Treating Ischemic Left Ventricular Dysfunction With Hypertonic Saline Administered After Coronary Occlusion in Pigs

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Objective(s): **The effects of hypertonic saline on ventricular function are controversial, whether it is increasing contractility or preload. There are no data, however, on the influence of hypertonic saline in a stunned myocardium.**

Design: **This study was prospective and randomized in order to analyze the effects of hypertonic saline solution (7.5%) on myocardial function and systemic hemodynamics in a porcine model of ischemia and reperfusion.**

Setting: **A university teaching hospital, animal research laboratory.**

Participants: **Twelve adult domestic swine.**

Interventions: **Myocardial stunning was produced by the complete occlusion of the proximal left anterior descending artery for 15 minutes followed by reperfusion. Five minutes after reperfusion, the animals were assigned to receive 4 mL/kg of hypertonic saline (n = 7) or normal saline (n = 5) over 10 minutes. Pressure-tipped catheters were placed in the left ventricular cavity and aorta. The dimensions of the left ventricle were measured with ultrasonic microcrystals. Cardiac output was measured with transit time ultrasound. Data were recorded continuously and compared before the occlusion, 5 minutes after reperfusion, and at the end of the infusion.**

Measurements and Main Results: **Compared with baseline, ventricular function was significantly depressed after left anterior descending artery occlusion. Left ventricular dP/dT and its end-systolic pressure-volume slope decreased (38% and 52%, respectively; $p < 0.05$), with a concomitant increase in systemic vascular resistance. The administration of hypertonic saline significantly improved left ventricular function (Emax 1,422 ± 198 mmHg/mL, and dP/dT 3.2 ± 0.4 mmHg/s *v* normal saline group values of 1,156 ± 172 and 2.5 ± 0.5, respectively; $p < 0.05$), cardiac output (2.5 ± 0.5 *v* 1.84 ± 0.4 L/min, $p < 0.05$), and lowered systemic vascular resistance (from 28.8 ± 2.3 to 23.5 ± 1.4, $p < 0.05$), with no significant changes with normal saline administration.**

Conclusions: **After transient myocardial ischemia, hypertonic saline administered over a short period of time acts as an inodilator by increasing contractility while simultaneously lowering systemic vascular resistance.**

KEY WORDS: ischemia, hypertonic, saline, coronary occlusion, myocardial stunning

TRANSIENT CORONARY ARTERY occlusion is associated with metabolic derangement that can prolong myocardial dysfunction.[1] Drug administration and manipulations that improve inotropic and/or vasodilatory properties have been shown to improve myocardial function without increasing oxygen consumption.[2,3] This protective effect is probably based on their ability to improve left ventricular (LV) performance and increase blood flow or supply to the ischemic myocardium.[3]

Other drugs like β-blockers are used to prevent and limit myocardial ischemic damage and improve perioperative outcome,[4] probably because of their ability to decrease myocardial oxygen demand. The beneficial effect as a result of decreased demand is an essential factor that has been shown in many studies evaluating the protective effect of drugs or manipulations with a positive effect on myocardial metabolism.[4-9]

The effects of manipulation by the administration of hypertonic solutions, such as hypertonic saline (HS), on myocardial contractility are controversial. Some studies suggest an increase in contractility,[10] whereas others show an improvement in ventricular function because of changes in preload rather than contractility.[11,12]

The direct effect of drugs (eg, inhalation anesthetics) or manipulation of coronary flow can influence not only myocardial oxygen supply but also alter coronary steal.[6] Previous animal studies showed that β-blockers can decrease lactate production and hemodynamic impairment caused by ischemia because of relative preservation of endocardial blood flow without steal.[9] During ischemia, HS may actually induce coronary steal due to its potential coronary flow effects; however, there are no data on the effects of HS on a stunned myocardium. Myocardial demand can be also influenced by drugs or manipulations that affect afterload. The vasodilatory effects of HS may be a mechanism whereby it would improve myocardial stunning. It is anticipated that afterload reduction would be a primary benefit from HS administration.

This study examined the effects of HS (7.5%) on global LV function and systemic hemodynamics in a stunned myocardium after temporary coronary occlusion in a porcine model. It was hypothesized that HS may be beneficial because of its ability to improve myocardial function as a result of increased myocardial oxygen supply as well as decreased demand.

METHODS

The protocol was approved by the Institutional Animal Care and Use Committee. The use of animals was in accordance with the guidelines established by the animal research division. Animals were handled in accordance with guidelines established by the National Institutes of Health (NIH publication 85-23, revised 1985).

Twelve domestic swine weighing 30 to 35 kg were premedicated with intramuscular ketamine (35 mg/kg) and anesthetized with isoflurane in 100% oxygen. A tracheostomy was then performed and the animals mechanically ventilated at 12 breaths/min, with tidal volumes of 12 mL/kg, to maintain an end-tidal CO_2 between 32 and 36 mmHg.

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Anesthesia and mechanical ventilation were maintained with the use of a Narkomed 4 anesthesia machine (North American Dräger, Telford, PA). Pancuronium was used for muscle relaxation only to facilitate the surgical preparation. A 7F pressure-tipped, flotation pulmonary artery catheter (Millar Instruments Inc, Houston, TX) was inserted via the right internal jugular vein into the main pulmonary artery through an 8F Cordis introducer (Arrow International, Reading, PA). A 7F triple-lumen, central venous catheter was placed through the left internal jugular vein. The left carotid artery was exposed, and a 5F pressure-tipped catheter (Millar Instruments Inc) was placed and advanced into the ascending aorta for continuous arterial pressure monitoring. A median sternotomy was then performed and the heart placed in a pericardial cradle. A 5F pressure-tipped catheter was inserted via a small stab wound in the apex into the LV cavity for measurement of LV pressure.

The left anterior descending (LAD) coronary artery was isolated proximal to the first major branch running diagonally and loosely encircled with a cardiac pacing wire ligature.[3] Ultrasonic flow probes were placed in the ascending aorta and distal LAD artery. An aneroid constrictor was placed in the LAD between the first and second diagonal arteries. Two pairs of ultrasonic dimension tranducers were placed in the subendocardium on the short axis proximal to an LAD artery occluder and the long axis of the LV. The inferior vena cava was encircled with an umbilical tape to produce acute reductions in preload.

Maintenance of intravascular volume was accomplished with lactated Ringer's solution administered by continuous infusion through a peripheral vein at a rate of 10 mL/kg/h. Normothermia (pulmonary artery temperature of 37°C) was maintained by the application of a warming blanket. All animals were allowed to stabilize for 1 hour after the surgical preparation prior to data collection.

Hemodynamic measurements included systemic arterial pressure, pulmonary artery pressure, LV pressure, central venous pressure, cardiac output (CO), left ventricular pressure first-time derivative (LV dP/dT). Electrocardiogram (standard lead II) and heart rate findings were recorded continuously, and CO was measured with transit time ultrasound in the ascending aorta. Pulmonary and systemic vascular resistances were calculated by using standard formulas[13]: PVR = MPAP − PAOP/CO and SVR = MAP − CVP/CO using Wood units in dyne/sec/cm^3, where MPAP = mean pulmonary artery pressure, CO = cardiac output, SVR = systemic vascular resistance, MAP = mean arterial pressure, and CVP = central venous pressure. All transducers were connected to a biomedical amplifier (Grass model 7D; Grass Instruments Co, Quincy, MA). The signals were digitized and continuously recorded at 200 Hz on a personal computer for later analysis (Sonometrics Corp, London, Ontario, Canada).

Left ventricular volumes were derived automatically by changes in dimension determined from sonomicrometry in the long and short axes. The formula of an ellipsoid was assumed, using commercially available software (Sonometrics Corp). The slope of the LV end-systolic pressure-volume relationship (Emax) was calculated. The study used measurements of Emax and dP/dT as contractility parameters. Emax is a relatively load-independent index of contractility, whereas dP/dT is afterload dependent.

A constrictor was placed on the LAD between the first and second diagonal arteries. Ischemia was produced by reducing the flow in the LAD by approximately 80% to 100%. This was very comparable to previous and similar model studies of coronary stenosis, which created similar hemodynamic and metabolic changes in dogs[3,4,6-9] and pigs.[5] Flow meter probes were placed on the aortic root and the LAD artery for cardiac output and coronary flow measurements.

Two pairs of ultrasonic dimension transducers were placed in the subendocardium on the short axis proximal to an LAD artery occluder and the long axis of the LV. During each period of data collection, the inferior vena cava was constricted with umbilical tape for approximately 6 to 8 beats in order to construct a series of pressure-volume loops. Emax was then determined using commercial software (Sonometrics Corp).

Ischemia was produced by reducing the flow in the LAD artery by approximately 80% to 100%. The mid-LAD artery was occluded for 15 minutes followed by reperfusion. Measurements were taken during 4 time periods: baseline, end of ischemia, 5 minutes after reperfusion, and at the conclusion of the infusion.

After reperfusion of the LAD artery, the animals were selected to receive 4 mL/kg of 7.5% saline (HS group, n = 7) or the same volume of normal saline (NS or control group, n = 5) infused via a central venous catheter over 10 minutes. Animals were assigned randomly to each group. The surgical fluid preparation, data collection, and data analysis were performed by different team members who were blinded and separate from one another.

Values were expressed as mean ± standard deviation. A 2-way analysis of variance was used, followed by a Student Newman-Keuls test for multiple comparisons. Results are expressed as mean ± standard deviation; $p < 0.05$ was considered statistically significant.

RESULTS

Baseline hemodynamic data and LV function were similar between groups (Table 1 and Fig 1). Coronary occlusion produced myocardial ischemia with a significant impact on CO, left ventricular end-diastolic pressure, and contractility (dP/dT and Emax) (Table 1 and Fig 1). During LAD occlusion and early reperfusion, contractility and CO were significantly depressed, and heart rate and SVR increased in both groups (Table 1). Compared with baseline, ventricular function was significantly depressed after LAD occlusion. Left ventricular dP/dT and Emax decreased (38% and 52%, respectively; $p < 0.05$) with a concomitant increase in SVR.

After HS, but not NS administration, contractility (dP/dT and Emax) (Fig 1) and CO (Table 1) improved significantly with a concomitant reduction of SVR (Table 1). The administration of HS significantly improved LV function (Emax 1,422 ± 198 mmHg/mL and dP/dT 3.2 ± 0.4 mmHg/s *v* normal saline group values of 1,156 ± 172 and 2.5 ± 0.5, respectively; $p < 0.05$), cardiac output (2.5 ± 0.5 *v* 1.84 ± 0.4 L/min, $p < 0.05$), and lowered SVR (from 28.8 ± 2.3 to 23.5 ± 1.4 dyne/sec/cm^3, $p < 0.05$), with no significant changes with normal saline. Mean blood pressure was reduced after HS infusion compared with the control and ischemic period values (Table 1).

DISCUSSION

The main finding in this study was that HS is beneficial in treating a stunned myocardium after transient ischemia when compared with normal saline because of its ability to improve myocardial function as well as decreasing afterload. The only other study using hypertonic solutions for acute myocardial ischemia and reperfusion could not show improvement in ventricular function and contractility.[11] However, in that study, HS was given before myocardial ischemia, and prevention of myocardial deterioration is a different issue from restoration and reversal of deterioration. The results of the present study showed that under general anesthesia, during ischemic cardiac dysfunction after transient coronary insufficiency, the use of HS was associated with an improved profile of ventricular function and systemic hemodynamics. The administration of

Table 1. Measured and Calculated Hemodynamic and Contractility Data in Different Stages

	Baseline		Ischemia		Early Reperfusion		Postinfusion	
	Control	HS	Control	HS	Control	HS	Control	HS
Measured hemodynamic variables								
HR (beats/min)	112 ± 20*	110 ± 23*	135 ± 22	132 ± 28	130 ± 18	128 ± 20	127 ± 10	127 ± 22
MBP (mmHg)	62 ± 12	68 ± 10	68 ± 18	63 ± 14	65 ± 17	64 ± 19	67 ± 10	56 ± 12*
CO (L/min)	2.4 ± 0.6	2.7 ± 0.5*†	1.7 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.5	1.8 ± 0.4	2.5 ± 0.5‡†
LVEDP (mmHg)	5 ± 3*	6 ± 3*	18 ± 7	17 ± 10	15 ± 8	17 ± 5	14 ± 5	12 ± 5†
CVP (mmHg)	10 ± 2	12 ± 4	14 ± 3	9 ± 5	11 ± 3	12 ± 4	10 ± 4	14 ± 2
Calculated hemodynamic variables								
SVR (dyne/sec/cm^3)	26.2 ± 1.9	27.2 ± 2.3	30.2 ± 2.5	31.0 ± 2.1	29.4 ± 1.8	28.8 ± 2.3	28.8 ± 2.0	23.5 ± 1.4*

NOTE. Measurements taken during 4 time periods: baseline, end of ischemia, 5 minutes after (=early) reperfusion, and at the conclusion (=post) of the infusion, with saline preload (group C) or HS preload (group HS). Each animal received 4 mL/kg of 7.5% saline (HS group, n = 7) or normal saline (control group, n = 5). Data expressed as mean values ± SD of the mean.

Abbreviations: HS, hypertonic saline; HR, heart rate; MBP, mean blood pressure; CO, cardiac output; LVEDP, left ventricular end-diastolic pressure; SVR, systemic vascular resistance; CVP, central venous pressure.

*$p < 0.05$ compared with all other periods in the same group.

†$p < 0.05$ compared with ischemia and early reperfusion period in the same group.

‡$p < 0.05$ compared with the same period in the control group.

HS during early reperfusion was associated with improved contractility and decreased SVR. In contrast, the use of a similar preload volume of saline did not change cardiac dysfunction. Hypertonic saline may thus be preferable to isotonic saline solutions in surgical patients with postischemic myocardial dysfunction who require intravenous fluid replacement.

The limitations of this study involve the short-term effects evaluated because fluid load was limited (4 mL/kg), and the

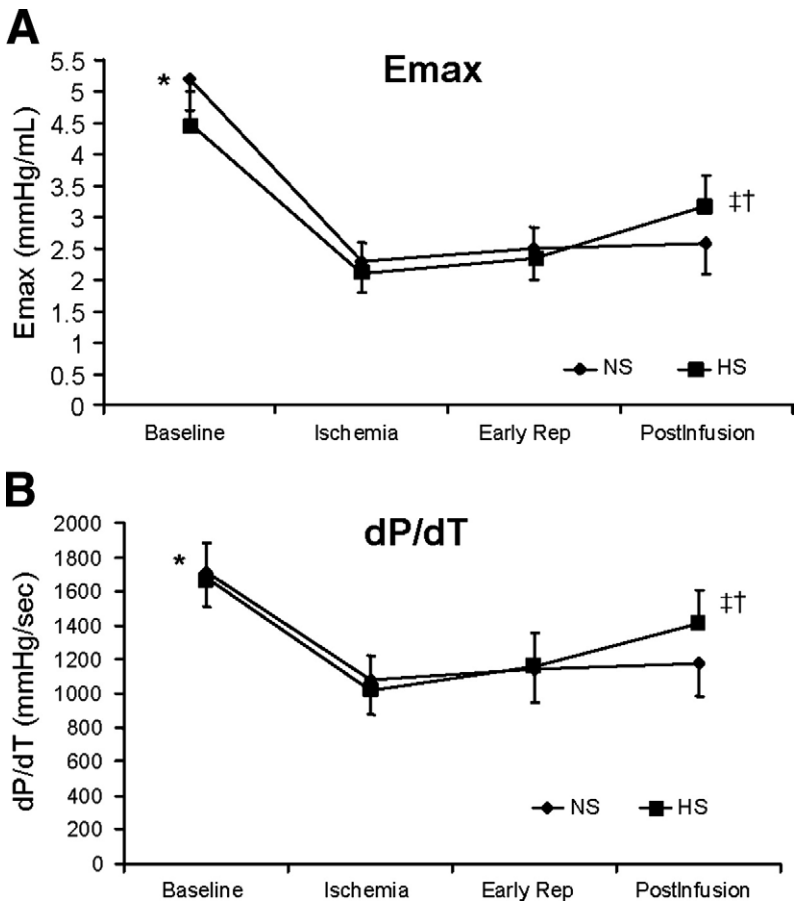

Fig 1. (A) Measured load-independent contractility (Emax) in different stages. Measurements were taken during 4 time periods: baseline, end of ischemia, 5 minutes after (=early) reperfusion, and at the conclusion (=post) of the infusion, with saline preload (group C) or hypertonic saline (HS) preload (group HS). Each animal received 4 mL/kg of 7.5% saline (HS group, n = 7) or normal saline (NS) (control group, n = 5). (B) Measured load-dependent contractility (dP/dT) in different stages. Measurements were taken during 4 time periods: baseline, end of ischemia, 5 minutes after (=early) reperfusion and at the conclusion (=post) of the infusion, with saline preload (group C) or hypertonic saline preload (group HS). Each animal received 4 mL/kg of 7.5% saline (HS group, n = 7) or normal saline (NS) (control group, n = 5). Early Rep, early reperfusion. *$p < 0.05$ compared with all other periods in the same group. †$p < 0.05$ compared with ischemia and early reperfusion periods in the same group. ‡$p < 0.05$ compared with same period in the control group.

immediate time period (10 minutes) tested after ischemia and reperfusion was brief. However, the benefits of this specific study are also related to the minimal volume load required and the immediate, rather than the long-term, effects on the hemodynamics of an ischemic myocardium during reperfusion. Despite demonstrating inodilator properties by HS, the main goal of this study was not to compare HS with any vasodilator but with a similar volume load of crystalloid. There is clinical importance related to the type and volume of fluid required during cardiac procedures in acute ischemic and immediate reperfusion conditions (eg, during off-bypass cardiac procedures in ischemic and hypovolemic patients).

In the postischemic study, increased myocardial performance with a concomitant decrease of calculated SVR were noted. Decreased calculated SVR could be caused by increased CO but also by directly decreased oxygen demand, with reduction of systemic pressures (MAP postinfusion period, Table 1). The benefit of using a limited volume of preload in ischemic patients can contribute to decreased demand. The decreased afterload (SVR) and lower filling pressures (left ventricular enddiastolic pressure) may produce a decreased level of demand. The consistency of the HS solution may preserve myocardial cellular integrity as well as function and supply. The preservation of contractility (Emax and dP/dT) and CO shown could be the result of increased supply.

Decreased demand is an essential factor in many studies evaluating the protective effect of drugs or manipulations that show a positive effect on myocardial O_2 and lactate metabolism.[4-9] Compared with isotonic solutions, the lesser volumes of hypertonic solutions are associated with equivalent or improved systemic blood pressure, CO, and survival in experimental animals.[14] This is a valuable clinical advantage in treating ischemic cardiac patients. Similar findings were noted in a comparison of 7.5% HS and normal saline administered to patients undergoing elective surgical correction of chronic dissecting thoracic and abdominal aortic aneurysms.[15] Patients who received HS over a 10-minute period immediately after aortic unclamping maintained higher pulmonary arterial and wedge pressures, higher cardiac index, and lower SVR than those who received an equal volume of normal saline during the same time period. In another study, the use of 7.5% HS, in combination with 4.2% dextran 70, administered during air ambulance transport, improved hemodynamic function and appeared to enhance survival in severely injured patients compared with using lactated Ringer's solution,[16] whereas the volumes of HS infused were almost half. Resuscitation with a small volume of hypertonic-hyperoncotic solution in experimental hemorrhagic shock allowed the recovery of systemic and splanchnic hemodynamic and oxygen transport, without an increase in pulmonary artery pressure.[17] In the combat environment, it would be reasonable to believe that small-volume fluid resuscitation can be performed with hypertonic solutions.[18]

Hypertonic saline solutions have been proven to be beneficial during resuscitation from shock and trauma and in many major surgical procedures (eg, aortic reconstructive and radical cancer surgery) or in any procedure in which extensive blood loss and fluid shifts may be anticipated, including the treatment of shock.[15,19] Because the osmolality of the administered solution exceeds that of intracellular water and sodium, and chloride ions cannot freely cross cell membranes, the extracellular fluid becomes slightly hyperosmolar. A gradient for water to pass from the cells into the extravascular compartment is established, and the extracellular volume is expanded by approximately 2.5 L after the infusion of 1 L of hypertonic saline.[20,21] Because electrolytes freely cross capillary membranes, the fluid is divided between the intravascular and extravascular compartments according to their relative volumes.[22] Although hypertonic saline solutions increase the intravascular volume more than would the same volume of a balanced salt solution, they do so at the expense of a decreased intracellular volume.[23] If large volumes of previously administered balanced electrolyte solutions have already increased intracellular volume (and most solutions used are, in effect, slightly hypotonic), hypertonic saline is therapeutic as a reduction agent in perioperative fluid gain and peripheral or intracellular edema. Thus, hypertonic solutions can restore and preserve intracellular (including myocardial cell) volume and consistency and the myocyte activity associated with it. Ischemic cells should benefit from the enhanced restoration of normal cellular volume and transmembrane potential, indicating a reversal of the cellular abnormalities induced by the insult.[24]

This study did not measure regional myocardial blood flow and did not determine myocardial oxygen supply and demand. However, HS has been shown to improve myocardial blood flow during cardiopulmonary resuscitation.[19] The mechanism by which hypertonic solutions may be beneficial to insulted cardiac tissue is probably similar to that for insulted brain tissue.[25-27] Similar findings of preserving cerebral blood flow were reported when 10% or 7.5% saline was administered to stroke and post-traumatic patients with significantly increased intracranial pressure who were resistant to mannitol.[28,29]

This combined effect on demand and supply may be similar to the known protective effect of preoperative treatment with β-blockers (decreasing consumption and demand) in combination with the known protective effect of preischemic treatment with PDE inhibitors (reversing myocardial depression and increasing supply).[5] On the other hand, β-adrenergic agonists, which are commonly used in cardiac patients to increase contractility, thereby reversing myocardial depression during ischemia while increasing demand (or without decreasing demand), may not be beneficial. Thus, the relative advantage of using a solution like HS is in avoiding the use of cardiac agonists.

This study also did not evaluate survival. However, 7.5% HS appears to be more effective with respect to survival than 0.9%, 5%, or 10% saline solutions. Similar results were found after resuscitation with hypertonic sodium lactate (500 mOsm/L) and lactated Ringer's solution in patients undergoing major cardiovascular (aortic reconstructive) surgery.[30]

On the "downside" are reports comparing HS and normal saline resuscitation in experimentally produced, controlled, and uncontrolled hemorrhagic shock. When hemorrhage was controlled, hypertonic resuscitation was superior to isotonic, as has been shown in most other studies. When uncontrolled hemorrhage was present, however, survival was significantly reduced in the hypertonic group.[31,32] Thus, under conditions of "uncontrolled" hemorrhage, when surgical bleeding causes hemodynamic instability, the use of HS is not recommended.

This study evaluated only the short-term effects of HS, thus avoiding the potential complications of long-term, continuous, or repeated HS administration. Using lesser volumes in this study (4 mL/kg) was advantageous[14] in reaching short-term hemodynamic goals without getting into long-term complications. The complication of major concern with continuous large volume administration is the potential development of hypernatremia. However, complications associated with hypernatremia have not been reported in clinical trials or in any case in which careful monitoring of serum sodium was used. Hypernatremia, when it occurs, is usually transient. Other concerns, in addition to hypertonicity, are hyperchloremic acidosis and the risk of central pontine myelinolysis. The latter worry appears groundless and is apparently related to chronically hyponatremic patients following too rapid a correction (>2 mEq/h). Concerns about hyperchloremic metabolic acidosis also appear to be unwarranted. Current evidence suggests that substitution of acetate for chloride does not improve resuscitation outcome in experimental animals, although the pH tends to be more normal.[33]

In conclusion, this study has potential clinical applications (eg, during off-pump myocardial revascularization) when temporary coronary artery occlusion is performed. Hypertonic saline administration should strongly be considered in patients with acute ischemic LV dysfunction and before other inotropic drugs, such as β-adrenergic stimulants, or large volume of crystalloids are used. Hypertonic saline should be considered in patients with coronary artery disease and myocardial ischemia because it improves ventricular function and can protect against myocardial ischemia, without increasing myocardial demand. The recommendation derived from this study is that the administration of a limited (4 mL/kg) load of HS for a short period (10-15 minutes), not given in a continuous, long-term infusion or during uncontrolled hemorrhage or unstable hemodynamic conditions, can be beneficial in patients with postischemic dysfunction who require limited volume replacement. The data suggest that further research on the use of HS in cardiac surgical patients is worthwhile.

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