Cariporide enables hemodynamically more effective chest compression by leftward shift of its flow-depth relationship

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Cariporide enables hemodynamically more effective chest compression by leftward shift of its flow-depth relationship. Am J Physiol Heart Circ Physiol 288: H2904–H2911, 2005. First published February 11, 2005; doi:10.1152/ajpheart.01181.2004.—When given during closed-chest resuscitation, cariporide (4-isopropyl-methylsulfonylbenzoyl-guanidine methanesulfonate; a selective inhibitor of the Na+/H+ exchanger isofrom-1) enables generation of viable perfusion pressures with less depth of compression. We hypothesized that this effect results from greater blood flows generated for a given depth of compression. Two series of 14 rats each underwent 10 min of untreated ventricular fibrillation followed by 8 min of chest compression before defibrillation was attempted. Compression depth was adjusted to maintain an aortic diastolic pressure (ADP) between 26 and 28 mmHg in the first series and between 36 and 38 mmHg in the second series. Within each series, rats were randomized to receive cariporide (3 mg/kg) or NaCl (0.9%; control) before chest compression was started. Blood flow was measured using 15-μm fluorescent microspheres. Less depth of compression was required to maintain the target ADP when cariporide was present in both series 1 (13.6 ± 1.2 vs. 16.6 ± 1.2 mm; P < 0.001) and series 2 (15.3 ± 1.0 vs. 18.9 ± 1.5 mm; P < 0.001). Despite less compression depth, the cardiac index in cariporide-treated rats was comparable to control rats in series 1 (11.1 ± 0.7 vs. 11.3 ± 1.4 ml·min⁻¹·kg⁻¹; P = not significant) but higher in series 2 (15.5 ± 2.3 vs. 9.9 ± 1.4 ml·min⁻¹·kg⁻¹; P < 0.05). Increases in compression depth (from series 1 to series 2) increased myocardial, cerebral, and adrenal blood flow in cariporide-treated rats. We conclude that cariporide enhances the efficacy of chest compression by leftward shift of the flow-depth relationship.

ventricular fibrillation; cardiopulmonary resuscitation; defibrillation; sodium-hydrogen antiporter; fluorescent microspheres

Despite efforts to promote adequate forward blood flow during closed-chest resuscitation, the flow generated rarely exceeds 20% of the resting cardiac output and often fails to meet the metabolic requirements for successful cardiac resuscitation (9, 10, 27). Interventions that could enhance forward blood flow during closed-chest resuscitation are thus actively sought. To this end, insights on the mechanisms by which blood flow is generated during closed-chest resuscitation may help identify strategies for enhancing such blood flow. Clinical and experimental studies agree that a cardiac pump is a predominant mechanism in which forward blood flow results fully or partly from direct compression of the heart between the sternum and the spine (8, 28, 29, 32). This mechanism suggests that factors that determine blood flow in normally beating hearts may also play a role during chest compression. Studies with animal models have shown a direct relationship between forward blood flow and depth of compression (3, 4). However, this flow is limited by a maximum compression depth beyond which there is no additional hemodynamic benefit but disproportionate risk of injury to the chest wall and intrathoracic visera (24, 25, 31). Thus chest compression seems to operate within a very limited flow-depth relationship. In addition, recent observations of animal models and human victims of cardiac arrest demonstrate that ischemic contracture develops during closed-chest resuscitation and leads to progressive left ventricular (LV) wall thickening and reductions in ventricular cavity size, which in turn limit ventricular preload, forward blood flow, and the perfusion of vital organs (2, 14, 22, 39). This phenomenon may in part explain the time-dependent reductions in the hemodynamic efficacy of closed-chest resuscitation (35). In humans, ischemic contracture has been described as myocardial firmness and found to compromise resuscitability (39).

We recently reported that ischemic contracture can be minimized by inhibition of the Na+/H+ exchanger isofrom-1 (NHE-1) using cariporide (4-isopropyl-methylsulfonylbenzoyl-guanidine methanesulfonate; Refs. 2, 13). We therefore reasoned that if cariporide can prevent ischemic contracture (thus preserving ventricular cavity size), it could lead to hemodynamically more efficient closed-chest resuscitation and thereby enable greater forward blood flow to be generated for a given depth of compression. To test this hypothesis, we used a rat model of ventricular fibrillation (VF) and closed-chest resuscitation in which systemic and regional blood flows were measured using fluorescence microspheres (15, 16, 30, 41, 42). The depth of chest compression was adjusted to attain pre-determined aortic diastolic pressures in rats randomized to receive either cariporide or 0.9% NaCl immediately before chest compression was started.

METHODS

These studies were approved by our Institutional Animal Care and Utilization Committee and were conducted in accordance with institutional guidelines.

Animal preparation. Twenty-eight adult male Sprague-Dawley rats (body wt, 477–560 g) were anesthetized with pentobarbital sodium (loading dose, 45 mg/kg ip; maintenance dose, 10 mg/kg ip every 30 min). Core temperature was maintained between 36.5 and 37.5°C with
an infrared heating lamp. A 5-Fr cannula was orally advanced into the trachea and used for positive-pressure ventilation during cardiac resuscitation and the postresuscitation interval. Proper placement was verified using an infrared CO₂ analyzer (CO₂SMO model 7100; Novametrix Medical Systems). A polyethylene (PE)-50 catheter was advanced through the right carotid artery into the left ventricle for measurement of pressure and injection of fluorescent microspheres. The tip of the catheter was positioned at = 4 mm from the aortic valve guided by pressure waveforms. Additional PE-50 catheters were advanced through the left femoral artery into the abdominal aorta for monitoring aortic pressure and through the right femoral artery into the descending thoracic aorta for blood withdrawal after injection of microspheres (reference organ). PE-50 catheters were also advanced through the left femoral vein into the right atrium for pressure measurement and through the right femoral vein into the inferior vena cava for blood infusion. A lead II ECG was recorded using subcutaneous needles. A 3-Fr catheter (C-PUM-301J; Cook) was advanced through the right external jugular vein into the superior vena cava, and a precurved guide wire was advanced through its lumen into the right ventricle. The guide wire was used for electrical induction of VF. A bolus of heparin sodium (600 IU/kg) was administered at the end of each experiment. After each experiment, these pressures were measured at the end of chest compression, these pressures were measured at the end of chest compression. The lower withdrawal rate during chest compression was possible given the lesser tracer dilution in low-flow states. The pressure in the withdrawal line was monitored continuously to verify uninterrupted blood withdrawal. Reference blood samples were also transferred to SPUs, and the remnant microspheres were flushed into the SPU using 0.02% Tween 80. In preliminary studies, dilution curves were constructed by measuring microsphere fluorescence in the reference organ at 30-s intervals. From these curves, we determined that collection times of 4.0 min during spontaneous circulation and 5.5 min during chest compression sufficed to sample >95% of the injected microspheres. An equal amount of blood from a same-colony donor rat was infused concurrently into the inferior vena cava.

The heart, brain, kidneys, and adrenal glands were removed after completion of the experiment and fixed in 10% formalin for 48 h. Organs were then freed from fatty and connective tissues. The atria and the right ventricle were removed, thereby isolating the left ventricle for processing. The cerebellum and midbrain were removed to isolate each cerebral hemisphere for processing. The kidneys and adrenal glands were processed intact. The samples or organs were weighed and placed in individual SPUs.

The samples were processed at the Institute for Surgical Research in Munich, Germany by Dr. Eckart Thein using a previously reported robotic processing system (42). The process entailed isolation of microspheres by tissue digestion and filtration and subsequent dissolution of microspheres in organic solvent to release the fluorescent dye. The fluorescence intensities measured in samples with equal solvent volumes (representing the total number of microspheres in the sample) were used to calculate the various rates of regional blood flow according to

\[ Q_{o} = \frac{F_{o}}{F_{ref}} \times Q_{ref} \]  

where \( Q_{o} \) is the organ/tissue fluorescence, \( F_{o} \) is the reference organ blood fluorescence, and \( Q_{ref} \) is the reference organ blood flow (in ml/min).

For cardiac output measurement, the organ/tissue of unknown flow becomes the whole body (total flow). Its fluorescence, which was determined from the injected microspheres, was calculated according to

\[ Q_{o} = \frac{F_{o}}{F_{ref}} \times Q_{ref} \]  

where \( F_{o} \) is the organ/tissue fluorescence, \( F_{ref} \) is the reference organ blood fluorescence, and \( Q_{ref} \) is the reference organ blood flow (in ml/min).


**Enhanced Flow-Depth Relationship by Cariporide**

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Compression depth measurements. For the first series (see Experimental series), compression depth was measured at the end of the resuscitation protocol recording the maximum piston displacement. For the second series, a displacement transducer (DSPL; World Precision Instruments) was incorporated to enable continuous monitoring of piston displacement.

VF and resuscitation protocols. VF was induced by delivering a 60-Hz alternating current to the right ventricular endocardium (1.0–6.0 mA) for an uninterrupted interval of 3 min (44). After 10 min of untreated VF, chest compression was started using an electronically controlled and pneumatically driven (50 psi) chest compressor (CJ-80623; CJ Enterprises) set to deliver 200 compressions/min with a controlled and pneumatically driven (50 psi) chest compressor (CJ-80623; CJ Enterprises) set to deliver 0.39 ml/100 g body wt of 100% oxygen every two compressions. Defibrillation was attempted at 8 min of chest compression by delivering a maximum of two 2-J monophasic transthoracic shocks (Lifepak 9P; Physio-Control). If VF persisted or an organized rhythm with a mean aortic pressure of ≤25 mmHg ensued, chest compression was resumed for 30 s. The defibrillation-compression cycle was repeated up to three additional times, increasing the energy of individual shocks (if VF persisted) to 4 J and then to 8 J for the last two cycles. Successful resuscitation was defined as the return of an organized cardiac rhythm with a mean aortic pressure of ≥60 mmHg for ≥5 min. Rats were monitored for a maximum of 120 min postresuscitation.

Experimental series. Two series were conducted, each of which included 14 rats. The depth of compression was adjusted to maintain a target aortic diastolic pressure between 26 and 28 mmHg in series 1 and between 36 and 38 mmHg in series 2. These levels promoted coronary perfusion pressures that exceeded the 20-mmHg threshold for successful resuscitation in rats (44). In both series, rats were randomized to receive a 3-mg/kg bolus of cariporide dissolved in 0.9% NaCl or an equal amount of 0.9% NaCl (control) into the right atrium immediately before chest compression was started. Cariporide (Aventis Pharma Deutschland) is a highly selective NHE-1 inhibitor with no apparent effects on the Na+/Ca2+ exchanger or fast Na+ currents at levels not exceeding 10 μmol/l (34).

Statistical analysis. Differences between groups for continuous variables were analyzed using one-way ANOVA. Alternative non-parametric tests were used if the data failed the tests for normality or equal variance. Categorical variables were analyzed using Fisher exact test. The data are presented as means ± SD unless stated otherwise. A two-tail value of P < 0.05 was considered significant.

RESULTS

Baseline measurements were comparable within and between series with the exception of blood flow to the right cerebral hemisphere, which was ≈24% lower than blood flow to the left cerebral hemisphere. Differences of varying magnitude persisted during chest compression and postresuscitation and were attributed to ligation of the right carotid artery needed for vascular access to the left ventricle.

Depth of compression. Chest compression, which was started after the 10-min interval of untreated VF, gradually increased the aortic diastolic pressure and reached the target levels of 26–28 mmHg in series 1 and 36–38 mmHg in series 2 by minute 2 of chest compression. The compression depth required to maintain such levels was significantly less in rats treated with cariporide (Fig. 1). The effects on coronary perfusion pressure are shown in Fig. 2. In series 1, the coronary perfusion pressure remained stable throughout chest compression at levels that were similar in both groups. In series 2, a higher coronary perfusion pressure was initially generated as planned. However, numerical declines in coronary perfusion pressure that did not reach statistical significance were observed beyond minute 5 of chest compression in control rats despite continuous increases in the depth of compression (Fig. 3). The maximally allowed piston travel of 20 mm was reached in four control rats but in none of the cariporide-treated rats.

Effects on blood flow. Figure 4 depicts the effects on systemic and regional blood flow during chest compression. As shown (Fig. 4, top left), the presence of cariporide in series 1 allowed generation of cardiac indices comparable to those generated in control rats (11.1 ± 0.7 vs. 11.3 ± 1.4 ml·min⁻¹·kg⁻¹; P = not significant [NS]) but with significantly less depth of compression. In series 2, the presence of cariporide allowed generation of higher cardiac indices (15.5 ± 2.3 vs. 9.9 ± 1.4 ml·min⁻¹·kg⁻¹; P < 0.05 by one-way ANOVA) also with significantly less depth of compression. The systemic vascular resistance (Fig. 4, top right) was comparable in both treatment groups in series 1 but was numerically higher in control rats in series 2. Thus there was no evidence that cariporide increased systemic vascular resistance. Like the effects on cardiac index, cariporide enabled blood flow to the left ventricle, kidneys, cerebral hemispheres, and adrenal glands to be generated with less depth of compression. Increasing the depth of compression in cariporide-treated rats was accompanied by statistically significant increases in blood flow to the left ventricle, cerebral hemispheres, and adrenal glands and numerical increases in blood flow to the kidneys. In control rats, there were numerical increases (P = NS) in blood flow to left ventricle, cerebral hemispheres, and left adrenal gland with statistically significant increases in blood flow to the right adrenal gland. Blood flow to the kidneys was numerically decreased.

All rats in series 1 were successfully resuscitated and all but one control rat survived for 120 min postresuscitation. In series
2, all cariporide-treated but only five control rats were successfully resuscitated and survived the postresuscitation interval (Table 1). As previously reported (13), spontaneous defibrillation occurred in seven cariporide-treated rats in series 1 after 6.8 ± 1.3 min of chest compression and in six cariporide-treated rats in series 2 after 5.5 ± 1.3 min of chest compression. In control rats, spontaneous defibrillation occurred in one rat in series 1 after 6.8 min of chest compression and in two rats in series 2 after 6.7 ± 0.2 min of chest compression. As a result, cariporide-treated rats had a shorter duration of VF and required fewer electrical shocks and less cumulative energy for successful resuscitation (Table 1).

Postresuscitation (Figs. 5 and 6), lower cardiac index with reduced LV function was documented in both series without significant differences among groups. Cariporide-treated rats, however, had higher mean aortic pressures in series 1 and lower LV end-diastolic pressures in both series (Fig. 5). Blood flow was preferentially distributed to heart and brain but without significant differences among groups (Fig. 6).

**DISCUSSION**

The present studies demonstrate capability of the NHE-1 inhibitor cariporide to enhance the hemodynamic efficacy of closed-chest resuscitation by enabling comparable or even higher systemic and regional blood flows to be generated with less depth of compression.

**Hemodynamic effects of chest compression.** Control rats represented the very limited hemodynamic effects of present closed-chest resuscitation techniques. In series 1, the forward blood flow generated corresponded to only 7% of the baseline cardiac index and did not increase in series 2 despite a 14% increase in the depth of compression. Although higher aortic diastolic and coronary perfusion pressures were initially attained in series 2, maintenance of such pressure required progressive increases in the depth of compression that reached depths considered maximal in four of seven rats. We previously proposed that this phenomenon may in part be related to progressive development of ischemic contracture with consequent reductions in ventricular cavity size, preload, and the capability of chest compression to generate forward blood flow (2, 13). However, the need for deeper compressions may also originate from reductions in preload as a result of diminished venous return. To this end, full reexpansion of the chest cavity with creation of negative intrathoracic pressure between compressions is presently recognized as an important determinant of effective chest compression (36). However, with prolonged and deeper compressions, permanent chest wall deformation occurs, which potentially compromises elastic recoil and venous return (7). A detrimental vicious cycle can be envisioned in which the depth of compression is progressively increased in an attempt to offset declining forward blood flow as a result of ischemic contracture. Deeper compressions, in turn, disrupt the integrity of the chest wall and its resultant elastic recoil, further reducing venous return and erroneously signaling the need for greater depth of compression. As the hemodynamic effects of chest compression spiral down and the risk of laceration of intrathoracic structures increases, a situation arises in which successful resuscitation becomes exceedingly improbable.

**Effect of cariporide.** Cariporide fundamentally modified the hemodynamic response to chest compression. In series 1, cariporide allowed chest compression to promote systemic and regional blood flows of magnitude comparable to those in control rats but with significantly less depth of compression. In series 2, increases in depth of compression were accompanied by commensurate increases in systemic and regional blood flow. More importantly, higher flow rates were attained without having to progressively increase the depth of compression. Thus cariporide, by shifting the flow-depth relationship of chest compression to the left, enabled more effective and stable closed-chest resuscitation. The beneficial effects of cariporide most likely stemmed from amelioration of ischemic contrac-
The evidence that cariporide ameliorates ischemic contracture is based on observations in animal models of coronary occlusion and reperfusion by García-Dorado and coworkers (12) and in models of VF and resuscitation by our group (2, 13). In our studies in an isolated rat heart model of VF, cariporide attenuated progressive increases in LV pressures during low-flow perfusion and prevented postischemic leftward shifts of the diastolic pressure-volume curve (13). In a pig model of VF in which the heart was imaged using transesophageal echocardiography, cariporide prevented progressive LV wall thickening and enabled hemodynamically more effective chest compression (2).

**Mechanism of action.** The precise cellular mechanism by which cariporide exerts its beneficial effects during resuscitation from VF is the subject of ongoing research. Consistent evidence from work in settings of ischemia and reperfusion other than cardiac arrest indicate that NHE-1 is activated by the profound intracellular acidosis that accompanies ischemia (1). NHE-1 activation prompts Na\(^+\) entry to cardiomyocytes in exchange for H\(^+\). However, because the Na\(^+\)/K\(^+\) ATPase pump becomes disabled during ischemia (5), Na\(^+\) accumulates in the cytosol and drives Ca\(^{2+}\) entry through the sarcolemmal Na\(^+\)/Ca\(^{2+}\) exchanger operating in its reverse mode (19, 21). Cytosolic and mitochondrial Ca\(^{2+}\) overload in conjunction with ATP depletion and oxidative stress would open the mitochondrial permeability transition pore and lead to mitochondrial swelling, depolarization, uncoupling of oxidative phosphorylation, and release of proapoptotic factors (17, 18). The beneficial effect of cariporide during myocardial ischemia and reperfusion is thought to result primarily from inhibition of NHE-1, thereby limiting Na\(^+\)\(\rightarrow\)Ca\(^{2+}\) exchange and subsequent mitochondrial Ca\(^{2+}\) overload (37, 38, 40). In addition, recent studies suggest that NHE-1 inhibitors may also have direct effects on mitochondrial ion-exchange mechanisms, increasing the threshold for opening of the mitochondria permeability transition pore (20). The extent to which these effects account for the beneficial effects observed during cardiac arrest needs further clarification.

**Microspheres technique.** Adequate mixing of microspheres in the bloodstream and proper sampling in the reference organ is critical to secure reliable measurement of blood flow. Although double-chamber mixing after left atrial injection is considered preferable to single-chamber mixing after LV injection, previous studies (6) have shown similar microsphere distribution after left atrial or LV injection. The comparable blood flows to paired organs (with the exception of cerebral hemispheres because of right carotid ligation) would support

date and preservation of ventricular preload. Preservation of preload would allow higher rates of blood flow to be generated for a given depth of compression. It is also conceivable that part of the benefit resulted from refraining from maximally compressing the chest and thus preserving the integrity of the chest wall, its corresponding elastic recoil, and venous return.

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adequate mixing of microspheres after LV injection in the present studies. We also verified that microspheres were delivered into the left ventricle by visualizing in each instance the characteristic LV pressure waveform during injection, which is critical during chest compression when the LV catheter may be displaced out of the cavity. Systemic heparinization along with continuous pressure monitoring of the withdrawal line ensured uninterrupted collection of microspheres into the reference organ. We also secured in preliminary studies that adequate reference-organ collection times were allowed during spontaneous circulation and during chest compression. Incomplete collection would falsely overestimate blood flow. The very low flow rates measured during chest compression would argue otherwise. In addition, the cardiac indices measured during spontaneous circulation were highly comparable to those measured by thermodilution in separate experiments under essentially identical experimental conditions (128 at baseline, 63 at 15 min postresuscitation, and 65 ml·min⁻¹·kg⁻¹ at 60 min postresuscitation in 10 rats; unpublished data).

**Limitations of study.** The need for prolonged electrical stimulation to induce self-sustaining VF, the use of pentobarbital anesthesia, the relatively pliable chest wall of rats, and the absence of underlying cardiovascular disease limit extrapolation of the findings to larger animal models and humans. The rat model, however, has proven to be remarkably useful for developing new concepts in resuscitation research which have been reproduced in larger animal models of VF and resuscitation.

In addition, bolus administration of cariporide may yield blood levels that are substantially higher than those for which selectivity has been defined. We recently documented (unpublished) in a pig model of VF plasma levels of cariporide more than three orders of magnitude the concentration needed to completely inhibit NHE-1 activity in isolated cardiomyocites (10 μmol/l) and fully protect the myocardium in isolated rat heart models of ischemia and reperfusion (1 μmol/l; Ref. 33) after bolus injection (3 mg/kg) into the right atrium during chest compression. These high levels would predict loss of isoform selectivity and inhibition of slowly inactivating Na⁺ currents (33, 43). However, no adverse effects were noted, and inhibition of slowly inactivating Na⁺ current may also contribute to myocardial protection during ischemia and reperfusion (26).

**Clinical implications.** Ultimate extension of these findings to clinical settings could have important implications for closed-chest resuscitation. Present techniques are not only limited by reduced hemodynamic efficacy but also by substantial risk of injury to the chest wall and intrathoracic viscera (24, 25, 31). Postmortem studies have shown a high incidence of rib fractures, sternal fracture, mediastinal hemorrhage, and life-threatening laceration of heart and great vessels. Thus enabling critical organ blood flow to be generated with less depth (force)

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**Fig. 5.** Hemodynamic and left ventricular function at baseline (BL) and at 15 and 60 min postresuscitation (PR) in rats treated with cariporide (open bars) and 0.9% NaCl (closed bars). MAP, mean aortic pressure; +dP/dt max, maximal rate of pressure rise; LVEDP, left ventricular end-diastolic pressure; LVSWI, left ventricular stroke work index. Values are means ± SE; *P < 0.05 vs. 0.9% NaCl by one-way ANOVA.

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**Fig. 6.** Systemic and regional blood flows at baseline (BL) and at 15 and 60 min postresuscitation (PR) in rats treated with cariporide (open bars) and 0.9% NaCl (closed bars). CI, cardiac index; L, left; R, right. Values are means ± SE; *P < 0.05; †P < 0.01 vs. left cerebral hemisphere by one-way ANOVA.
of compression, minimizing chest wall injury, and preserving elastic recoil would be highly desirable. Previous work (2) on our pig model of VF supports the extension of these findings to a larger animal species. NHE-1 is known to be expressed in human myocardium (45), and NHE-1 inhibition has been shown to protect myocardium in patients undergoing coronary artery bypass grafting (Expedition trial, unpublished data).

We have previously reported (23) that NHE-1 inhibition enhances the effects of vasopressor agents during chest compression, ameliorates reperfusion arrhythmias, prevents rebrillation, and improves postresuscitation myocardial function (2, 13). The present studies strengthen the rationale of NHE-1 inhibition during cardiac resuscitation by demonstrating beneficial effects on the flow-depth relationship of chest compression.

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