Mechanisms Underlying Afterload-Induced Exacerbation of Myocardial Infarct Size
Role of T-Type Ca\(^{2+}\) Channel

Mahmood S. Mozaffari, Champa Patel, Stephen W. Schaffer

Abstract—One consequence of elevated afterload pressure is the activation of the angiotensin II type 1 receptor and nonspecific cation channels with subsequent Ca\(^{2+}\) accumulation via the Na\(^+/\)H\(^+\)/Na\(^+/\)Ca\(^{2+}\) exchanger combination and the T-type or L-type Ca\(^{2+}\) channels. Intracellular Ca\(^{2+}\) overload is cytotoxic, in part, by inducing the mitochondrial permeability transition (MPT) pore. Therefore, we tested the hypotheses that: (1) increased afterload pressure worsens myocardial ischemia-reperfusion injury in healthy heart, (2) the Na\(^+/\)H\(^+\)/Na\(^+/\)Ca\(^{2+}\) exchanger combination and both the T-type and L-type Ca\(^{2+}\) channels are involved in the exacerbating impact of high afterload pressure on infarct size, and (3) elevated afterload enhances infarct size in part via the MPT pore. Accordingly, the effect of candesartan (angiotensin II type 1 receptor antagonist), cariporide (inhibitor of the Na\(^+/\)H\(^+\) exchanger), mibefradil (T-type Ca\(^{2+}\) channel blocker), diltiazem (L-type Ca\(^{2+}\) channel blocker), or cyclosporine A (inhibitor of MPT pore) were examined. The elevation in afterload pressure from 80 to 160 cmH\(_2\)O increased baseline myocardial performance but caused larger infarcts and worsened recovery of mechanical function after ischemia reperfusion. Whereas mibefradil abrogated the effect of high afterload pressure on infarct size, the other agents reduced infarct size at both afterload pressures. Hearts exposed to mibefradil, diltiazem, or cariporide displayed greater functional recovery than those exposed to candesartan or cyclosporine A, revealing that an uncoupling exists between reduced cell death and recovery of mechanical function of the viable portions of the myocardium. The data also uncovered an important link between pressure-mediated exacerbation of infarct size and T-type Ca\(^{2+}\) channel activity. (Hypertension. 2006;47:912-919.)

Key Words: myocardial reperfusion injury \(\bullet\) angiotensin II \(\bullet\) calcium channel blockers \(\bullet\) cyclosporin \(\bullet\) rats

We showed recently that elevations in afterload pressure exacerbate infarct size in the hearts of 9-month-old hypertensive and hypertensive-glucose-intolerant rats. This observation suggests that high perfusion pressure and attendant increase in mechanical stress tip the balance between cell survival and cell death in favor of the latter. Because muscle stretching activates the angiotensin II (Ang II) type 1 (AT\(_1\)) receptor through either the release of preformed Ang II or an Ang II–independent mechanism, one likely cause of the afterload effect is the activation of the AT\(_1\) receptor. It is known that AT\(_1\) receptor activation regulates the activities of key Ca\(^{2+}\) transporters, such as the Na\(^+/\)H\(^+\)/Na\(^+/\)Ca\(^{2+}\) exchanger combination and the T-type or L-type Ca\(^{2+}\) channels, which are important mediators of intracellular Ca\(^{2+}\) [Ca\(^{2+}\)], overload in the ischemic-reperfused heart and hypoxic cardiomyocyte. Prominent among the diverse consequences of excessive [Ca\(^{2+}\)], accumulation is the induction of the mitochondrial permeability transition (MPT) pore, which increases matrix volume by allowing solutes and water to enter the mitochondria. Because of the increase in matrix volume, the mitochondrial outer membrane ruptures, releasing cytochrome c, which, in turn, executes apoptosis. In addition, MPT induction uncouples the mitochondria, leading to inhibition of ATP synthesis and facilitating cell death by necrosis. These events can be disrupted by pharmacological inhibition of MPT pore with cyclosporine A.

Another mechanism that could account for the promotion of cell death in the pressure-overloaded, ischemic cell is the activation of nonselective cation channels. These channels cause partial depolarization of the cardiomyocyte, allowing Ca\(^{2+}\) entry via the T-type Ca\(^{2+}\) channel. They also elevate intracellular Na\(^+\) [Na\(^+\)], which would be expected to enhance Ca\(^{2+}\) via the Na\(^+/\)Ca\(^{2+}\) exchanger. Ca\(^{2+}\) entry is also facilitated by enhanced flux through the L-type Ca\(^{2+}\) channel. Like the first mechanism, excessive hypoxia-mediated Ca\(^{2+}\) accumulation should worsen infarct size, with the effect being greater at high afterload pressure.

To provide more information on the cause of pressure-mediated worsening of infarct size, we tested the hypotheses that: (1) elevation in afterload pressure increases myocardial...
infarct size and is associated with poor recovery of myocardial function after an ischemia-reperfusion insult in hearts of healthy young Sprague-Dawley rats, (2) the adverse effect of elevated afterload pressure on infarct size is largely prevented by inactivation of transporters involved in hypoxia-mediated Ca\(^{2+}\) accumulation, such as the Na\(^+/\)H\(^+\) -Na\(^+/\)Ca\(^{2+}\) exchanger combination and both the L-type and T-type Ca\(^{2+}\) channels, and (3) pressure-mediated exacerbation of infarct size is linked to MPT induction. The use of young and healthy Sprague-Dawley rats in these studies avoids the potential confounding influence of age and disease and rules out the possibility that the effect of afterload pressure on infarct size is strain related; our previous studies on the impact of high afterload pressure on infarct size were carried out in hearts of aging Wistar-Kyoto rats with systemic hypertension and impaired glucose tolerance.\(^1\)

**Methods**

Male Sprague-Dawley rats (290 to 345 g; 9 to 11 weeks of age) were purchased from Harlan Laboratories (Indianapolis, IN). The animals were housed in a room that was maintained at constant humidity (60±5%), temperature (24±1°C), and light cycle (6:00 AM to 6:00 PM). The use of animals for this study was approved by the Institutional Animal Care and Use Committee. For all of the isolated heart perfusion experiments, the animals were heparinized (1000 U/kg) and decapitated before removing the hearts and perfusing them on a Langendorff apparatus. The perfusion medium was standard Krebs-Henseleit buffer (37°C) containing 11 mmol/L of glucose and equilibrated with 95% O\(_2\)-5% CO\(_2\). The use of animals for this study was approved by the Institutional Animal Care and Use Committee.

**Results**

**Effect of High Afterload Pressure on the Healthy Heart**

An elevation in the afterload pressure from 80 to 160 cmH\(_2\)O significantly increased baseline coronary flow rate and contractile function, with the rate-pressure-product (RPP), the index of contractility (maximum +dP/dt), and the rate of myocardial relaxation (maximum −dP/dt) all increasing (Figure 1A through 1D). Induction of regional ischemia reduced those parameters with the effect being more pronounced for hearts exposed to the higher perfusion pressure (Figure 1A, 1C, and 1D). Restoration of coronary circulation caused a transient increase in coronary flow rate followed by a decline to values achieved during the ischemic phase; the coronary flow rate remained significantly higher for hearts perfused at the higher perfusion pressure (Figure 1A). Contractile function further deteriorated during the reperfusion phase, with the impairment in function greatest for hearts that were exposed to the higher afterload pressure (Figure 1C and 1D). Consistent with this observation, end-diastolic pressure increased more in hearts perfused at the higher afterload pressure (Figure 1E). The exacerbating influence of elevated afterload pressure on ischemia-reperfusion injury was additionally evident by the significantly larger infarcts in hearts exposed to the afterload pressure of 160 cmH\(_2\)O (Figure 1F; insert shows images of tetrazolium-stained heart slices).

**Role of AT\(_1\) Receptors**

Candesartan-treated hearts displayed a generally lower coronary flow rate (≈21% to 24%), although the RPP, maximum +dP/dt (eg, contractility), and maximum −dP/dt (eg, relaxation) remained similar to those of their untreated counterparts during the stabilization phase (Figures 2 through 4). Candesartan treatment did not improve functional recovery of hearts perfused at either 80- or 160-cmH\(_2\)O perfusion pressure (Figure 4). Yet, the treatment caused a marked reduction in infarct size of all of the hearts examined (Figure 5). The ≈80% reduction in infarct size was nearly identical for hearts perfused at the 2 afterload pressures.

**Role of the Na\(^+/\)H\(^+\) Exchanger**

Cariporide treatment (10 μmol/L) caused a significant reduction in the baseline coronary flow rate of hearts perfused at the 2 afterload pressures (Figure 3). The RPP was slightly elevated in hearts perfused at the higher perfusion pressure (17%; P<0.05; Figure 2). However, indices of myocardial contractility and relaxation were lower for cariporide-treated hearts at the lower perfusion pressure (Figure 4). After the ischemia-reperfusion insult, cariporide-treated hearts displayed an ≈2-fold greater (P<0.05) recovery of contractility at the higher afterload pressure (Figure 4). The treatment also caused a significant reduction in myocardial infarct size (Figure 5). However, the percentage reduction in infarct size was greater for hearts exposed to the lower (≈70%) than the...
higher (~55%) afterload pressure. Interestingly, inclusion of 20 μmol/L of cariporide in the perfusion medium did not additionally reduce infarct size of hearts perfused at 160 cmH2O (16.6 ± 2.6%; n = 4).

**Role of T-Type Ca2+ Channels**

At 0.3 μmol/L, mibefradil increased baseline coronary flow rate but had no adverse effect on mechanical function (Figures 2 through 4). The treatment also had little effect on the decline in mechanical function during ischemia. However, it significantly improved functional recovery in hearts reperfused at an afterload pressure of 160 cmH2O (Figure 4). Mibefradil also attenuated the increase in end-diastolic pressure of hearts perfused at the higher afterload pressure (54.8 ± 8.5 and 29.2 ± 7.9 mm Hg for the untreated control and mibefradil-treated hearts, respectively). The cardioprotective effect of mibefradil was additionally reflected in the significant reduction in infarct size. Indeed, mibefradil treatment eliminated the afterload-dependent exacerbation of infarct size without affecting infarct size of hearts perfused at an afterload pressure of 80 cmH2O (Figure 5).
Role of L-Type Ca\(^{2+}\) Channel
Diltiazem (10 μmol/L) caused a significant depression in contractile function (maximum ±dP/dt and RPP) but little change in coronary flow rate (Figures 2 through 4). During ischemia reperfusion, coronary flow rates were similar in the control and diltiazem groups (Figure 3). Although contractile function was severely reduced during the stabilization period, contractile function during the reperfusion period remained surprisingly elevated (Figure 4). These data are consistent with the significant reduction in infarct size in the diltiazem group versus the control group at both 80 and 160 cmH\(_2\)O (Figure 5).

Role of MPT Pore
Cyclosporine A treatment did not affect the coronary flow rate but reduced the RPP, myocardial contractility, and relaxation at an afterload pressure of 80 but not 160 cmH\(_2\)O (Figures 2 through 4). The treatment had no effect on recovery of mechanical function in the reperfused heart (Figure 4). Nonetheless, cyclosporine A treatment significantly reduced infarct size at both afterload pressures, with the effect being more pronounced for hearts exposed to the higher perfusion pressure (53% versus 34% reduction; Figure 5).

Discussion
Pressure overload is known to activate multiple and divergent signaling pathways. One of the important signaling pathways arises on release of preformed Ang II from the cardiomyocyte. Stretching may also directly activate the AT\(_1\) receptor independent of Ang II.\(^{2–4}\) The net effect is the activation of multiple Ang II-linked pathways capable of impacting the ischemic myocardium. Consistent with this notion, candesartan treatment dramatically reduced infarct size in hearts perfused at an afterload pressure of either 80 or 160 cmH\(_2\)O. Because the candesartan-mediated decline in infarct size at the 2 afterload pressures was similar on a percentage basis (~80%), the cardioprotection appears to be independent of the mechanical stress. This apparent uncoupling between the effects of mechanical stress and those of Ang II action may relate to the complexity of the renin–angiotensin system in the ischemic-reperfused heart.\(^{15–17}\) However, it is important to point out that Ang II plays a major role in ventricular

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**Figure 2.** Hearts were perfused with buffer lacking or containing 1 of the following drugs: candesartan (100 nM), cariporide (10 μmol/L), mibefradil (0.3 μmol/L), diltiazem (10 μmol/L), or cyclosporine A (0.2 μmol/L). Elevation in the afterload pressure significantly increased baseline RPP in all groups except the diltiazem-treated group. The number of animals for each group is indicated in parenthesis above its corresponding bar graph. Data are mean±SEM. *P<0.05 vs counterparts perfused at an afterload pressure of 80 cmH\(_2\)O. **P<0.05 vs control counterparts perfused at a similar afterload pressure.

**Figure 3.** Elevation in the afterload pressure was associated with significant increase in coronary flow rate. Data are mean±SEM; number of hearts/group is indicated on Figure 2. *P<0.05 vs counterparts perfused at an afterload pressure of 80 cmH\(_2\)O. **P<0.05 vs untreated controls perfused at the same afterload pressure.
remodeling. Therefore, chronic, rather than acute, exposure to an AT1 receptor antagonist is likely to dramatically alter the long-term outcome of an ischemic event.

In addition to activating AT1 receptor function, mechanical stress also stimulates nonspecific cation channels.10,11 By elevating [Na\(^+\)], the nonspecific cation channels are thought to also elevate [Ca\(^{2+}\)]\(_{\text{i}}\) levels by affecting Na\(^+\)/Ca\(^{2+}\) flux. Another consequence of mechanical stress-mediated activation of the nonspecific cation channels is the partial depolarization of the cardiomyocyte allowing Ca\(^{2+}\) entry via the T-type Ca\(^{2+}\) channel. Although there is every reason to expect that the nonspecific cation channels play an important role in

Figure 4. Increased afterload pressure significantly increased myocardial contractility (maximum +dP/dt; A) and relaxation (maximum −dP/dt; B) for all groups except the diltiazem-treated group. All hearts, except those treated with diltiazem, showed a significant reduction in myocardial contractility and relaxation by the end of the reperfusion phase. Data are mean±SEM; number of hearts/group is indicated on Figure 2. *P<0.05 vs stabilization values in the same group. **P<0.05 vs counterparts perfused at 80 cmH\(_2\)O. #P<0.05 vs untreated control counterparts at the same afterload pressure and the same condition.

Figure 5. Each treatment reduced infarct size at either afterload pressure but mibebradil abrogated the effect of high afterload pressure on infarct size. The number of animals for each group is indicated in parenthesis above its corresponding bar graph. Data are mean±SEM. *P<0.05 vs counterparts perfused at an afterload pressure of 80 cmH\(_2\)O. #P<0.05 vs untreated controls perfused at the same afterload pressure.
The Ca\textsuperscript{2+}-linked transporters located downstream from the AT\textsubscript{1} receptor and the nonspecific cation channels appear to play central roles in the adverse effects of elevated afterload on ischemia-reperfusion injury. One of these transporters is the Na\textsuperscript{+}/H\textsuperscript{+}-Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger combination. Regulation of the Na\textsuperscript{+}/H\textsuperscript{+} exchanger is complex,\textsuperscript{18,19} likely accounting for the unusual response of Na\textsuperscript{+}/H\textsuperscript{+} exchanger in the ischemic-reperfused heart. Figure 5 shows that cariporide (10 \mu mol/L) reduced infarct size by 70% in hearts perfused at an afterload pressure of 80 cmH\textsubscript{2}O but by only 55% in hearts perfused at 160 cmH\textsubscript{2}O. Because higher concentration (20 \mu mol/L) of cariporide did not additionally reduce infarct size, higher afterload pressure does not appear to affect the sensitivity of the myocardium to the cardioprotective effect of cariporide. Nonetheless, by preventing the coupling of flux through the Na\textsuperscript{+}/H\textsuperscript{+}-Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger combination, cariporide would presumably limit the elevation in [Ca\textsuperscript{2+}]i during ischemia.\textsuperscript{5} However, there are several reasons for diminished importance of the Na\textsuperscript{+}/H\textsuperscript{+} exchanger in the pressure-overloaded myocardium. First, other sources of Ca\textsuperscript{2+} influx, such as the T-type Ca\textsuperscript{2+} channel, assume a more important role. Second, although mechanical stress activates the Na\textsuperscript{+}/H\textsuperscript{+} exchanger, it also activates nonspecific cation channels that can elevate both [Na\textsuperscript{+}]i and [Ca\textsuperscript{2+}]i, independent of the exchanger.\textsuperscript{10} Third, stress activation of the \( \epsilon \) isoform of protein kinase C and of the mitogen-activated protein kinases may partially counter the adverse effects of Na\textsuperscript{+}/H\textsuperscript{+} exchanger activation on the ischemic heart.\textsuperscript{20,21} Although the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger is regulated by Ang II,\textsuperscript{22} its role in afterload-induced exacerbation of infarct size remains to be determined.

Another transport system that may be regulated by elevated afterload pressure is capacitative Ca\textsuperscript{2+} entry.\textsuperscript{23} This is a recently described phenomenon in which depletion of sarcoplasmic reticular Ca\textsuperscript{2+} stores activates Ca\textsuperscript{2+} uptake by the cardiomycocyte. Ang II stimulates the process by promoting the formation of inositol triphosphate, which, in turn, induces capacitative Ca\textsuperscript{2+} entry.\textsuperscript{23} Although this is an interesting and important mechanism in the development of cardiac hypertrophy\textsuperscript{24} and the diabetic heart,\textsuperscript{25} it may not be an important contributor to afterload-induced exacerbation of infarct size. First, although candesartan would be expected to block Ang II–induced activation of capacitative Ca\textsuperscript{2+} entry, hypoxia also interferes with the process.\textsuperscript{26} Second, although candesartan protects the ischemic heart, it does not specifically inhibit afterload-induced exacerbation of infarct size.

Another transporter affected by elevated afterload pressure is the T-type Ca\textsuperscript{2+} channel. Inhibition of the channel with the antagonist mibebradil specifically abrogates the exacerbating impact of high afterload pressure on infarct size while improving recovery of contractile function. Although there has been some concern about the specificity of mibebradil, it is noteworthy that mibebradil is the only inhibitor used in the present study of which the actions are closely linked to changes in afterload pressure. At the concentration of 0.3 \mu mol/L, mibebradil has no effect on contractile function of the normal heart, ruling out a major role for the L-type Ca\textsuperscript{2+} channel in the observed actions of mibebradil.\textsuperscript{27} Although there has been some discussion that mibebradil affects flux through the Na\textsuperscript{+}/H\textsuperscript{+} and Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger combination,\textsuperscript{5} in contrast to mibebradil, the Na\textsuperscript{+}/H\textsuperscript{+} exchange inhibitor cariporide preferentially improves the status of hearts perfused at lower afterload pressures. Moreover, mibebradil significantly alters hypoxia-mediated Ca\textsuperscript{2+} accumulation in isolated cardiomyocytes exposed to medium containing cariporide.\textsuperscript{5} Finally, the only other major transporter altered by mibebradil is the tetrodotoxin-Na\textsuperscript{+} channel.\textsuperscript{28} Although this transporter is unaffected by stretch,\textsuperscript{29} one cannot discount the possibility that ischemia and (or) afterload pressure could modulate its activity.

The potential role for the T-type Ca\textsuperscript{2+} channel in ischemia-reperfusion injury has received little attention, primarily because of the perception that levels of the transporter are too low in the adult heart.\textsuperscript{30} However, chronic hypoxia induces the expression of the \( \epsilon \text{iso}\) T-type Ca\textsuperscript{2+} channel gene in PC12 cells.\textsuperscript{31} Moreover, chronic treatment with mibebradil benefits the rat after myocardial infarction.\textsuperscript{32} According to Mocanu et al.,\textsuperscript{13} mibebradil is capable of limiting infarct size in adult rat heart despite the low abundance of T-type Ca\textsuperscript{2+} channels within ventricular tissue. In a related study, Arh and Budhanna\textsuperscript{33} reported that greater cardioprotection was achieved with mibebradil treatment than with classical L-type Ca\textsuperscript{2+} channel blockers. These beneficial effects of mibebradil probably relate to the contribution of the T-type Ca\textsuperscript{2+} channel toward hypoxia-mediated Ca\textsuperscript{2+} accumulation.\textsuperscript{5}

The characteristics of the T-type Ca\textsuperscript{2+} channel are consistent with an important role in the pressure-overloaded myocardium, particularly during periods of ischemia. First, mechanical stress activates nonspecific cation channels that promote partial depolarization of the cell. Because the T-type Ca\textsuperscript{2+} channel is activated at a lower voltage than the L-type Ca\textsuperscript{2+} channel, the T-type Ca\textsuperscript{2+} channel would be preferentially affected by mechanical stress-induced cellular depolarization.\textsuperscript{27} Second, the T-type Ca\textsuperscript{2+} channel is activated by Ang II,\textsuperscript{2} an effector released from the pressure-overloaded myocardium.\textsuperscript{2} Third, the cardiomyocyte is partially depolarized during ischemia.\textsuperscript{34}

The importance of the T-type Ca\textsuperscript{2+} channel relative to the L-type Ca\textsuperscript{2+} channel in afterload-induced alterations in infarct size is also illustrated by the diltiazem results. At a concentration of diltiazem that suppresses myocardial performance (eg, RPP) by \( \approx 50\% \) to 70%, infarct size was reduced at 80 and 160 cmH\textsubscript{2}O by 58% and 66%, respectively. Therefore, diltiazem does not selectively prevent the effects of elevated afterload on infarct size. Moreover, diltiazem-treated hearts exhibited a unique pattern of contractile function recovery from ischemia, actually exceeding preischemic levels.

A major consequence of elevated [Ca\textsuperscript{2+}]i is induction of MPT pore, a critical event in the transition from reversible to irreversible reperfusion injury.\textsuperscript{7–9} Cyclosporine A acts as a potent inhibitor of MPT pore opening by preventing the binding of cyclophilin D to adenine nucleotide translocase, thereby tipping the balance between cell death and cell survival in favor of the latter.\textsuperscript{7–9} Consistent with its cardio-
protective effect, cyclosporine A treatment reduced infarct size in hearts exposed to both afterload pressures, with the effect being greater at the higher perfusion pressure. The observation that cyclosporine A reduced infarct size at both low and high perfusion pressures, whereas mibefradil treatment selectively reduced infarct size in hearts exposed to the higher perfusion pressure, suggests that the activation of the T-type Ca\(^{2+}\) channel is uniquely sensitive to elevated afterload pressure while multiple factors contribute to the modulation of MPT pore by afterload pressure.

Other than altering myocyte function, elevated afterload also increases perfusion pressure, thereby enhancing coronary flow (Figure 3). One would anticipate that the elevation in coronary flow would improve cardiac perfusion and reduce infarct size. This proved not to be the case, because coronary flow remained higher for hearts perfused at the higher afterload pressure throughout the ischemia-reperfusion protocol. Nonetheless, infarct size was significantly worse in hearts subjected to the greater perfusion pressure. Moreover, there was no correlation between drug-induced improvements in coronary flow rate and reductions in infarct size. Therefore, afterload-mediated alterations in coronary flow do not appear to be the dominant factor affecting infarct size at elevated afterload.

Finally, it is rather perplexing that the marked reduction in infarct size is not consistently accompanied by a marked improvement in functional recovery of the myocardium. Indeed, aside from diltiazem, only cariporide and mibefradil displayed partial improvement in contractile recovery, whereas candesartan showed no improvement despite its remarkable ability to limit infarct size. The uncoupling between infarct size and functional recovery has been reported previously\(^1\) and may relate to differences in pathways that regulate cell death and myocyte contraction. Nonetheless, our acute observations do not preclude the possibility that cardiac remodeling associated with long-term recovery from ischemia-reperfusion injury may diminish the extent of uncoupling.

**Perspectives**

Ischemic heart disease is the underlying cause of most cases of acute myocardial infarction, congestive heart failure, arrhythmias, and sudden cardiac death. The demonstration that pressure overload, per se, markedly increases the susceptibility of the myocardium to ischemia-reperfusion injury underlines the importance and significance of strict blood pressure control. Indeed, load-dependent apoptosis is believed to contribute to development of myocardial dysfunction in the chronically overloaded heart.\(^35\) Thus, an understanding of the mechanisms by which perfusion pressure regulates cell survival and influences functional recovery of the myocardium would be of major clinical relevance. This investigation assumes added importance because of the observed uncoupling between the remarkable efficacy of the pharmacological agents in reducing infarct size and their ability to improve functional recovery. This paradox presents a dilemma when promoting an agent as “truly” cardioprotective. Therefore, effective control of perfusion pressure, per se, may provide a novel approach that is capable of reducing both infarct size and promoting functional recovery of the viable portions of the myocardium.

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