfunction. We performed a post hoc study of several additional animals that received high energy shocks administered without inducing ventricular fibrillation cardiac arrest. Mean left ventricular ejection fraction did not decline over time in these animals. No decrease in left ventricular ejection fraction over the study period of 24 h was seen. Therefore, we believe that defibrillation injury itself did not play a significant role in the well described left ventricular dysfunction seen in the animals after resuscitation.

Discussion

The present study demonstrates marked stunning of the myocardium after successful CPR, with resultant systolic and diastolic dysfunction that was maximal between 2 and 5 h after resuscitation, showed improvement at 24 h and normalized by 48 h after resuscitation. Because all study animals had normal coronary arteries before ischemic insult, it could be postulated that the effects in older hearts or hearts with coronary disease may be even more dramatic than those shown herein.

Global myocardial stunning after resuscitation. The strict definition of myocardial stunning includes the persistence of left ventricular dysfunction after the return of normal myocardial blood flow. Although the return of normal baseline function was seen, no myocardial blood flow was measured in the original study. Therefore, several animals were studied post hoc with the same protocol, including 10 min of untreated ventricular fibrillation before CPR and subsequent successful resuscitation. Myocardial blood flow was unchanged between baseline and 5 h after resuscitation, whereas left ventricular ejection fraction decreased significantly by 5 h after resuscitation. These data show convincingly that this is true myocardial "stunning," with normal coronary blood flow at the time that left ventricular function is markedly depressed, although full recovery is seen within several days.

The importance of this observation is that aggressive supportive therapy may well be indicated in the first 48 h after arrest in those patients with resultant severely decreased ventricular function, with the expectation that part of this dysfunction is myocardial "stunning" and thus reversible.

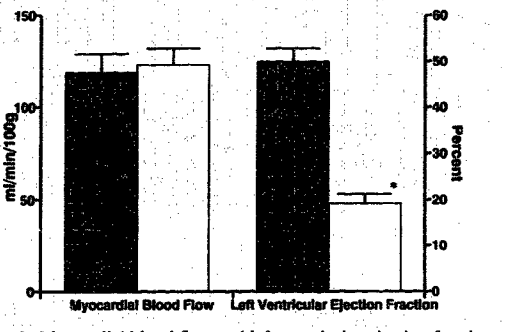

Figure 2. Myocardial blood flow and left ventricular ejection fraction at both baseline **(solid bar)** and at 5 h **(open bar)** after resuscitation. No difference in myocardial blood is seen, but a large decrease is seen in ejection fraction. *$p \leq 0.05$.

The concept of myocardial stunning is well accepted (25,26). Regional myocardial stunning from various periods of coronary occlusion and reperfusion correlates well with the length of ischemic injury. Both systolic contraction and diastolic relaxation remain impaired after myocardial blood flow is restored but eventually return to normal (27). The concept of a postresuscitation syndrome and resultant global myocardial stunning is relatively new.

Postresuscitation syndrome. It has long been recognized that initial resuscitation from cardiac arrest does not ensure long-term survival. Approximately 60%–70% of patients originally resuscitated from cardiac arrest died in hospital before discharge (2–5). The most common causes of postresuscitation deaths before discharge appear to be central nervous system injury and myocardial failure. Shoenenberger et al. (5), in their report of 141 cardiac arrests, found that of the 50 patients initially resuscitated, only 18 survived to hospital discharge. The most common causes of death after resuscitation in their series were central nervous system damage, myocardial failure and infection (5).

Negovsky (28) was the first to describe a postresuscitation syndrome with multiple-organ damage after cardiac arrest and successful resuscitation. Investigators at the University of Pittsburgh have also reported a "cardiovascular postresuscitation syndrome." Cerchiari et al. (11) studied myocardial filling pressures and cardiac output before and after normothermic ventricular fibrillation (no blood flow) cardiac arrest of 7.5, 10 or 12.5 min in duration, reversed by standard external CPR. Central venous pressure increased at 30 min in all three groups but returned to baseline levels by 1 h. There was no change in mean pulmonary artery pressure. Pulmonary artery occlusive pressure increased in all three groups at 30 min but returned to normal, except in the group undergoing the most prolonged untreated period of cardiac arrest (12.5 min), where it remained elevated above control levels throughout the first 6 h after resuscitation. Cardiac index decreased in all three groups until 6 h. After 6 h, it remained significantly lower than control levels only in the group with 12.5 min of untreated ventricular fibrillation.

Tang et al. (12) recently published a report of progressive myocardial dysfunction after CPR using an isolated perfused rat heart preparation. They found that after a 4-min period of untreated ventricular fibrillation and an additional 5 min of precordial compressions, myocardial dysfunction could be documented at 2 and 20 min after resuscitation. Pressure-volume relation showed a marked compromise in systolic contraction, as well as diastolic compliance, 20 min after resuscitation. These investigators have also recently described an increase in severity of postresuscitation myocardial dysfunction with an increase in the time of untreated ventricular fibrillation from 4 to 8 min and with the administration of epinephrine during the resuscitation effort (29).

Systolic and diastolic left ventricular dysfunction. To our knowledge, the present report is the first in an in vivo model of cardiac arrest to elucidate the time course of left ventricular systolic and diastolic dysfunction after CPR. From these data it is clear that a dramatic decrease in systolic and diastolic left ventricular function is present even as early as 30 min after resuscitation. Such dysfunction continues for at least the first 5 h after resuscitation, and is partially recovered by 24 h, recovering fully by 48 h. The compromise in systolic left ventricular function is manifested by the decreased ejection fraction, the decreased fractional shortening and the decreased peak systolic left ventricular pressure/end-systolic volume ratio. Contrast ventriculography, as well as echocardiography, shows the global nature of this systolic dysfunction. This contrasts with more focal insults occurring with isolated coronary occlusion and reperfusion. End-systolic left ventricular peak pressure/end-systolic left ventricular volume ratios were also calculated to evaluate contractile function. Many investigators believe this variable to be more independent of preload and afterload conditions than ejection fraction (23,24). This ratio indicated severe ventricular contraction dysfunction in our model.

Reduced left ventricular diastolic function was also demonstrated. This was seen by the increase in left ventricular and diastolic pressure, the hemodynamically determined isovolumetric relaxation constant (tau) and by the transthoracic Doppler-echocardiographic variables of mitral valve deceleration time and left ventricular isovolumetric relaxation times.

The degree of left ventricular systolic dysfunction after cardiac arrest and resuscitation correlated with the duration of cardiac arrest insult. In the group undergoing 15 min of untreated ventricular fibrillation, mean left ventricular ejection fraction at 5 h was significantly lower than in animals undergoing only 10 min of untreated ventricular fibrillation (Table 1). There was no significant difference in coronary perfusion pressures during the CPR period between the two groups. The difference in 5-h ejection fractions seems to reflect the difference in the duration of untreated cardiac arrest rather than differences in the performance of CPR.

The degree of left ventricular dysfunction seen in the present study further suggests that transient myocardial failure may be a significant cause of death after initial resuscitation. Such data suggest that strategies centered on improving left ventricular function and circulatory support after resuscitation may increase long-term survival after cardiopulmonary arrest and restoration of spontaneous circulation.

We found that the aggressive CPR needed to revive animals after 10 and 15 min of untreated ventricular fibrillation cardiac arrest produced no more trauma than that previously seen with other resuscitation therapies. Using a previously published trauma scoring system, we found no difference in mean trauma scores among the animals studied for left ventricular dysfunction after CPR than those previously studied with standard CPR (21). Postmortem TTC staining showed no evidence of myocardial infarction, including no subendocardial infarction in the three animals so studied.

Study limitations and clinical considerations. The phenomenon of global myocardial stunning resulting from cardiac arrest and successful resuscitation is well documented. However, the time course for recovery may be dependent on the model used. In the present study, normal healthy pigs were utilized, whereas most victims of cardiac arrest have some degree of organic heart disease and often significant coronary artery lesions. It is not known how quickly left ventricular function will return to prearrest levels after cardiac arrest in subjects with abnormal hearts.

To successfully complete these experiments, anesthesia must be provided for the experimental animals. It is well recognized that all volatile anesthetic agents, including those used here, have some detrimental effects on left ventricular function (30). Great efforts were made to minimize the required amount of anesthesia, but it must be acknowledged that even small amounts may affect the degree of ventricular dysfunction. However, similar levels of anesthesia were used throughout the entire project, with minimal variations seen from animal to animal.

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