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Internal Countershock Produces Myocardial Damage and Lactate Production Without Myocardial Ischemia in Anesthetized Dogs

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The global myocardial extraction of lactate was measured in 13 halothane anesthetized dogs to assess the effect of electric countershock applied directly to the heart. Seven animals received two countershocks of 30 delivered joules each, while six animals were not shocked but were atrially paced to a rate of 190–200, both with and without occlusion of the vena cava to produce a mean arterial pressure of 40–50 mmHg. All animals had substantially positive lactate extraction in the baseline state (36 ± 10% for countershock group *vs.* 41 ± 3% for pacing group). Myocardial lactate extraction reached a markedly negative nadir 2.5 min after countershock (−19 ± 15%), but returned toward normal by 6 min (10 ± 6%). Lactate extraction was not significantly changed from baseline in the pacing group. The relationship between changes in regional myocardial blood flow (radiolabeled microspheres) and post-countershock myocardial damage (technetium pyrophosphate uptake) was assessed in six dogs shocked as above. Mean myocardial blood flow was increased minimally immediately after countershock (0.78 ± 0.08 $ml \cdot min^{-1} \cdot g^{-1}$ *vs.* 1.16 ± 0.3), but there was no difference in blood flow between damaged and undamaged tissue at either time point. The epicardial-to-endocardial ratio of blood flow was unchanged after countershock (0.97 ± 0.05 *vs.* 0.99 ± 0.08). There was no relationship between myocardial damage and either the absolute amount of blood flow after countershock (r = −0.03) or the change in blood flow compared with the pre-shock period (r = 0.01). These results show a dramatic reduction in aerobic metabolism immediately following electric countershock. The comparison with animals paced to profound tachycardia in the presence of systemic hypotension indicates that hemodynamic changes after countershock are not responsible for these changes. The lack of association between reduced myocardial blood flow and post-countershock myocardial damage does not support the hypothesis that post-countershock damage is caused by decreased myocardial perfusion. The authors speculate that the post-countershock anaerobic myocardial metabolism and myocardial lesions might be induced through direct damage of myocardial mitochondria. (Key words: Heart: lactate extraction; metabolism; myocardial blood flow. Heart, arrhythmia: defibrillation; electroconversion.)

ELECTRIC COUNTERSHOCK can produce necrotic myocardial lesions in both animals[1–5] and humans[6–8] by a mechanism which is not well established. We have previously shown[4] that newborn piglets were much more resistant to post-countershock myocardial damage than has been reported for adult dogs. We attributed this to the enhanced anaerobic metabolic capability of the newborn's myocardium,[9] since ultrastructural analysis of post-countershock myocardial lesions using electron microscopy[3,10,11] has demonstrated disruption of mitochondria in myocytes which are in the pathway of the countershock current. The early occurrence of mitochondrial disruption suggested that the formation of necrotic lesions could be due to alterations in myocardial aerobic metabolic capacity, which are particularly intense in those myocardial regions exposed to high current density. If post-countershock myocardial lesions are linked to impaired myocardial aerobic metabolism, then the ability of the heart to extract and utilize lactate would likely be reduced following countershock. We, therefore, investigated global myocardial energy metabolism in anesthetized dogs given two countershocks directly to the heart by measuring myocardial lactate extraction.

Because any change in lactate extraction could also represent a reduction in myocardial blood flow to certain portions of the heart, which might in itself cause myocardial necrosis, we measured blood flow using radiolabeled microspheres in damaged and undamaged myocardium before and after countershock in another group of dogs, and related these changes to myocardial damage measured by the uptake of technetium^{99m} pyrophosphate (TC PYP).

Methods

LACTATE EXTRACTION STUDIES

After institutional approval by the Animal Research Committee, 13 mongrel dogs were anesthetized with halothane in oxygen by mask. Halothane allowed satisfactory surgical anesthesia with a single anesthetic agent without adjuvant drugs. The trachea was intubated with

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a cuffed endotracheal tube and controlled ventilation was initiated with a volume limited ventilator to achieve an end-tidal CO_2 concentration (Beckman LB-2) of 4–4.5% or a P_{CO_2} of 35–40 mmHg (blood gas analysis). Inspired halothane concentration was maintained at 1.25–1.75% as necessary to provide adequate anesthesia and a mean arterial pressure (MAP) below 100 mmHg. Maintenance fluid infusion of 5% dextrose with Lactated Ringer's solution was started *via* a foreleg vein at 4 $ml \cdot kg^{-1} \cdot hour^{-1}$. Surgical blood loss was replaced with either normal saline (3 ml per ml shed blood) or Hetastarch solution (1 ml per ml shed blood). The right and left femoral arteries were percutaneously cannulated for blood pressure monitoring and arterial blood sampling. The ECG (lead II), arterial pressure, and end-tidal CO_2 (if measured) were continuously recorded (Beckman 5111 or Gould 2800).

A right thoracotomy was performed in the 4th intercostal space and the right atrium cannulated with an 8 French introducer. Heparin, 2000 units, was administered intravenously along with lidocaine, 1.5 $mg \cdot kg^{-1}$. A 7 French balloon-tipped catheter was manually guided 1–2 cm into the coronary sinus and the balloon inflated. Free flow of blood through the coronary sinus catheter was confirmed. Coronary sinus flow was not measured because of frequent coronary sinus blood sampling during the experimental protocol. The dogs were divided into two groups. One group (n = 7) received electric countershocks directly to the heart; the second (n = 6), a control group designed to assess the role of tachycardia and hemodynamic impairment on myocardial aerobic metabolism, received no countershock, but was paced to atrial tachycardia with and without hypotension by inflow occlusion.

Countershock Group

Baseline blood samples were drawn simultaneously from the coronary sinus and the femoral artery for measurement of lactate. Two damped sine-wave countershocks of 30 delivered joules each were administered directly to the heart using 5 cm diameter electrode paddles placed opposite each other on the right and left ventricular walls. There was a 1-min interval between shocks. Blood samples were drawn simultaneously from the coronary sinus and the femoral artery at the following elapsed times after beginning countershock: 30 s (between shocks); 1.5 min; 2.5 min; 3.5 min; and 6 min. In one animal, the coronary sinus catheter was dislodged prior to the 6-min sample. All other samples were included for this animal.

Atrial Tachycardia/Hypotension Group

After thoracotomy and insertion of the coronary sinus catheter, two pacing wires were sewn into the right atrium. Baseline samples for lactate were drawn simultaneously from the coronary sinus and the femoral artery. Atrial pacing was begun at a rate from 190–200 beats/min. Simultaneous blood samples were drawn at 30 s, 1.5 min, 2.5 min; 3.5 min, and 6 min after pacing was initiated. These times were equivalent to blood sampling times in the countershock group. An additional pair of samples were obtained 5 min after cessation of pacing.

After a 10-min rest period, another baseline sample was obtained. Atrial pacing to a rate of 190–200 was again initiated, and the inferior vena cava constricted by a partially occlusive tie in order to drop the mean arterial pressure to 40–50 mmHg. Blood samples were obtained at 3 min and 5 min after vena caval occlusion, and again 5 min after cessation of pacing and restoration of vena caval flow. The animal was then killed by injection of T61 (Taylor Pharmacal, Decatur, Illinois), or potassium chloride.

Regional Blood Flow and Myocardial Damage Studies

Six additional mongrel dogs were prepared as described above, except that a large-bore cannula was placed in the left atrium for injection of microspheres, and no coronary sinus catheter was placed. When hemodynamically stable after completion of cannulation lidocaine, 1.5 $mg \cdot kg^{-1}$ was administered. Approximately 1.5×10^6 15 μ ^{113}Sn microspheres (New England Nuclear) were injected into the left atrium over 20 s. The microspheres were suspended in saline solution with 0.01% Tween 80, and were mechanically agitated until injection. Blood samples were withdrawn from the femoral artery at a constant rate by a withdrawal pump starting 1 min before injection, and continuing until 3 min after injection. The reference syringe was weighed before and after withdrawal to determine the exact reference flow (specific gravity of blood assumed to be 1.050).

After completion of reference blood withdrawal, two damped sine-wave countershocks of 30 joules each were delivered directly to the heart as described above. At 2.5 min elapsed time, a second injection of microspheres (^{95}Nb) was made, with reference sampling as described. In these experiments, the animal remained anesthetized for an additional 4 h, at which time 10–13 mCi of technetium^{99m} pyrophosphate (Pyrolite, New England Nuclear) was injected.[3] One hour later, the animal was killed by lethal injection as described above, and the heart was removed. Ventricular tissue was dissected to provide samples from visible lesions, an outer zone (approximately 1 cm) surrounding each lesion, and normal tissue remote from the lesions which included the interventricular septum. Each specimen (excluding those from the septum) was subdivided into an epicardial half and an endocardial half.

Each sample was weighed in a preweighed counting tube, and was counted for gamma-ray activity in a Searle 1185 multichannel gamma counter. Because technetium^{99m} has a short half-life, it was counted first using a window of 120–160 kev, to a total of 40,000 counts. Background in this window was less than 5 counts per minute. Subsequently, the samples were counted for ^{95}Nb activity with a window of 750–900 kev and for ^{113}Sn activity using a window of 300–450 kev. In each case, they were counted to a total of 4000 counts, with a background of less than 5 counts per minute. Using pure samples of each isotope, the crossover rate between windows was determined and all specific activities were corrected for crossover as necessary.

The corrected specific activity of ^{113}Sn and ^{95}Nb of each sample allowed calculation of myocardial blood flow by comparison with the total activity of reference blood specimens (averaged from 3 separate scintillation vials for each isotope) drawn at constant flow rate.[12] A blood flow was, therefore, calculated for each specimen before and after countershock. The ratio of mean epicardial flow to mean endocardial flow was determined before and after countershock, and for samples determined by technetium uptake to be damaged *versus* undamaged. In pilot studies, we found that these techniques could readily demonstrate a lack of change in blood flow in sham dogs (prepared as above but not countershocked) and could detect a significant reduction in myocardial blood flow in animals with ligated coronary arteries.

Technetium pyrophosphate uptake was represented as a sample to normal ratio (TC PYP SNR) by dividing each sample's technetium specific activity by the mean activity of several samples from the interventricular septum; thus, each animal was its own control. Samples with a SNR > 3.0 were considered to be damaged. This method has been validated in prior studies[2–5,13] of post-countershock myocardial damage.

Analytical Techniques

Blood samples for plasma lactate levels were obtained in tubes containing sodium fluoride, which inhibits red cell anaerobic metabolism. All samples were kept on ice until assayed. Plasma lactate levels were determined in duplicate using the YSI 23L lactate analyzer,[14] which was standardized with distilled water before each analysis and with a 5 mmole $\cdot$ l^{-1} solution every five samples.

Calculations and Statistical Methods

The fractional myocardial extraction of lactate was calculated as:

$$\text{Percent Extraction} = \frac{(\text{Femoral artery lactate} - \text{Coronary sinus lactate})}{\text{Femoral artery lactate}} \times 100$$

Comparison of the extraction of lactate between blood sampling times within groups was made using one-way analysis of variance with repeated measures followed by the one-tailed Student's t test for paired samples for comparison to baseline values. Differences at equivalent blood sampling times between groups were assessed using the one-tailed Student's t test for non-paired samples. One-tailed tests were used because the hypothesis tested was specifically that a reduction in lactate extraction would occur in the countershock group; an increase in extraction is included in the null hypothesis.

The relationship between myocardial damage as measured by technetium uptake (SNR) *versus* either absolute post-countershock blood flow or change in myocardial blood flow was assessed by the Pearson product moment. The differences in mean myocardial blood flow, or epicardial/endocardial ratio before and after countershock, were treated by paired t test. For clarity of the graphics, all data are presented as mean ± the standard error of the mean. Statistical significance was considered at $P < 0.05$.

Results

Hemodynamic Effects

Following thoracotomy and cannulation of the coronary sinus, all animals in the lactate extraction study were hemodynamically stable with a mean arterial pressure of 80 ± 5 mmHg. Following two countershocks, there was a drop in mean arterial pressure to 58 ± 4 mmHg at 2.5 min elapsed time, which was still 59 ± 4 mmHg at 6 min elapsed time. There was a high incidence of dysrhythmias, primarily atrial tachycardia, with rates between 110 and 190 beats/min. There were frequent premature ventricular contractions and occasional short runs (<5 beats) of ventricular tachycardia in the first 2 min after countershock. No animal had sustained ventricular tachycardia.

Animals given atrial pacing maintained stable atrial tachycardia (rate 190–200), which promptly returned to a normal sinus rhythm immediately after cessation of pacing. Mean arterial pressure during pacing alone was 60 ± 5 mmHg; when vena caval occlusion was added, the mean arterial pressure was 47 ± 3 mmHg.

Myocardial Metabolism

In the baseline state, all animals demonstrated substantial fractional myocardial extraction of lactate. There was no significant difference between groups at baseline. Arterial lactate did not change appreciably after countershock. There was, however, a marked reduction in myocardial lactate extraction, which became net lactate production at 1.5, 2.5, and 3.5 min after initiating countershock (fig. 1). Positive net lactate extraction had returned by 6 min elapsed time.

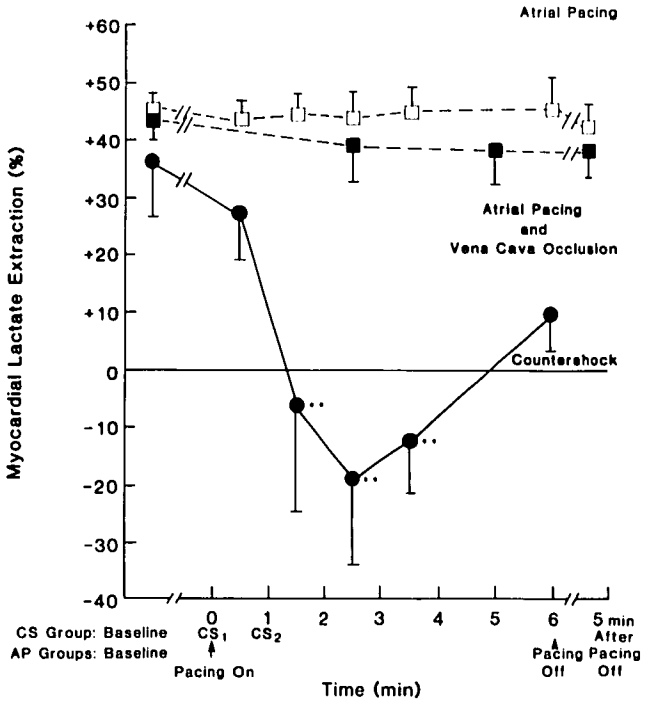

FIG. 1. Myocardial lactate extraction (%) before and after electric countershock or atrial pacing. Black circles are the countershock group (n = 7) in which lactate extraction dropped significantly (*$P < 0.025$ *versus* baseline) after two countershocks (CS_1 and CS_2). Open boxes represent the atrial pacing (AP) group (n = 6) which were atrially paced to 190–200 beats/min. Black boxes are data from the pacing group which were again paced to atrial tachycardia with the addition of vena caval occlusion to produce a mean arterial pressure of 40–50 mmHg. Error bars represent the standard error of the mean. There was no change in lactate extraction in the pacing groups which were both significantly different ($P < 0.01$) from the countershock group after the two countershocks.

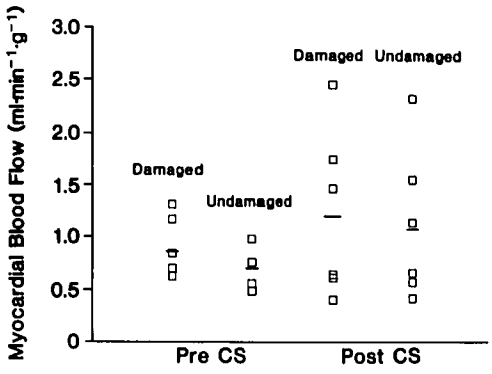

FIG. 2. Mean myocardial blood flow in the pre-countershock and post-countershock states. Damaged refers to samples which later demonstrated myocardial damage with a technetium pyrophosphate SNR > 3.0. Undamaged are samples with a SNR < 3.0. Myocardial blood flow did not significantly differ before (PRE CS) and after (POST CS) countershock or between damaged or undamaged tissue. Horizontal bars represent the mean. Each symbol represents the indicated subset of tissue for an individual animal.

Myocardial lactate extraction was not significantly changed during atrial tachycardia, with or without hypotension from vena caval occlusion (fig. 1). The difference in lactate extraction between the two groups was statistically significant at the same elapsed times as noted above ($P < 0.01$).

Myocardial Blood Flow and Myocardial Damage Studies

Hemodynamic changes similar to those observed in the lactate extraction studies occurred. Mean arterial pressure was 67 ± 7 mmHg before countershock, 58 ± 4 mmHg at 2.5 min, and 57 ± 3 mmHg at 6 min elapsed time. Supraventricular arrhythmias were noted as above. At the time of post-countershock microsphere injection, all animals had a stable cardiac rhythm (usually supraventricular tachycardia) with a mean blood pressure above 50 mmHg. The time of second microsphere injection corresponded to the nadir of lactate extraction, as determined above.

Figure 2 shows the mean myocardial blood flow before and after countershock for samples which were determined by technetium uptake to be either damaged or undamaged. Myocardial blood flow was not significantly different between damaged or undamaged tissue at either time, indicating no *a priori* abnormality in the tissue which became damaged. There was a variable blood flow response to countershock, and some animals substantially increased flow. However, there was no systematic change.

The epicardial-to-endocardial blood flow ratio was not significantly changed by countershock, as shown in figure 3. This ratio was no different in damaged tissue compared to undamaged tissue.

Myocardial lesions were visible at 5 h after countershock in all six animals. Of the samples identified as damaged by TC-PYP uptake, 74% were from visible lesions, and 21% were from border zones. Thus, the tissue identified as damaged by the TC-PYP SNR value corresponded closely to the specific lesion, which was in the area underlying each electrode paddle. The two parts of figure 4 show the relationship between myocardial damage as assessed by the TC-PYP SNR and either the absolute amount of myocardial blood flow after countershock (fig. 4A), or the change (post minus pre) in myocardial blood flow (fig. 4B) for each of 157 damaged samples. There clearly was no relationship between myocardial damage and either absolute blood flow (r = −0.03) or change in blood flow (r = 0.014). Myocardial damage occurred at any level of flow, and with either an increase or decrease in flow compared to the baseline state. The blood flow and blood flow change of samples without myocardial damage (SNR < 3) distributed no differently than the damaged samples.

Discussion

Two high energy countershocks applied directly to the heart resulted in a consistent and profound change in myocardial lactate metabolism. The heart, which normally is able to take-up lactate and utilize it for aerobic metabolism, was unable to maintain net lactate uptake, and, in fact, became a net lactate producer. The conversion of the heart to global net lactate production signals a substantial impairment of aerobic metabolism in at least certain parts of the myocardium.[15]

The reduction in aerobic metabolism clearly appears to be related to countershock itself, and not to post-countershock hemodynamic alterations, since control animals atrially paced to tachycardias exceeding those seen after countershock with or without concommitant hypovolemic hypotension failed to demonstrate any significant reduction in lactate extraction. While inflow obstruction may not exactly duplicate the mechanism of post-countershock hypotension, it provided for profound hypotension greatly exceeding that which was actually seen following countershock.

The finding that mean myocardial flow was unchanged immediately after countershock is in agreement with other studies demonstrating that regional myocardial blood flow is unchanged at 20 min[16] and at 24 h[2] after shock, although there is one report[3] of a modest decrease in blood flow after 4 h at the countershock energy dose we used. Our demonstration of the complete lack of association between the occurrence or severity of myocardial damage and either the absolute blood flow or the change in blood flow after countershock does not support the hypothesis that a reduction in perfusion is responsible for the post-countershock necrotic lesions. The finding that myocardial blood flow was not generally decreased, even in damaged samples, at a time when global myocardial lactate extraction was uniformly negative makes it extremely unlikely that the impairment of aerobic metabolism is caused primarily by regional ischemia due to altered perfusion.

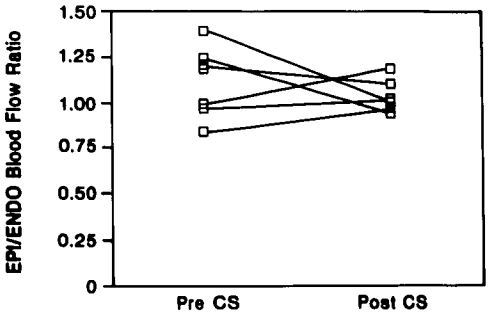

FIG. 3. Epicardial to endocardial blood flow ratio before and after countershock. Each symbol represents the mean epicardial/endocardial ratio for all samples from a single animal. There is no significant difference between before (PRE CS) and after (POST CS) countershock. There was no difference in this ratio between damaged and undamaged samples (not shown).

We continue to hypothesize that the impairment of aerobic metabolism is linked to mitochondrial dysfunction related to morphologic abnormalities of mitochondria in myocardium exposed to an intense electric shock.[3,10,11] This would, in turn, lead to the formation of localized myocardial lesions in those areas unable to maintain sufficient energy production through anaerobic pathways, even in the pressure of abundant blood flow, since there would be less functioning sub-cellular machinery to utilize the oxygen supply.

Experimental studies have clearly established that myocardial damage may be caused by electric countershock, and our observation that significant changes in myocardial lactate metabolism may occur after countershock indicates that this therapy might have significant adverse effects beyond the previously documented myocardial lesions. However, whether countershock at energy levels commonly in use produces metabolic effects of clinical significance in the human myocardium during cardiac surgery or during cardiopulmonary resuscitation remains to be determined.

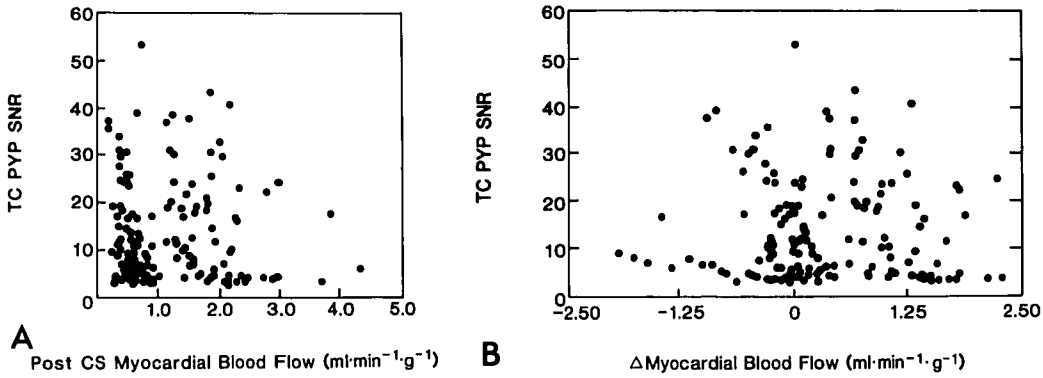

FIG. 4. Relationship between myocardial damage measured by technetium pyrophosphate sample to normal ratio (TC PYP SNR) and both the absolute level of post-countershock blood flow (*A*) or the change in myocardial blood flow between before and after countershock (*B*). Each point is one of 157 myocardial samples showing post-countershock damage (SNR > 3). There is no correlation between myocardial damage and eitehr absolute myocardial blood flow (r = −0.03) or change in blood flow (r = 0.01). The distribution of both absolute blood flow and blood flow change in samples without post-countershock damage (not shown) also demonstrated a similarly random distribution.

In summary, we have demonstrated a substantial reduction in global myocardial lactate extraction following high energy internal electric countershock, suggesting a marked impairment of myocardial aerobic metabolism. Myocardial ischemia does not account for the metabolic abnormalities, since myocardial blood flow was not reduced after countershock, and no association between post-countershock myocardial damage and either the absolute level of blood flow or the change in blood flow could be demonstrated. We speculate that the etiology of the metabolic alterations and the post-countershock lesions may involve direct electrical disruption of mitochondria.

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