Mitochondrial permeability transition pore as a target for cardioprotection in the human heart

Selvaraj Shanmuganathan, Derek J. Hausenloy, Michael R. Duchen, and Derek M. Yellon. Mitochondrial permeability transition pore as target for cardioprotection in the human heart. Am J Physiol Heart Circ Physiol 289: H237–H242, 2005; doi:10.1152/ajpheart.01192.2004.—After an episode of myocardial ischemia, opening of the mitochondrial permeability transition pore (mPTP), at the onset of reperfusion, is a critical determinant of myocyte death. We investigated the role of the mPTP as a target for cardioprotection in the human heart. We subjected human atrial tissue, harvested from patients undergoing cardiac surgery, to a period of lethal hypoxia and investigated the effect of suppressing mPTP opening at the onset of reoxygenation. We found that suppressing mPTP opening at the onset of reoxygenation with known mPTP inhibitors cyclosporin A (CsA, 0.2 μmol/l) and sanguinolent A (SfA, 1 μmol/l) improved recovery of baseline contractile function from 29.4 ± 2.0% under control conditions to 48.7 ± 2.2% with CsA and 46.1 ± 2.3% with SfA (P < 0.01) and 2 improved cell survival from 62.8 ± 5.3% under hypoxic control conditions to 91.4 ± 4.1% with CsA and 87.2 ± 6.2% with SfA (P < 0.001). Furthermore, with a cell model in which oxidative stress was used to induce mPTP opening in human atrial myocytes, we demonstrated directly that CsA and SfA mediated their cardioprotective effects by inhibiting mPTP opening, as evidenced by an extension in the time required to induce mPTP opening from 116 ± 8 s under control conditions to 189 ± 10 s with CsA and 183 ± 12 s with SfA (P < 0.01). We report that suppressing mPTP opening at the onset of reoxygenation protects human myocardium against lethal hypoxia-reoxygenation injury. This suggests that, in the human heart, the mPTP is a viable target for cardioprotection.

Experimental procedures

Materials. CsA (Sigma, Poole, UK) was dissolved in 50% ethanol and added to the buffer such that the final ethanol concentration was <0.005%. SfA (Novartis Pharma, Basel, Switzerland) was dissolved in DMSO (Sigma) and added to the buffer such that the final DMSO concentration was <0.01%. Tetrathiomolybdate methyl ester (TMMR; Molecular Probes Europe, Leiden, The Netherlands) was dissolved in DMSO. All other reagents were of standard analytical grade.

Human atrial trabecula model of hypoxia-reoxygenation. Experiments were performed on human atrial trabeculae, isolated from right atrial appendages, harvested from patients undergoing coronary artery bypass surgery. Prior ethical approval for this study was granted by the Ethics and Clinical Investigations Panel of the Middlesex Hospital, London, UK. Patients with a previous history of atrial arrhythmias, treatment with antiarrhythmic drugs, right ventricular failure, or diabetes mellitus were not included in the study.

Atrial trabeculae (of diameter ≤1 mm and length ≥2 mm) were isolated from the atrial appendage specimen, suspended horizontally in an organ bath, and superfused with modified Tyrode buffer comprising (in mM) 118.5 NaCl, 4.8 KCl, 24.8 NaHCO3, 1.2 KH2PO4, 1.44 MgSO4·7H2O, 1.8 CaCl2·2H2O, 1.0 glucose, and 10.0 pyruvic acid, oxygenated with a 95% O2-5% CO2 gas mixture, to maintain pH between 7.35 and 7.45, a partial pressure of O2 between 50 and 60 kPa, and a partial pressure of CO2 between 4.0 and 6.0 kPa. The temperature in the bath was maintained at 37°C with a heat exchanger (Technic Circulator C 85-A, Cambridge, UK). The developed contrac-

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tile force of the atrial trabeculae was amplified and recorded with Powerlab/8sp (AD Instruments).

Atrial trabeculae were stimulated at 1 Hz and allowed to stabilize for 90 min. They were excluded if by the end of the stabilization period the maximal developed pressure, after stretching, was <1.0 g.

They were then subjected to a period of simulated ischemia (SI), which comprised 90 min of perfusion with glucose-free hypoxic Tyrode buffer containing (in mM) 118.5 NaCl, 4.8 KCl, 24.8 NaHCO₃, 1.2 KH₂PO₄, 1.44 MgSO₄·7H₂O, 1.8 CaCl₂·2H₂O, 7.0 choline chloride, and 10.0 pyruvic acid and pacing at 3 Hz. The hypoxic buffer was bubbled with 95% N₂-5% CO₂ to lower the partial pressure of O₂ of the buffer in the organ bath to <7 kPa (pH 7.24–7.34). The atrial trabeculae were then subjected to simulated reperfusion comprising perfusion for 120 min with oxygenated Tyrode buffer and pacing at 1 Hz.

Atrial trabeculae were randomly assigned to the following treatment groups (see Fig. 1). In the control group (n = 6), atrial trabeculae were given either normal buffer or buffer containing the 0.005% ethanol or 0.02% DMSO vehicle controls for the first 30 min of the reoxygenation period. In the hypoxic preconditioning group (n = 6), immediately before the lethal 90-min period of hypoxia atrial trabeculae were subjected to 3 min of hypoxic substrate-free buffer and pacing at 3 Hz, followed by 7 min of reoxygenation with the normal oxygenated buffer and pacing at 1 Hz. This group was included as a positive control to verify that cardioprotection could be demonstrated in this atrial trabecula model of hypoxia-reoxygenation (39). In the CsA group (n = 6) and the SfA group (n = 6), after the lethal 90-min hypoxic period trabeculae were given either CsA (0.2 μmol/l) or SfA (1.0 μmol/l) for the first 30 min of reoxygenation, followed by a further 90 min of reoxygenation with normal buffer. These concentrations of CsA and SfA have been demonstrated to inhibit mPTP opening in the isolated, perfused rat heart (7, 18, 21, 22).

At the end of the reoxygenation period, the contractile function expressed as a percentage of the baseline force of contraction was determined for each atrial trabecula. In addition, the width and length of each atrial trabecula were measured and all specimens were then assigned to three categories: live (AV negative, PI negative, and rod-shaped), apoptotic (AV positive, PI negative), and necrotic cells (AV positive, PI positive).

**Human atrial myocyte model of hypoxia-reoxygenation.** Experiments were performed on atrial myocytes isolated from right atrial appendages harvested from patients undergoing coronary artery bypass surgery. Human atrial myocytes were isolated by enzymatic digestion with both protease and collagenase digestion (20). Because of the fragility of the human cardiomyocytes and the difficulty in isolating human myocytes, cell viability after isolation was in the order of 20–30%, which compares favorably with other studies in which human myocytes were used (20). After isolation, the cells were allowed to stabilize for 60 min in oxygenated medium calcium (MC) solution comprising (in mM) 120 NaCl, 5.4 KCl, 5 MgSO₄, 5 pyruvate, 20 glucose, 20 taurine, 10 HEPES, and 0.05 Ca²⁺ (pH 7.4) at 37.0°C.

They were then subjected to lethal SI as follows, by replacing the oxygenated MC buffer with ischemic buffer containing (in mM) 137 NaCl, 12 KCl, 0.49 MgCl₂, 0.9 CaCl₂·H₂O, 4 HEPES, and 20 Na-lactate (16) and incubating them at 37°C for 20 min in a hypoxic chamber (containing 20 g sodium dithionate) in an atmosphere of 0% O₂-5% CO₂ balanced with argon (BOC Gases). At the end of the SI period, the buffer was replaced with oxygenated MC buffer and incubated at 37.0°C for 30 min (to simulate reperfusion). Cell viability was assessed after 30 min of reoxygenation with light and fluorescent microscopy.

Isolated atrial myocytes were randomly assigned to the following treatment groups (see Fig. 2 for experimental protocol). In the time control group (n = 5), cells were left in normoxic conditions at 37.0°C for the duration of the experimental protocol to act as time controls. In the hypoxic control group, cells were subjected to 20 min of hypoxia followed by 30-min reoxygenation with either normal buffer (n = 6) or buffer containing the vehicle controls, either DMSO (n = 3) or ethanol (n = 3). In the CsA group (n = 6) and the SfA group (n = 6), cells were subjected to 20 min of hypoxia followed by 30-min reoxygenation with buffer containing either CsA (0.2 μM) or SfA (1.0 μM).

At the end of the 20-min reoxygenation period, the cells were incubated in the dark for 10 min with annexin V-Fluos (AV, 20 μM; Roche). Propidium iodide (PI, 3 nM; Sigma) was then added to the myocytes, and the samples were analyzed immediately with a fluorescence microscope. AV was shown previously to detect the early stages of apoptosis by binding to the phosphatidylserine residues, which are translocated to the external face of the cell membrane (1). Cellular necrosis was determined with PI, which binds to the nuclei of cells whose plasma membrane have become permeable (17).

For each treatment group, the numbers of rod-shaped, AV-stained, and PI-stained cells were counted in three randomly chosen fields by an operator blinded to the treatment and an average was taken. Results were then expressed as a percentage of the cells counted in the time control group and were assigned to three categories: 1) live cells (AV negative, PI negative, and rod-shaped), 2) apoptotic cells (AV positive, PI negative), and 3) necrotic cells (AV positive, PI positive).

**Human atrial myocyte model for induction and detection of mPTP opening.** Human myocytes were isolated as above and suspended in Tyrode buffer containing (in mM) 120 NaCl, 5.4 KCl, 5 MgSO₄, 5 pyruvate, 20 glucose, 20 taurine, 10 HEPES, and 0.05 Ca²⁺ (pH 7.4) at 37.0°C. They were then subjected to lethal SI as follows, by replacing the oxygenated MC buffer with ischemic buffer containing (in mM) 137 NaCl, 12 KCl, 0.49 MgCl₂, 0.9 CaCl₂·H₂O, 4 HEPES, and 20 Na-lactate (16) and incubating them at 37°C for 20 min in a hypoxic chamber (containing 20 g sodium dithionate) in an atmosphere of 0% O₂-5% CO₂ balanced with argon (BOC Gases). At the end of the SI period, the buffer was replaced with oxygenated MC buffer and incubated at 37.0°C for 30 min (to simulate reperfusion). Cell viability was assessed after 30 min of reoxygenation with light and fluorescent microscopy.
Seeded human atrial myocytes were incubated with the fluorescent dye TMRM (3 μM) for 15 min at 37°C, washed, and visualized with confocal fluorescence microscopy as described below. TMRM, a lipophilic cation, accumulates selectively in mitochondria according to the mitochondrial membrane potential (15). Laser illumination of mitochondrial TMRM generates oxidative stress, used in this model to induce mPTP opening, that is detected by the loss of mitochondrial membrane potential, which in this model appears as an increase in TMRM fluorescence intensity. The relatively high concentration of TMRM in the mitochondria causes autoquenching of fluorescence, such that the fluorescence signal becomes a nonlinear function of dye concentration; therefore, mitochondrial depolarization results in the loss of dye into the cytosol, where the signal increases (4). After loading with TMRM, the cells were randomly assigned to the following treatment groups:

1. Control group (n = 11 in total): incubation in MC medium in the presence or absence of the DMSO and ethanol vehicle controls;
2. CsA group (n = 10): incubation with CsA (0.2 μM) for 15 min at 37°C; and
3. SfA group (n = 10): incubation with SfA (1.0 μM) for 15 min at 37°C.

The coverslip with adherent myocytes was placed in a chamber and mounted on the stage of a Zeiss 510 CLSM confocal microscope equipped with ×40 oil immersion, quartz objective lens (numerical aperture 1.3). The cells were illuminated with the 543-nm emission line of a HeNe laser. For all photosensitization experiments, all conditions of the confocal imaging system (laser power, confocal pinhole, optical slice, and detector sensitivity) were identical, to ensure comparability between experiments. The fluorescence of TMRM was collected with a 585-nm long-pass filter, and images were analyzed with Zeiss software (LSM 2.8).

Statistical analysis. All results are presented as group means ± SE. For comparison between more than two groups, factorial one-way ANOVA was used. Where a significant F-value was obtained, Fisher’s protected least significance difference post hoc test was applied for between-group comparisons. Results were considered significant when P ≤ 0.05.

RESULTS

Samples were obtained from 32 patients with stable ischemic heart disease (25 men and 7 women; age range 48–75 yr, mean age 67 yr). If two or three suitable trabeculae could be isolated from a single atrial appendage, each atrial trabecula was allocated to one of three groups (3 sets of apparatus were used simultaneously). Ten atrial trabeculae were excluded because of poor baseline contractile function.

**Human atrial trabecula model of hypoxia-reoxygenation.** Baseline characteristics were similar in all groups (see Table 1). Figure 3 portrays the contractile function expressed as a percentage of the baseline contractile function measured at the end of the period of stabilization. In all treatment groups, SI resulted in a similar reduction in contractile function, which er’s protected least significance difference post hoc test was applied for between-group comparisons. Results were considered significant when P ≤ 0.05.

**Table 1. Physical characteristics of human atrial trabecula study groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Length, mm</th>
<th>Mass, mg</th>
<th>Area, mm²</th>
<th>Force, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4.18 ± 0.5</td>
<td>0.88 ± 0.03</td>
<td>0.63 ± 0.09</td>
<td>1.43 ± 0.2</td>
</tr>
<tr>
<td>CsA</td>
<td>3.28 ± 0.3</td>
<td>0.85 ± 0.09</td>
<td>0.49 ± 0.08</td>
<td>1.51 ± 0.2</td>
</tr>
<tr>
<td>SfA</td>
<td>3.43 ± 0.3</td>
<td>0.75 ± 0.04</td>
<td>0.47 ± 0.04</td>
<td>1.30 ± 0.1</td>
</tr>
<tr>
<td>Hypoxic preconditioning</td>
<td>3.71 ± 0.3</td>
<td>0.77 ± 0.06</td>
<td>0.60 ± 0.01</td>
<td>1.24 ± 0.2</td>
</tr>
</tbody>
</table>

Data presented are means ± SE. CsA, cyclosporin A; SfA, sanglifehrin A.

**Fig. 2.** Experimental protocols for human atrial myocyte model of hypoxia-reoxygenation.

**Fig. 3.** Change in human atrial trabecula contractile function expressed as % of baseline contractile function at different time intervals (min) during simulated ischemia (SI) and reoxygenation (R). The presence of either CsA or SfA for the first 30 min of reoxygenation improved the recovery of contractile function to a similar extent as hypoxic preconditioning (HPC). Values are means ± SE; n ≥ 6/group. *P < 0.001.
Table 2. Effect of inhibiting mPTP opening at time of reoxygenation on human atrial myocyte viability and apoptotic and necrotic components of cell death

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>SE</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live Cells</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>17.2</td>
<td>2.4</td>
<td>1.1</td>
<td>100</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>10.8</td>
<td>2.2</td>
<td>0.9</td>
<td>62.8±5.3</td>
</tr>
<tr>
<td>CsA</td>
<td>15.8</td>
<td>1.7</td>
<td>0.7</td>
<td>91.9±4.1*</td>
</tr>
<tr>
<td>SfA</td>
<td>15.0</td>
<td>2.6</td>
<td>1.1</td>
<td>87.2±6.2*</td>
</tr>
<tr>
<td><strong>Necrotic Cells</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>43.4</td>
<td>6.9</td>
<td>3.1</td>
<td>100</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>54.8</td>
<td>2.5</td>
<td>1.0</td>
<td>126.3±2.3</td>
</tr>
<tr>
<td>CsA</td>
<td>48.5</td>
<td>4.0</td>
<td>1.6</td>
<td>111.8±3.8*</td>
</tr>
<tr>
<td>SfA</td>
<td>47.6</td>
<td>2.9</td>
<td>1.2</td>
<td>109.8±2.7*</td>
</tr>
<tr>
<td><strong>Apoptotic Cells</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>39.6</td>
<td>7.0</td>
<td>3.1</td>
<td>100</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>34.2</td>
<td>2.5</td>
<td>1.0</td>
<td>86.3±2.6</td>
</tr>
<tr>
<td>CsA</td>
<td>36.2</td>
<td>4.0</td>
<td>1.6</td>
<td>91.3±4.1</td>
</tr>
<tr>
<td>SfA</td>
<td>37.5</td>
<td>4.5</td>
<td>1.8</td>
<td>94.7±4.6</td>
</tr>
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</table>

The absolute numbers of cells and the numbers of cells in the 3 different treatment groups, normalized and expressed as mean ± SE % of the cells counted in the time control group, are displayed. The presence of the mitochondrial permeability transition pore (mPTP) inhibitors (CsA and SfA) at the time of reoxygenation 1 increases the number of live cells (annexin V negative and propidium iodide negative) and 2 attenuates the number of necrotic cells (annexin V positive and propidium iodide positive) but 3 has no effect on the number of apoptotic cells (annexin V positive and propidium iodide negative). *P < 0.01 compared with hypoxia treatment.

was evident within 15–30 min after the onset of SI, with a further reduction in contractile function occurring over the ensuing SI period. During reoxygenation in the control group, there was an improvement in contractile function to a maximum of 29.4 ± 2.0% of the baseline developed force by the end of the reoxygenation period (Fig. 3). Hypoxic preconditioning of the atrial trabeculae before the lethal hypoxia-reoxygenation injury resulted in a significant improvement in the force of contraction compared with the control group (29.4 ± 2.0% in control vs. 48.7 ± 4.3% with hypoxic preconditioning; \( P < 0.001 \); Fig. 3). Treatment with CsA and SfA for the first 30 min of the reoxygenation period resulted in a significant improvement in the force of contraction compared with the control group (29.4 ± 2.0% in control vs. 48.7 ± 2.2% with CsA and 46.1 ± 2.3% with SfA; \( P < 0.001 \); Fig. 3).

Human atrial myocyte model of hypoxia-reoxygenation. After exposure of the atrial myocytes to hypoxia-reoxygenation, the numbers of live, apoptotic, and necrotic cells were determined and the numbers of live, apoptotic, and necrotic cells were then normalized to the percentage of cells in the time control group. In the hypoxic control group of atrial myocytes, exposure to 20 min of hypoxia and 30-min reoxygenation resulted in 62.8 ± 5.3% live cells, 126.3 ± 2.3% necrotic cells, and 86.3 ± 2.6% apoptotic cells (see Table 2). After exposure to 20 min of hypoxia, treatment with CsA and SfA for the 30-min reoxygenation period resulted in a significant improvement in the percentage of live cells [62.8 ± 5.3% in the hypoxic control vs. 91.4 ± 4.1% with CsA (\( P = 0.0006 \)) and 87.2 ± 6.2% with SfA (\( P = 0.003 \)); Table 2]. Treatment with CsA and SfA also resulted in a significant reduction in the percentage of necrotic cells compared with the hypoxic control group [126.3 ± 2.3% in the hypoxic control vs. 111.8 ± 3.8% with CsA (\( P = 0.01 \)) and 109.8 ± 2.7% with SfA (\( P = 0.004 \)); Table 2]. However, the percentage of apoptotic cells in all three treatment groups did not differ [86.3 ± 2.6% in the hypoxic control vs. 91.3 ± 4.1% with CsA (\( P = 0.42 \)) and 94.7 ± 4.6% with SfA (\( P = 0.18 \)); Table 2].

Human atrial myocyte model for induction and detection of mPTP opening. Confocal fluorescence imaging of human atrial myocytes loaded with TMRM revealed mitochondria as fluorescent bands orientated with the longitudinal axis of the cell (see Fig. 4A). TMRM localizes selectively to the mitochondria according to the mitochondrial membrane potential. Figure 4 shows representative images extracted from a time sequence in which a human atrial myocyte was loaded with TMRM and subjected to laser-induced oxidative stress and demonstrates the sequential changes that take place in mitochondrial membrane potential over time. Laser illumination first induces global mitochondrial membrane depolarization, signifying mPTP opening, of the cell in the upper part of the image (Fig. 4A). Subsequently, cell depolarization occurs, indicating opening of the mPTP.
Continued laser-induced oxidative stress results in the global mitochondrial membrane depolarization of the cell in the lower part of the image (Fig. 4C).

The time taken to induce mPTP opening, indicated by global mitochondrial membrane depolarization, was $115.6 \pm 7.8$ s in the control group (Fig. 5). The presence of either DMSO or ethanol vehicle did not influence the time required to induce mPTP opening. The presence of CsA or SfA significantly prolonged the time taken to induce mPTP opening from $115.6 \pm 7.8$ s in control to $189.1 \pm 10.2$ s with CsA ($P < 0.0001$; Fig. 5) and $183 \pm 12.2$ s with SfA ($P < 0.0001$; Fig. 5), indicating that these drugs were able to delay oxidative stress-induced mPTP opening.

DISCUSSION

In this study, we have demonstrated for the first time with human cardiac muscle the role of the mPTP as a viable target for myocardial protection. Subjecting human atrial tissue to two different models of hypoxia-reoxygenation (to simulate hypoxia-reoxygenation injury), we found that pharmacologically inhibiting mPTP opening at the time of reoxygenation was cardioprotective. Using a cell model for inducing and detecting mPTP opening, we then demonstrated for the first time that the cardioprotective effects induced by CsA and SfA at the time of reoxygenation were mediated by the inhibition of mPTP opening.

The human atrial trabecula model has been demonstrated by our group (2, 5, 6, 37, 39) and others (8, 9) to be a reproducible and robust model of hypoxia-reoxygenation injury, with the percentage recovery of baseline contractile function a reproducible measure of protection. Using this model, we demonstrated that inhibition of mPTP opening for the first 30 min of reoxygenation was able to improve the recovery of contractile function to levels similar to those obtained by hypoxic preconditioning, implicating the mPTP as a critical determinant of hypoxia-reoxygenation injury in human myocardium.

In the next part of the study, we used a human atrial myocyte model of hypoxia-reoxygenation injury to demonstrate the protective effect of inhibiting mPTP opening at the time of reoxygenation on cell viability and on the mode of cell death. Interestingly, we found that inhibiting mPTP opening at the time of reoxygenation improved cell viability, with an attenuation in necrotic but not apoptotic cell death. Inhibition of mPTP opening has been demonstrated to protect against both necrotic and apoptotic cell death (10). However, in our human model of hypoxia-reoxygenation injury we were only able to demonstrate a reduction in the necrotic component of cell death. We can speculate that this may be due to the limited reoxygenation time. It may well be that if we had extended the reperfusion time a difference in the apoptotic component of cell death might have been observed between control and treatment groups. An alternative explanation could be that the opening of the mPTP only mediates necrotic and not apoptotic cell death, as suggested by a recent study that demonstrated that the overexpression of cyclophilin D (a component of the mPTP) promoted necrotic cell death but appeared to inhibit apoptotic cell death (29).

The opening of the mPTP has been demonstrated to be a critical determinant of cell death in many different animal models of ischemia-reperfusion injury, and to our knowledge this study is the first to demonstrate a role for the mPTP in the human heart. A previous study (35) demonstrated that CsA could protect slices of human atrial tissue from hypoxia-reoxygenation injury, but in that study CsA was given before the period of hypoxia and the mPTP was not investigated. In our study, we specifically administered two different mPTP inhibitors at the time of reoxygenation, the time period when the mPTP is believed to open. In addition, we demonstrated directly in the human atrial myocyte that these drugs exert their protective effect by inhibiting mPTP opening.

In this study, it was important to demonstrate that two different known mPTP inhibitors were cardioprotective in our human atrial models of hypoxia-reoxygenation injury, especially because CsA can also protect by inhibiting calcineurin. Importantly, the mPTP inhibitor SfA is a more specific inhibitor of mPTP as it does not inhibit calcineurin (7, 34).

In this study, the mPTP inhibitors were given at the time of reoxygenation, immediately after the period of hypoxia, to target the opening of the mPTP that has been demonstrated to occur during the first few minutes of reoxygenation/reperfusion (12, 19, 30, 33). The implications of these findings are of crucial importance in the clinical arena of myocardial protection, in which a cardioprotective strategy that can be applied during the reperfusion phase is far easier to implement than one applied before the index ischemic episode given the unpredictable onset of an acute myocardial infarction. Therefore, in the clinical settings of ischemia-reperfusion injury, such as after an acute myocardial infarction or at the time of cardiac surgery, intervening at the time of reperfusion offers a viable cardioprotective strategy that is under the control of the operator.

In conclusion, we show for the first time in the human muscle model that inhibiting the opening of the mPTP at the time of reoxygenation protects the human myocardium from lethal hypoxia-reoxygenation injury. Inhibition of the opening of mPTP may therefore provide a novel target for cardioprotection in the clinical settings of reperfusion.

GRANTS

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REFERENCES


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