Interactive effects of K^+, acid, norepinephrine, and ischemia on the heart: implications for exercise

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O'Neill, Mark, Claire E. Sears, and David J. Paterson. Interactive effects of K^+, acid, norepinephrine, and ischemia on the heart: implications for exercise. *J. Appl. Physiol.* 82(4): 1046–1052, 1997.—We tested the hypothesis that cardiac ischemia uncouples the beneficial interaction among hyperkalemia, acidosis, and raised plasma catecholamines when these chemicals are changed to mimic their exercise levels. Potassium chloride, lactic acid, and norepinephrine (NE) were infused intravenously for 2 min into anesthetized, artificially ventilated, thoracotomized rabbits during either occlusion of the left circumflex artery (3 min; $n = 10$) or after a period of prolonged ischemia (20 min; $n = 7$) that led to a small infarction. NE (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv) offset the negative cardiac effects of hyperkalemia (up to 8.7 ± 0.7 mM) and acidosis (arterial pH 7.09 ± 0.03) in normal hearts. Cardiac performance was not significantly depressed by either acute or chronic ischemia before any infusions. However, the protective effect of NE during acute ischemia or after prolonged ischemia with hyperkalemia and acidosis was substantially reduced. These results show that cardiac ischemia attenuates the protective action of NE and increases the depressive effects of hyperkalemia and acidosis. Whether myocardial ischemia amplifies the cardiotoxic effects of hyperkalemia and acidosis during vigorous exercise by attenuating the beneficial effect of catecholamines remains to be determined.

rabbit; arrhythmia

THE HARMFUL CARDIAC EFFECTS of raised arterial potassium ($[K^+]_a$) and acid ($[H^+]_a$) and high sympathetic activity are well known (4, 9, 10). However, when K^+, acid, and catecholamines are increased simultaneously to mimic their exercise concentrations in whole animals or isolated cardiac tisue, they are tolerated because they minimize each other's harmful effects (19, 24, 29, 31). Heavy exercise amplifies the negative cardiac effects of underlying ischemia by increasing the incidence of ventricular arrhythmias (3), myocardial infarction (22), and sudden cardiac death (33). Acute myocardial ischemia facilitates the occurrence of ventricular arrhythmias during electrical stimulation of cardiac sympathetic nerves or during infusion of catecholamines (14, 35). It also causes rapid local increases of extracellular K^+ concentration ($[K^+]_o$) and acid (15) and promotes arrhythmias as a consequence of inhomogeneities in cardiac excitability, conduction velocity, and refractoriness (11). Thus cardiac ischemia may uncouple the beneficial interactions among K^+, acid, and catecholamines and depress cardiac performance.

Therefore, the purpose of the study was to investigate the effect of norepinephrine (NE) on cardiac performance when $[K^+]_a$ and arterial pH (pH_a) were changed to mimic their exercise concentrations {$[K^+]_o$ 8.6 mM (20) and pH 6.8 (28)} in the anesthetized rabbit during a period of acute regional ischemia (3 min) or after a period of prolonged ischemia (20 min) that led to a small infarction.

METHODS

Experiments were performed in accordance with the National Institutes of Health (NIH) *Guide for the Care and Use of Laboratory Animals* [DHHS Publication No. (NIH) 85–23, Revised 1985, Office of Science and Health Reports, Bethesda, MD 20892] and under a British Home Office Project Licence (PPL 30/00608).

Anesthesia

New Zealand White rabbits (3.1 ± 0.1 kg) of either gender were premedicated with Hypnorm [0.3 ml/kg im; fentanyl (0.315 mg/ml) and fluanisone (10 mg/ml), Janssen]. A surgical plane of anesthesia was gradually induced 20 min later with 0.8–1.5% halothane in 100% oxygen via an Ayre's T piece with a mask and anesthetic bag. A 23-gauge intravenous catheter was inserted into an ear vein for administration of supplementary anesthetic (Sagatal; pentobarbital sodium diluted to 12 mg/ml in sterile saline) as required. Stainless steel electrodes were inserted subcutaneously into each limb and into the chest wall to monitor the electrocardiogram. Heart rate was monitored continuously, and the corneal reflex was tested regularly to ensure adequate anesthesia.

Surgery

A tracheostomy was performed, and an endotracheal tube (3.5 or 4 mm ID, Portex) was inserted 4 cm into the trachea and secured. Catheters (Portex) were inserted into a femoral artery and vein and into the left carotid artery for sampling of arterial blood, intravenous infusion of test solutions and anesthetic, and monitoring of arterial blood pressure (ABP), respectively. Animals were artificially ventilated (Oxford, Mark II ventilator, Penlon) on 100% oxygen, with tidal volume and frequency adjusted to maintain arterial P_{CO_2} between 35 and 45 Torr. A midline thoracotomy was performed, and the chest was retracted laterally. The pericardium was removed, and a catheter (Y-can, 23 gauge, Wallace) was inserted into the left ventricle via the apical dimple. The heart was covered with warm moist gauze, and the thoracic cavity was covered by plastic film to reduce fluid loss and cooling. The cranial projections of the sympathovagal trunk were located in the neck, ligated, and cut.

Ischemia

Regional myocardial ischemia was induced by proximal occlusion of the left circumflex artery, which supplies most of the free surface of the left ventricle in the rabbit (7). A 3.5-mm silk suture (Ethicon) ligature was placed around the artery without dissecting the vessel. A snare was formed by threading the suture through a length of polyethylene tubing. Traction on the ligature occluded the artery.

Measurements

Systemic ABP and left ventricular pressure (LVP) were measured by saline-filled pressure transducers (SensoNor

840, Norway) calibrated in the midaxillary line. The rate of rise of LVP (±LVdP/d*t*) was calculated by using a differentiator (unit 5270, time interval 33 or 100 ms according to the magnitude of the signal, Lectromed, UK). Heart rate was triggered from the R wave of lead II of the electrocardiogram or from the ABP and digitally displayed. In some rabbits, aortic flow was measured by an electromagnetic flow probe (MDL 1401, Skalar) attached to the ascending aorta. All signals were recorded onto a penwriter (MT8P, Lectromed). The analog inputs were passed to a real time data-acquisition system (MP 100, Biopac Systems) employing Acqknowledge 3.1 software for the Macintosh (Macintosh Quadra 950). Heart rate and LVdP/d*t* were also calculated by computer, and all data were stored on an optical disk (Panasonic 840).

Intensive Care

Body temperature was measured by a rectal thermistor and maintained at 38 ± 1°C by heating lamps above and beneath the operating table. A catheter was passed into the bladder via the urethra. Fluid was replaced by an intravenous sterile saline drip (~10–15 ml/h). Arterial blood samples were regularly withdrawn (90 µl) into preheparinized capillary tubes and analyzed for pH, blood gases, and electrolytes (Na^+, K^+, Ca^{2+}) (Radiometer ABL505, Copenhagen, Denmark). Respiratory acidosis was corrected by adjusting the ventilator. Metabolic acidosis was corrected by infusion of 4.2% sodium bicarbonate solution intravenously as required.

Protocols

Intravenous infusion rates for the solutions were as follows: 300 mM KCl at 1 $ml \cdot kg^{-1} \cdot min^{-1}$, 500 mM L-lactic acid at 1 $ml \cdot kg^{-1} \cdot min^{-1}$, and NE at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. On the basis of previous work from our laboratory (19, 24, 25, 29, 31), these concentrations were chosen to mimic some changes in arterial blood composition seen during exercise ($[K^+]_o$) up to 8.6 mM (20); pH 6.8 (28); local cardiac concentrations of NE estimated at ~1 µM (5). In all protocols, arterial blood samples were taken immediately before the infusion, at 30-s intervals during the infusions, and 1 and 3 min, respectively, after the infusions were stopped. For the purposes of this study, "acute" ischemia has been defined as ischemia lasting 3 min, whereas coronary ligation lasting 20 min is defined as "chronic" ischemia.

Acute ischemia. STEP 1. KCl and lactic acid were infused together for 2 min ($n = 10$).

STEP 2. KCl and lactic acid were infused in combination with NE for 2 min ($n = 10$).

STEP 3. The left coronary artery was occluded, and an infusion of KCl, lactic acid, and NE was begun within 5 s. The infusion lasted for 2 min, and the snare was released 1 min after the infusion was stopped ($n = 10$). Before test solutions were infused, a control coronary arterial occlusion (3 min) was performed ($n = 7$).

STEP 4. In three animals, the left coronary artery was occluded, and a control infusion of NE was performed as described in *step 3* above.

Chronic ischemia. STEP 1. KCl and lactic acid were infused together for 2 min in a fresh set of animals ($n = 7$).

STEP 2. KCl and lactic acid were infused in combination with NE for 2 min ($n = 7$).

STEP 3. The left coronary artery was occluded, and the occlusion was maintained for 20 min ($n = 7$). This time was chosen because it causes subendocardial necrosis in a small part of the left ventricle (8–15%) (8) without causing a significant reduction in resting hemodynamics. After release of the ligature and a return to stable hemodynamic values, *steps 1* and *2* were repeated.

Under conditions of both acute and chronic ischemia, the sequence of infusions was randomized. Repeat infusions were made when hemodynamics, pH_a, arterial blood gases, and $[K^+]_a$ had returned to baseline (~10 min).

Statistical Analysis

All data are expressed as means ± SE. A one-way analysis of variance for repeated measurements and a post hoc comparison by using Scheffé's test compared the effects of each intervention. A paired *t*-test was performed between measurements before and during ischemia for the same perfusion condition. $P < 0.05$ was accepted as being statistically significant.

RESULTS

Acute Ischemia

Hyperkalemia and acidosis. Figure 1 shows that simultaneous intravenous infusion of 300 mM KCl (1

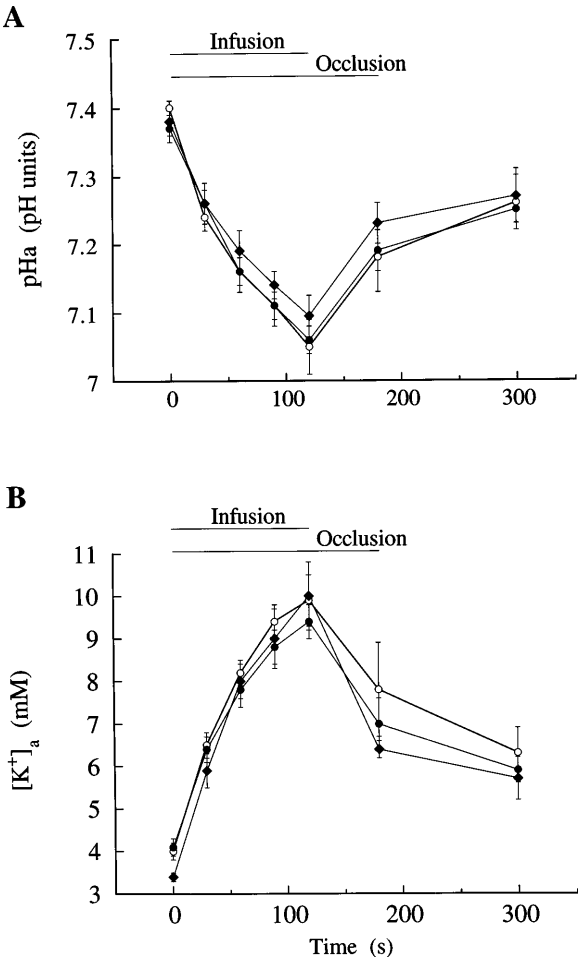

Fig. 1. Summary of results ($n = 10$ animals) showing effect of intravenous infusion of KCl and lactic acid (◆); KCl, lactic acid, and norepinephrine (NE; ●); and KCl, lactic acid and NE during a 3-min period of coronary arterial ligation (○; shown as occlusion bar) on arterial pH (pH_a; *A*) and arterial K^+ concentration ($[K^+]_a$; *B*) levels. All values for pH_a and $[K^+]_a$ were statistically different from control [analysis of variance (ANOVA), $P < 0.05$].

$ml \cdot kg^{-1} \cdot min^{-1}$) and 500 mM lactic acid (1 $ml \cdot kg^{-1} \cdot min^{-1}$) for 2 min elevated $[K^+]_a$ from 3.4 ± 0.1 to 10.0 ± 0.8 mM ($P < 0.01$) and decreased pH_a from 7.38 ± 0.02 to 7.10 ± 0.03 pH units ($n = 10$; $P < 0.01$). This was accompanied by hemodynamic depression (Figs. 2 and 3). Mean arterial pressure was reduced from 64 ± 5 to 55 ± 7 mmHg; the maximum rate of pressure development in the left ventricle ($+LVdP/dt_{max}$) was reduced from 3,814 ± 96 to 2,764 ± 520 mmHg/s, whereas heart rate did not change significantly. All hemodynamics returned to above control values by time (t) = 180 s except for heart rate, which remained below preinfusion values.

Hyperkalemia, acidosis, and NE. Simultaneous infusion of NE for 2 min (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv) offset the negative cardiac effects of KCl and lactic acid (Figs. 2 and 3). All values up to $t = 120$ s were significantly different from those measured during infusion of KCl and lactic acid alone (paired t-test). At $t = 120$ s, mean arterial pressure was 76 ± 8 mmHg with KCl, lactic acid, and NE compared with 55 ± 7 mmHg with KCl and lactic acid alone; $+LVdP/dt_{max}$ was 3,752 ± 773 mmHg/s with KCl, lactic acid, and NE compared with 2,764 ± 520 mmHg/s with KCl and lactic acid alone. An overshoot occurred in all parameters measured at $t =$ 180 s, and hemodynamics returned to control by $t = 300$ s.

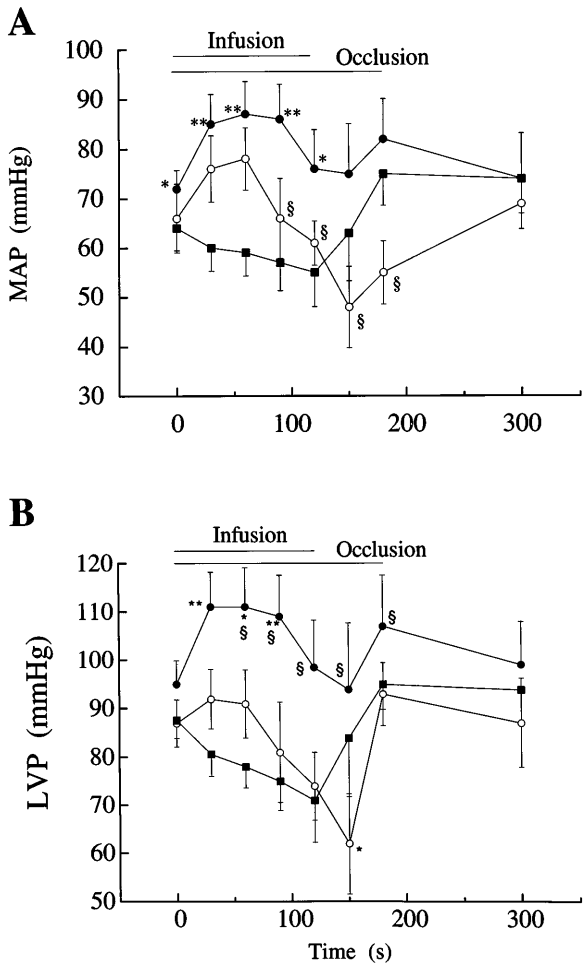

Fig. 2. Summary of results ($n = 10$ animals) showing effect of intravenous infusion of KCl and lactic acid (■); KCl, lactic acid, and NE (●); and KCl, lactic acid, and NE during a 3-min period of coronary arterial ligation (○) on mean arterial pressure (MAP; *A*) and left ventricular pressure (LVP; *B*). Note that occlusion offset protective effect of NE during hyperkalemia and acidosis. Significantly different: $*P < 0.05$; $**P < 0.01$ (ANOVA); $^{\S}P < 0.05$ between KCl, lactic acid, and NE and KCl, lactic acid, NE, and ischemia (t-test).

Acute coronary arterial ligation. Three-minute occlusion of the left circumflex coronary artery did not produce any significant change in hemodynamics. Mean arterial pressure fell from 75 ± 9 to 66 ± 9 mmHg; $+LVdP/dt_{max}$ decreased from 3,605 ± 507 to 3,365 ± 471 mmHg/s, and heart rate increased from 234 ± 12 to 248 ± 17 beats/min.

NE and acute ischemia. The effect of a 2-min infusion of NE (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ iv) during a 3-min period of coronary occlusion was examined in three animals. Hemodynamics were not significantly altered during the infusion (mean arterial pressure rose from 67 ± 9 to 77 ± 9 mmHg; $+LVdP/dt_{max}$ was elevated from 4,225 ± 716 to 5,572 ± 182 mmHg/s).

Hyperkalemia, acidosis, and NE and acute ischemia. The effect of simultaneous infusion of KCl, lactic acid, and NE during a period of coronary arterial occlusion was examined in 10 animals. Infusion and occlusion were begun at the same time, but the infusion was stopped after 120 s and the occlusion after 180 s (Fig. 2). The infusion elevated $[K^+]_a$ from 4.0 ± 0.2 to 9.9 ± 0.6 mM and decreased pH_a from 7.40 ± 0.01 to 7.05 ± 0.04 pH units ($P < 0.01$). Accompanying these changes were a decrease in mean arterial pressure (66 ± 7 to 48 ± 8 mmHg), LVP (87 ± 5 to 62 ± 10 mmHg, $P < 0.05$), $+LVdP/dt_{max}$ (3,644 ± 297 to 2,814 ± 707 mmHg/s), and heart rate (234 ± 9 to 202 ± 7 beats/min). This is in contrast to the elevated values seen for the same parameters during a combined infusion without coronary occlusion (Fig. 2). Coronary occlusion maintained for 1 min after the infusions prevented the hemodynamic recovery seen after control infusions without coronary occlusion (Fig. 2). In addition, the incidence of arrhythmias was greatly elevated by the combined infusion during coronary occlusion compared with coronary occlusion alone (e.g., Fig. 3*C*).

Chronic Ischemia

Chronic coronary arterial ligation. Complete occlusion of the left circumflex coronary artery for 20 min provoked arrhythmias in five of the seven animals studied. Two of these animals developed ventricular fibrillation that reverted to normal sinus rhythm either spontaneously or after cardiac massage. Ventricular premature beats (singles, bigeminy, and salvos) were the main arrhythmias seen and were not sustained for the duration of the occlusion but occurred in discreet trains after ~3–5 and 13–18 min of ischemia.

Hyperkalemia and acidosis postischemia. Twenty minutes of ischemia did not significantly alter baseline hemodynamics except during sustained arrhythmic activity. Resting heart rate was elevated from 222 ± 8 to 255 ± 20 beats/min. Infusing KCl and lactic acid decreased mean arterial pressure from 67 ± 6 to 43 ± 4

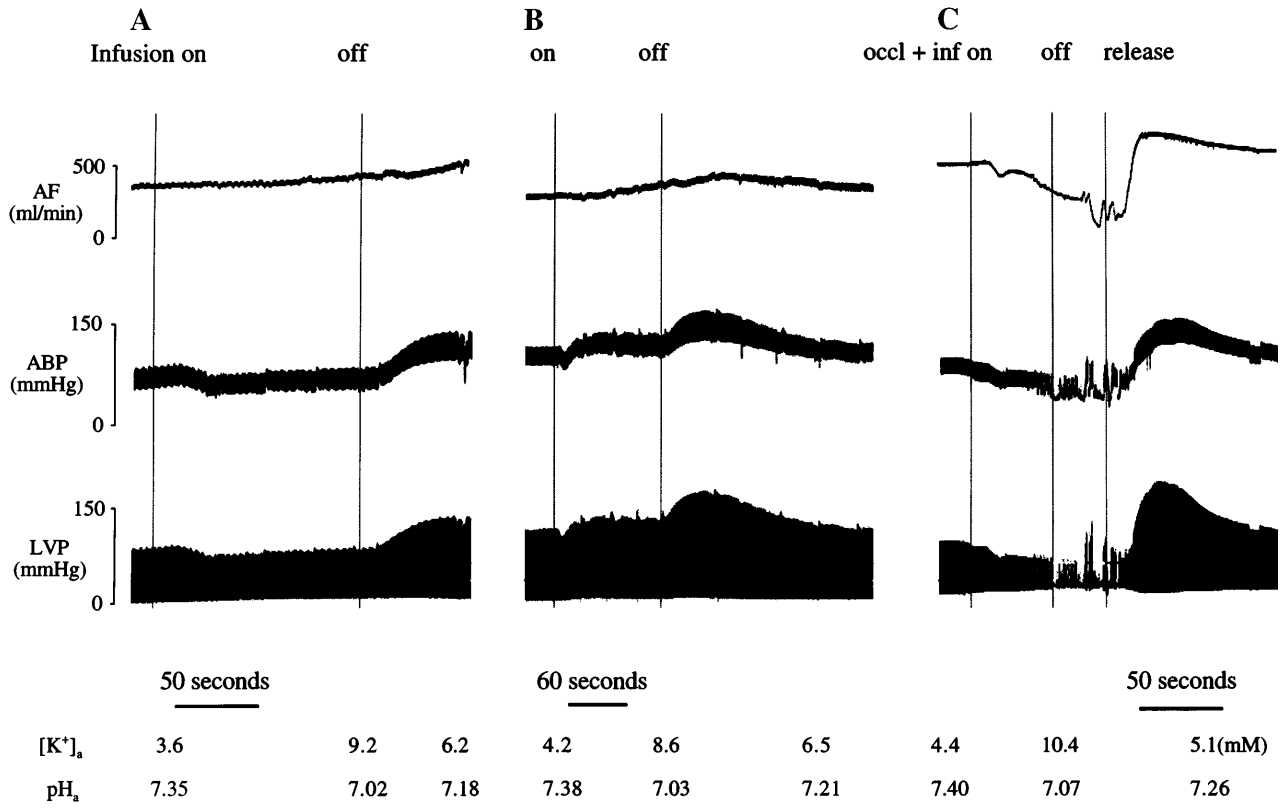

Fig. 3. Raw data traces from a representative animal showing effect of intravenous infusion (inf) of KCl, lactic acid, and NE on aortic flow (AF), arterial blood pressure (ABP), and LVP. *A*: KCl and lactic acid. *B*: KCl, lactic acid, and NE. *C*: KCl, lactic acid, NE, and simultaneous occlusion (occl) of left circumflex coronary artery. Values for $[K^+]_a$ and pH_a at beginning (on) and end (off) of each infusion period are shown. Acute cardiac ischemia superimposed on hyperkalemia, acidosis, and NE led to cardiac arrest.

mmHg ($P < 0.01$). Values for $+LVdP/dt_{max}$ postischemia closely paralleled the preischemia values, perhaps because of the postischemia tachycardia. Changes in pH_a and $[K^+]_a$ after 20 min of ischemia were not significantly different from preischemia control (Table 1).

Hyperkalemia, acidosis, and NE postischemia. The protective effect of NE during hyperkalemia and acidosis after ischemia was essentially abolished because there was no significant difference between the cardiovascular responses with or without NE after occlusion (Fig. 4). Mean arterial pressure was reduced from 71 ± 5 ($t = 0$ s) to 57 ± 6 mmHg ($t = 120$ s) compared with an increase from 64 ± 4 to 78 ± 7 mmHg before ischemia; $+LVdP/dt_{max}$ was decreased slightly from 2,815 ± 470 to 2,576 ± 884 mmHg/s postischemia. The same intervention before ischemia increased $+LVdP/dt_{max}$ from 2,896 ± 468 to 3,874 ± 1,081 mmHg/s. Heart rate was reduced from 248 ± 9 to 225 ± 3 beats/min. Changes in pH_a and $[K^+]_a$ were closely matched before and after ischemia (Table 1).

DISCUSSION

This paper reports that both acute regional cardiac ischemia and a period of prolonged ischemia, which led to a small infarction, substantially attenuated the protective effect of raised levels of NE against the negative cardiac effects of hyperkalemia and acidosis in vivo.

K^+, Acid, and Catecholamines and Cardiac Performance

NE can offset the negative effects of elevated K^+ and H^+ in whole animals and in the isolated heart (29), an effect that is mimicked by stimulation of cardiac sympathetic nerves (24) and elevation of plasma calcium (19). This response is virtually abolished by propranolol (24) and verapamil (25). Moreover, the negative cardiac effects of hyperkalemia and acidosis are enhanced by propranolol, but this response is reversed by an intravenous infusion of calcium chloride (19) or raised angiotensin II (non-adrenergic receptor-coupled pathway) in isolated cardiac tissue (31). Conversely, raised $[K^+]_o$ can offset adrenergic-induced arrhythmias in the pig (24) and in humans (6). Modulation of intracellular calcium, therefore, appears to be crucial in allowing the heart to cope with the large swings in catecholamines, acid, and raised $[K^+]_o$ as would be seen in vigorous exercise.

Does Acute Ischemia Exacerbate the Proarrhythmic Effects of Catecholamines?

Coronary arterial occlusion is associated with high cardiac adrenergic tone as a result of activation of the sympathosympathetic reflex (17) and local release

Table 1. *Arterial pH, blood gases, and electrolytes during an infusion of lactic acid and KCl and lactic acid, KCl, and NE before and after 20 min of coronary arterial occlusion*

	Time, s				
	$t = 0$	$t = 30$	$t = 60$	$t = 90$	$t = 120$
			Lactic acid and KCl preocclusion		
pH_a, U	7.37 ± 0.01	7.20 ± 0.02	7.14 ± 0.01	7.07 ± 0.01	7.02 ± 0.02
Pa_{O_2}, Torr	382 ± 47	361 ± 40.7	361 ± 43	348 ± 38	341 ± 34.6
Pa_{CO_2}, Torr	39.7 ± 2.0	51 ± 3.8	61.8 ± 3.9	69.2 ± 4.8	72 ± 4.6
$[HCO_3^-]_a$, mM	22.3 ± 1.1	20.2 ± 1.4	19.6 ± 1.3	19.3 ± 1.2	17.5 ± 0.3
$[K^+]_a$, mM	3.2 ± 0.3	5.7 ± 0.4	7.3 ± 0.2	8.5 ± 0.2	9.8 ± 0.4
			Lactic acid, KCl, and NE preocclusion		
pH_a, U	7.41 ± 0.02	7.26 ± 0.02	7.20 ± 0.03	7.14 ± 0.03	7.09 ± 0.03
Pa_{O_2}, Torr	387 ± 39	375 ± 38	383 ± 40	379 ± 39.8	366 ± 38
Pa_{CO_2}, Torr	39.2 ± 3.0	45.9 ± 2.7	54.4 ± 3.7	59.1 ± 4.0	63.7 ± 5.7
$[HCO_3^-]_a$, mM	24.0 ± 0.9	20.2 ± 1.4	20.4 ± 1.5	19.3 ± 1.5	18.4 ± 1.5
$[K^+]_a$, mM	3.4 ± 0.3	5.7 ± 0.5	7.0 ± 0.6	7.9 ± 0.6	8.7 ± 0.7
			Lactic acid and KCl postocclusion		
pH_a, U	7.38 ± 0.01	7.23 ± 0.02	7.13 ± 0.03	7.02 ± 0.05	7.00 ± 0.02
Pa_{O_2}, Torr	3.86 ± 53	378 ± 52	373 ± 50	349 ± 56	373 ± 51
Pa_{CO_2}, Torr	45.5 ± 2.1	59 ± 3.2	67.8 ± 2.8	69 ± 7.6	75.3 ± 3.1
$[HCO_3^-]_a$, mM	26.5 ± 1.0	24.5 ± 1.1	21.5 ± 1.0	18.7 ± 2.2	17.5 ± 0.6
$[K^+]_a$, mM	4.1 ± 0.3	6.7 ± 0.5	8.9 ± 0.7	9.8 ± 0.7	10.9 ± 0.7
			Lactic acid, KCl, and NE postocclusion		
pH_a, U	7.38 ± 0.02	7.17 ± 0.01	7.11 ± 0.03	7.03 ± 0.03	7.00 ± 0.04
Pa_{O_2}, Torr	397 ± 52	366 ± 56	393 ± 51	366 ± 53.9	355 ± 47
Pa_{CO_2}, Torr	40.3 ± 2.0	57.7 ± 2.2	64.2 ± 3.3	68.6 ± 4.1	71.0 ± 4.4
$[HCO_3^-]_a$, mM	23.1 ± 0.6	20.0 ± 0.4	19.3 ± 0.6	17.3 ± 0.6	15.8 ± 0.8
$[K^+]_a$, mM	3.5 ± 0.3	6.5 ± 0.3	7.7 ± 0.3	8.9 ± 0.5	9.7 ± 0.8

Values are means ± SE; $n = 7$ animals. pH_a, arterial pH; Pa_{O_2}, arterial P_{O_2}; Pa_{CO_2}, arterial P_{CO_2}; NE, norepinephrine; $[HCO_3^-]_a$, arterial bicarbonate concentration; $[K^+]_a$, arterial K^+ concentration.

mechanisms (32). Catecholamines are known to be harmful to the ischemic myocardium because they increase myocardial oxygen consumption (27), promote platelet aggregation (12), and increase the incidence of ventricular arrhythmia (26). In this study, it is unlikely that arrhythmias that are dependent on local or reflex release of cardiac catecholamines are responsible for the depression in cardiac performance seen during acute ischemia. Accumulation of K^+, acid, and especially adenosine during acute ischemia reduces transmitter release from sympathetic varicosities (23). There is also no significant increase in the catecholamine concentration in coronary venous effluent after 10 min of global ischemia in the isolated rabbit heart (34), and any rapid reflex activation of NE would be abolished in our preparation because the cardiac sympathovagal trunk was cut.

In the present study, arrhythmias were seen in six of the ten animals subjected to acute coronary occlusion plus infusion of K^+, acid, and NE. There were no arrhythmias during 3 min of occlusion alone, and hemodynamics were essentially unchanged when occlusion was accompanied by infusion of NE alone. Moreover, antiarrhythmic doses of propranolol enhance the negative inotropic effects of hyperkalemia and acidosis in normal rabbits (19) and during acute ischemia (unpublished observations). Therefore, it seems unlikely that our results can be explained by a proarrhythmogenic effect of NE.

Do Acute and Chronic Ischemia Affect the Efficacy of Catecholamines in Restoring Cardiac Function During Raised K^+ and Acidosis?

The left circumflex coronary artery is dominant in the rabbit and supplies most of the free left ventricular wall; therefore, the mass of cardiac tissue that is perfused will be decreased during acute ischemia involving this artery. Intravenous infusion of NE, K^+, and acid will have little direct influence on the ischemic area because of the poor collateral circulation that has been described for the rabbit. Although this may account, in part, for the decreased tolerance of the heart to K^+, acid, and NE during ischemia, occlusion of the artery alone did not significantly alter hemodynamics, whereas the protective effect of NE was attenuated by occlusion.

Chronic ischemia, resulting in infarction of a portion of the left ventricular myocardium, clearly plays a role in reducing the effectiveness of NE during hyperkalemia and acidosis. This may be related to a reduction in the sensitivity of the heart to NE, thereby amplifying the negative cardiac effects of hyperkalemia and acidosis. Within the first 15 min of coronary arterial occlusion, the final lateral borders of an infarction are established (8). Reperfusion after 15- or 30-min occlusion of rabbit left circumflex coronary artery consistently produces subendocardial necrosis that results in an infarction size of 8 or 15% of the ventricle, respec-

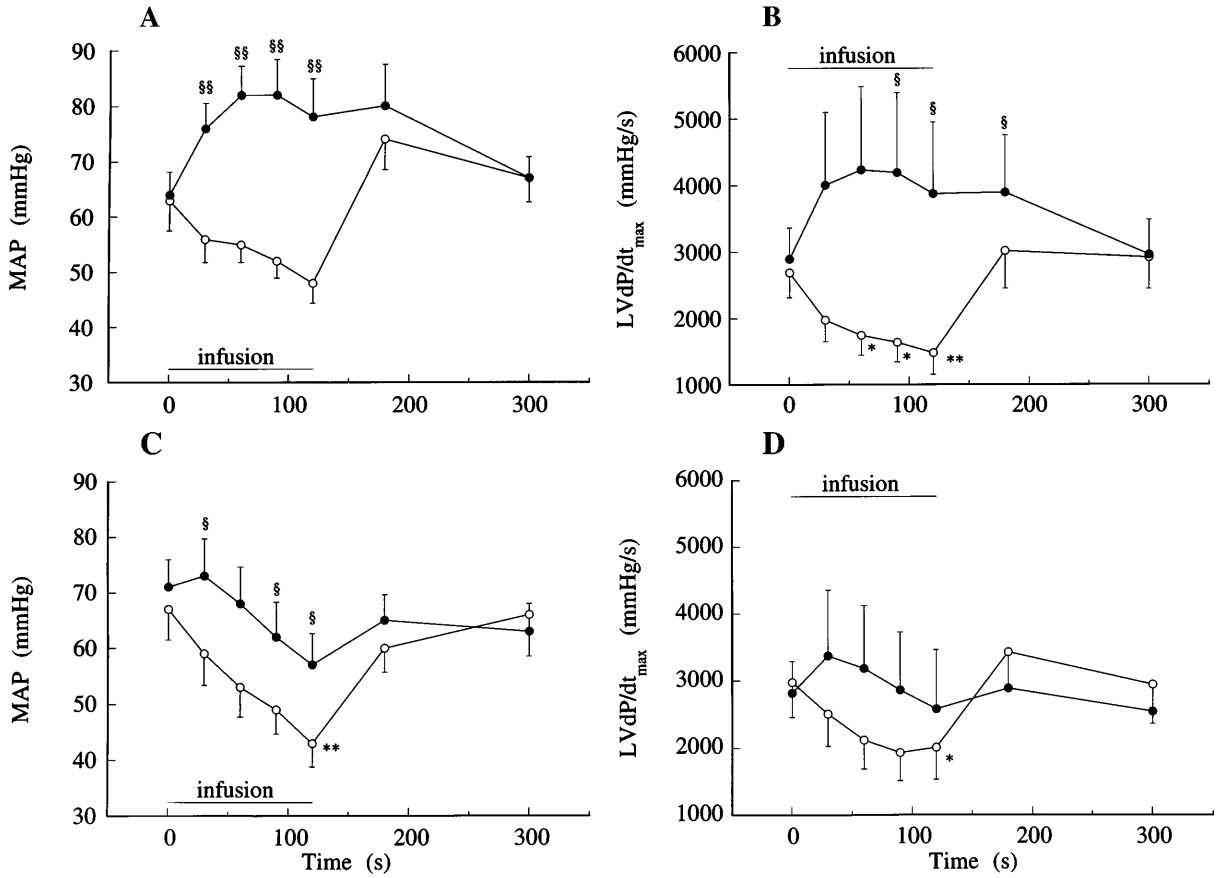

Fig. 4. Summary of results (n = 7 animals) for effect of a 20-min coronary occlusion on response to combined infusions of KCl and lactic acid (○) and KCl, lactic acid and NE (●). *A* and *B*: preocclusion responses. *C* and *D*: postocclusion responses. Note that period of occlusion did not result in altered baseline hemodynamics but attenuated protective effect of NE. LVdP/dt_{max}, maximum rate of pressure development in left ventricle. Significantly different: $^{*}P < 0.05$, $^{**}P < 0.01$ (ANOVA). $^{\S}P < 0.05$, $^{\S\S}P < 0.01$ (*t*-test).

tively. Even though reperfusion at 20 min rapidly reverses ECG segment depression, this is incomplete and suggests irreversible damage to cells in the ischemic area (7). Our protocol of 20-min ischemia is consistent with the intervention causing irreversible damage to a small area of ventricle.

The restorative action of catecholamines was substantially reduced and essentially ineffective in offsetting the depressive effects of hyperkalemia and acidosis (Fig. 4). This decreased effectiveness of the NE might be explained by a decrease in myofilament sensitivity to calcium, possibly due to activation of proteases by calcium overload during reperfusion (18).

Limitations of Study

Extrapolation of our results to a normal exercising subject is limited by the nature of our anesthetized, open-chest cardiac-denervated preparation. Clearly, there are multiple factors changing during exercise for which we have not controlled. In particular, peripheral and central neural activities as well as other chemical factors associated with exercise that were not simulated might have a bearing on our results. However, to test the hypothesis that myocardial ischemia may affect the efficacy of the protective effect of catecholamines on the heart during hyperkalemia and acidosis, it was necessary to delimit our protocol and study only the individual and collective effects of these factors. Therefore, our results may be related only to aspects of exercise, and thus further experiments are required to show their physiological significance.

Implications for Exercise in Ischemic Heart Disease

Most incidences of exercise- or stress-induced sudden cardiac death or myocardial infarction (21, 22) can be explained by an underlying cardiac pathology, where exercise is thought to amplify the negative effects of ischemia and infarction (2, 16). At rest, transient cardiac ischemia produces few arrhythmias (33), but occlusion of a coronary artery in dogs with a healed infarction 1 min before intense exercise was stopped and maintained for 1 min after exercise causes ventricular fibrillation (3). Furthermore, pretreatment with verapamil completely suppresses exercise-induced ventricular fibrillation in the dog, suggesting that the proarrhythmogenic effects of enhanced calcium entry are central to the development of ventricular fibrillation (2). However, unlike β-adrenergic antagonists, there is no compelling epidemiological evidence that

shows calcium-channel antagonists have a protective effect in patients' post-myocardial infarctions (13, 30).

Our results show that acute reversible ischemia, as well as infarction, disrupts the interplay among K^+, acid, and catecholamines. The decrease in functioning myocardial mass secondary to acute ischemia or infarction attenuates the protective effects of NE and enhances the negative inotropic effect of hyperkalemia and acidosis. Occasionally, these changes might provide a trigger for arrhythmogenesis and cardiac arrest. However, given the nature of our preparation, we cannot rule out the idea that exercise amplifies the negative cardiac effect of ischemia by enhancing the proarrhythmic nature of catecholamines (1).

In conclusion, our results confirm the protective role of NE in the structurally normal heart during hyperkalemia and acidosis and show that acute ischemia or a small infarction may offset this protection and increases the depressive effects of elevated K^+ and acid. Whether this process is relevant to exercise performance in subjects with ischemic heart disease or a healed infarction remains to be determined.

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REFERENCES

1. **Billman, G. E.** The antiarrhythmic and antifibrillatory effects of calcium antagonists. *J. Cardiovasc. Pharmacol.* 18: S107-S117, 1991.
2. **Billman, G. E.** Effect of calcium channel antagonists on susceptibility to sudden cardiac death: protection from ventricular fibrillation. *J. Pharmacol. Exp. Ther.* 248: 1334–1342, 1989.
3. **Billman, G. E., P. J. Schwartz, J. P. Gagnol, and H. L. Stone.** Cardiac response to submaximal exercise in dogs susceptible to sudden cardiac death. *J. Appl. Physiol.* 59: 890–897, 1985.
4. **Blake, J.** Observations on the physiological effects of various agents introduced into the circulation, as indicated by the haemadynamometer. *Edinb. Med. Surg. J.* 51: 330–345, 1839.
5. **Brock, J. A., and T. C. Cunnane.** Neurotransmitter release mechanisms at the sympathetic neuroeffector junction. *Exp. Physiol.* 78: 591–6614, 1993.
6. **Castleden, L. I. M.** The effect of potassium salts on cardiac irregularities. *Br. Med. J.* 1: 7–9, 1941.
7. **Coker, S. J.** Anesthetized rabbit as a model for ischemia- and reperfusion-induced arrhythmias: effects of quinidine and bretylium. *J. Pharmacol. Methods* 21: 263–279, 1989.
8. **Connelly, C., W. M. Vogel, Y. M. Hernandez, and C. S. Apstein.** Movement of necrotic wavefront after coronary artery occlusion in rabbit. *Am. J. Physiol.* 243 (*Heart Circ. Physiol.* 12): H682–H690, 1982.
9. **Corr, P. B., and R. A. Gillis.** Autonomic neural influences on the dysrhythmias resulting from myocardial infarction. *Circ. Res.* 43: 1–9, 1978.
10. **Gaskell, W. H.** On the tonicity of the heart and blood vessels. *J. Physiol. (Lond.)* 3: 48–75, 1880.
11. **Gettes, L. S.** Effect of ischaemia on cardiac electrophysiology. In: *The Heart and Cardiovascular System*, edited by H. A. Fozzard, E. Haber, R. B. Jennings, A. M. Katz and H. E. Morgan. New York: Raven, 1986, p. 1317–1341.
12. **Haft, J. I., and K. Fani.** Stress and the induction of intravascular platelet aggregation in the heart. *Circulation* 48: 164–169, 1973.
13. **Hansen, J. F.** Treatment with verapamil during and after an acute myocardial infarction: a review based on the Danish verapamil infarction trials I and II. *J. Cardiovasc. Pharmacol.* 18, *Suppl.* 6: S20–S25, 1991.
14. **Harris, A. S., O. Humberto, and A. J. Bocage.** The induction of arrhythmias by sympathetic activity before and after occlusion of a coronary artery in the canine heart. *J. Electrocardiol.* 4: 34–43, 1971.
15. **Hirche, H. J., C. Franz, L. Bos, R. Bissig, R. Lang, and M. Schramm.** Myocardial extracellular K^+ and H^+ increase and noradrenaline release as a possible cause of early arrhythmias following acute coronary artery occlusion in pigs. *J. Mol. Cell. Cardiol.* 12: 579–593, 1980.
16. **Hull, S. S., E. Vanoli, P. B. Adamson, R. L. Verrier, R. D. Foreman, and P. J. Schwartz.** Exercise training confers anticipatory protection from sudden death during acute myocardial infarction. *Circulation* 89: 548–552, 1994.
17. **Karlsberg, R. P., P. A. Penkoske, P. E. Cryer, P. B. Corr, and R. Roberts.** Rapid activation of the sympathetic nervous system following coronary artery occlusion: relationships to infarct size, site and haemodynamic impact. *Cardiovasc. Res.* 13: 523–531, 1979.
18. **Kusuoka, H., and E. Marban.** Cellular mechanisms of myocardial stunning. *Annu. Rev. Physiol.* 54: 243–256, 1992.
19. **Leitch, S. P., and D. J. Paterson.** Role of Ca^{2+} in protecting the heart from hyperkalaemia and acidosis in the rabbit: implications for exercise. *J. Appl. Physiol.* 77: 2391–2399, 1994.
20. **Medbo, J. I., and O. M. Sejersted.** Plasma potassium changes with high intensity exercise. *J. Physiol. (Lond.)* 421: 105–122, 1990.
21. **Mittleman, M. A., M. MacClure, J. B. Sherwood, R. P. Mulry, G. H. Tofler, S. C. Jacobs, R. Friedman, H. Benson, and J. E. Muller.** Triggering of acute myocardial infarction onset by episodes of anger. *Circulation* 92: 1720–1725, 1995.
22. **Mittleman, M. A., M. Maclure, G. H. Tofler, J. B. Sherwood, R. J. Goldberg, and J. E. Muller.** Triggering of acute myocardial infarction by heavy physical exertion. *New Engl. J. Med.* 329: 1677–1683, 1993.
23. **Miyazaki, T., and D. P. Zipes.** Presynaptic modulation of efferent sympathetic and vagal neurotransmission in the canine heart by hypoxia, high K^+, low pH, and adenosine. Possible relevance to ischaemia-induced denervation. *Circ. Res.* 66: 289–301, 1990.
24. **O'Neill, M., and D. J. Paterson.** Role of the sympathetic nervous system in cardiac performance during hyperkalaemia in the anaesthetised pig. *Acta Physiol. Scand.* 153: 1–11, 1995.
25. **O'Neill, M., D. M. Ryan, and D. J. Paterson.** Effect of verapamil on restoration of cardiac performance in raised $[K^+]_o$ by adrenergic stimulation in the rabbit. *Acta Physiol. Scand.* 154: 367–3766, 1995.
26. **Opie, L. H.** Calcium antagonists, ventricular arrhythmias, and sudden cardiac death: a major challenge for the future. *J. Cardiovasc. Pharmacol.* 18, *Suppl.* 10: S81–S86, 1991.
27. **Opie, L. H.** Metabolism of free fatty acids, glucose and catecholamines in acute myocardial infarction. Relation to myocardial ischaemia and infarct size. *Am. J. Cardiol.* 36: 938–953, 1965.
28. **Osnes, J.-B., and L. Hermansen.** Acid-base balance after maximal exercise of short duration. *J. Appl. Physiol.* 32: 59–63, 1972.
29. **Paterson, D. J., G. J. Blake, S. P. Leitch, S. M. Phillips, and H. F. Brown.** Effects of catecholamines and potassium on cardiovascular performance in the rabbit. *J. Appl. Physiol.* 73: 1413–1418, 1992.
30. **Poole-Wilson, P. A.** Angiotensin-converting enzyme inhibitors and calcium antagonists after acute myocardial infarction. *Am. J. Cardiol.* 75: 4E–9E, 1995.
31. **Ryan, D. M., and D. J. Paterson.** Restoration of cardiac contraction by angiotensin II during raised $[K^+]_o$ in the rabbit. *Acta Physiol. Scand.* 156: 419–427, 1996.
32. **Schömig, A.** Catecholamines in myocardial ischaemia. *Circulation* 82, *Suppl.* II: S13–S22, 1990.
33. **Vanoli, E., G. M. De Ferrari, M. Stramba-Badiale, S. S. Hull, R. D. Foreman, and P. J. Schwartz.** Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ. Res.* 68: 1471–1481, 1991.
34. **Wilde, A. A. M., R. J. G. Peters, and M. J. Janse.** Catecholamine release and potassium accumulation in the isolated globally ischaemic rabbit heart. *J. Mol. Cell. Cardiol.* 20: 887–896, 1988.
35. **Winbury, M. M., L. M. Hausler, N. A. Prioli, and L. Zitowitz.** Effect of epinephrine on cardiac rhythm in the miniature pig before and after coronary occlusion. *J. Pharmacol. Exp. Ther.* 138: 287–291, 1963.