Desflurane-induced post-conditioning against myocardial infarction is mediated by calcium-activated potassium channels: role of the mitochondrial permeability transition pore

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Editor’s key points
- The role of calcium-activated potassium channels in desflurane (DES)-induced cardiac post-conditioning was investigated.
- Coronary artery occlusion followed by reperfusion in mice was used to induce myocardial infarction.
- Protection by DES was mediated by calcium-activated potassium channels.
- The mitochondrial permeability transition pore was also involved.

Background. Desflurane (DES)-induced preconditioning is mediated by large-conductance calcium-activated potassium channels (BKCa). Whether BKCa are involved in anaesthetic-induced post-conditioning is unknown. We tested the hypothesis that DES-induced post-conditioning is mediated by BKCa upstream of the mitochondrial permeability transition pore (mPTP).

Methods. Pentobarbital-anaesthetized male C57Black/6 mice were subjected to 45 min coronary artery occlusion (CAO) and 3 h reperfusion. Animals received either no intervention or dimethylsulphoxide (DMSO, 10 μg kg⁻¹). DES (1.0 MAC, 7.5 vol%) was administered for 18 min, starting 3 min before the end of CAO. The following agents were given either alone or in combination with DES: the BKCa activator NS1619 (1 μg g⁻¹), the BKCa inhibitor iberiotoxin (IbTx, 0.05 μg g⁻²), the mPTP opener atractyloside (ATRA, 25 μg g⁻¹), and the mPTP inhibitor cyclosporine A (CYC A, 10 μg g⁻²). Infarct size (IS) was determined with triphenyltetrazolium chloride and the area at risk with Evans Blue, respectively.

Results. IS in control animals was 48(6)%. Neither DMSO, IbTx nor ATRA affected myocardial IS. DES alone or NS1619 alone or the combination reduced IS (P<0.05), CYC A alone or in combination with IbTx or DES also reduced IS (P<0.05). DES-induced reduction of myocardial IS was completely abolished by IbTx and was partially blocked by ATRA and ATRA partially blocked IS reduction by NS1619.

Conclusions. These data suggest that DES-induced post-conditioning against myocardial infarction is mediated by BKCa and mPTP. Cardioprotection by BKCa activator NS1619 might occur, at least in part, independently of mPTP.

Keywords: anaesthetics volatile, desflurane; heart; ischaemia; potassium channels

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Brief cycles of reperfusion and ischaemia immediately after prolonged myocardial ischaemia confer protection against ischaemia/reperfusion injury via reduction of lethal reperfusion injury.1 This phenomenon is known as ischaemic post-conditioning (IPOST).1

Volatile anaesthetics administered at the onset of reperfusion reduce myocardial IS to a similar extent as IPOST. This phenomenon is referred to as anaesthetic-induced post-conditioning (APOST).2 APOST has been demonstrated in various species, including rabbits,3,4 rats,5 and mice.2,6 and has been shown to reduce myocardial IS,2-4 to improve post-ischaemic left ventricular function7 and to possess antiarrhythmic properties against reperfusion-induced ventricular fibrillation.8

The intracellular mechanisms underlying protection by APOST are incompletely understood. A crucial role in the signalling pathways of APOST has been ascribed to mitochondrial ATP-dependent potassium channels (mKATP).5,9 The mKATP inhibitor 5-hydroxydecanoate has been shown to abolish isoflurane9 and sevoflurane-induced post-conditioning,3 whereas the mKATP opener diazoxide itself confers cardioprotection.10 Activation of mKATP channels results in a lower opening probability of the mitochondrial permeability transition pore (mPTP),11 a putative end-effector of protection by post-conditioning. Inhibition of mPTP opening prevents cell death by both necrosis and apoptosis12 and reduces myocardial IS.9,13
Besides mKATP channels, other mitochondrial potassium channels have been shown to possess cytoprotective properties. Large-conductance Ca\(^{2+}\)-activated potassium channels (BK\(_{Ca}\)) are located at the inner mitochondrial membrane in cardiac myocytes and are known as mediators of cardioprotection induced by tumour necrosis factor-\(\alpha\), sildenafil, ischaemic, and desflurane (DES)-induced preconditioning. Furthermore, BK\(_{Ca}\) have been shown to mediate ischaemic and morphine-induced post-conditioning. The involvement of BK\(_{Ca}\) in the signalling cascade of APOST has not been investigated to date. The current study tested the hypothesis that DES-induced post-conditioning against myocardial infarction is mediated by BK\(_{Ca}\) and investigated whether there is an interaction between BK\(_{Ca}\) and mPTP in mice in vivo.

### Methods

#### Animals

Male C57Black/6 mice (10–12 weeks old) were purchased from Harlan laboratories (Horst, The Netherlands). Animals were housed under controlled conditions (22°C, 55–65% humidity, 12 h light–dark cycle) and were allowed free access to water and a standard laboratory chow. All experimental procedures used in this investigation were reviewed and approved by the Animal Care and Use Committee of the Government of Lower Franconia, Bavaria, Germany. All experiments were in accordance with the Guide for the Care and Use of Laboratory Animals and conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society.

#### Instrumentation and surgical procedures

Instrumentation and surgical procedures were performed as described previously. Briefly, mice were anaesthetized with an i.p. of 60 mg kg\(^{-1}\) sodium pentobarbital (Merial, Hallbergmoos, Germany), repeated as needed to maintain anaesthesia surgically, tested by the deal withdrawal and corneal reflexes. Rectal temperature was maintained at 37.0 (0.1)°C using a servo-controlled heating-pad (FMI, Seeheim, Germany). After intubation of the trachea, animals were ventilated with 50%/50% air–oxygen mixture using a small rodent ventilator (SAR-P 830, CWE Inc., Ardmore, PA, USA) operating in the pressure-controlled mode. A three-lead needle-probe ECG was attached to continuously monitor heart rate and ST-segment elevation. Saline-filled polyethylene (PE)-catheters were placed into the right common carotid artery for measurement of mean arterial pressure (MAP) and into the right jugular vein for continuous fluid administration (20 \(\mu l\) g\(^{-1}\) h\(^{-1}\)). A left thoracotomy at the fourth intercostal space was performed and the left anterior descending coronary artery was exposed, as described previously. Coronary artery occlusion (CAO) was achieved using the hanging weight system and was verified by ST-segment elevation in the ECG and apparent paleness of the myocardial area at risk (AAR). Adequate reperfusion was verified by epicardial hyperaemia and reversion of ECG changes.

### Experimental protocol

The experimental protocol used in this study is illustrated in Figure 1. Mice were randomly assigned to one of the study groups (\(n=7\) per group) by opening a sealed envelope containing information about the study group immediately after completion of surgical procedures. All mice were allowed a 30 min equilibration period. Myocardial ischaemia was induced by 45 min CAO followed by 3 h of reperfusion.

#### Schematic diagram illustrating the experimental protocol.

All mice underwent 45 min of CAO followed by 3 h reperfusion. Mice received either no intervention (CON), DMSO, DES, BK\(_{Ca}\) activator NS1619 (NS1619) alone or in combination with DES (DES+NS1619), and BK\(_{Ca}\) inhibitor iberiotoxin (IbTx) alone or in combination with DES (DES+IbTx). To investigate the role of the mPTP, mice received mPTP opener atractyloside (ATRA) alone or in combination with DES (DES+ATRA), and mPTP inhibitor CYC A alone or in combination with DES (DES+CYC A). A possible interaction of BK\(_{Ca}\) and mPTP was revealed by combining mPTP opener atractyloside and BK\(_{Ca}\) activator NS1619 (NS1619+ATRA) and mPTP inhibitor CYC A and BK\(_{Ca}\) inhibitor iberiotoxin (IbTx+CYC A), respectively. Additionally, mice received ROS scavenger NAC either alone (NAC) or in combination with atractyloside and NS1619 (NS1619+ATRA+NAC).
Control animals (CON) received no treatment before CAO. In Group 2 (DMSO), the vehicle DMSO (10 μl g⁻¹) was injected i.p. 10 min before the end of CAO. DES was administered at a concentration of 1.0 minimum alveolar concentration (MAC, 7.5 vol%)²⁵ for 18 min, starting 3 min before the end of CAO. This type of application was chosen because the first minutes of reperfusion after CAO are critical for the success of post-conditioning.²⁵ Therefore, DES administration was started 3 min before reperfusion to allow an effective level of 1.0 MAC DES with the onset of reperfusion. The BKCa activator NS1619 (1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-benzimidazol-2-one, 1 μg g⁻¹ i.p., Sigma-Aldrich, Taufkirchen, Germany) was administered 15 min before the end of CAO, either alone (NS1619) or in combination with DES (DES+NS1619). The selective BKCa inhibitor iberiotoxin (0.05 μg g⁻¹ i.p., Bachem, Bubendorf, Switzerland)¹⁸ was given 15 min before the onset of reperfusion either alone (IbTx) or in combination with 1.0 MAC DES for 18 min (DES+IbTx).

The following experimental groups were conducted to investigate a possible involvement of the mPTP in cardioprotection afforded by DES-induced post-conditioning. The mPTP opener atracyloside (25 μg g⁻¹ i.p., Sigma-Aldrich)²⁶ was given 10 min before the end of CAO either alone (ATRA) or in combination with DES (1.0 MAC for 18 min, starting 3 min before the end of CAO, DES+ATRA). Furthermore, the mPTP inhibitor cyclosporine A (CYC A) (10 μg g⁻¹ i.p., Tocris Bioscience, Bristol, UK)¹³ was administered 10 min before the onset of reperfusion alone (CYC A) or in combination with 1.0 MAC DES for 18 min (DES+CYC A).

Two experimental groups were conducted to evaluate a possible interaction of BKCa and mPTP. In one group (NS1619+ATRA), mice received the BKCa activator NS1619 (1 μg g⁻¹ i.p. 15 min before reperfusion) in combination with the mPTP opener atracyloside (25 μg g⁻¹ i.p. 10 min before reperfusion). In the other group (IbTx+CYC A), mice were treated with the BKCa inhibitor iberiotoxin (0.05 μg g⁻¹ i.p. 15 min before reperfusion) and the mPTP inhibitor CYC A (10 μg g⁻¹ i.p. 10 min before reperfusion).

In two more experimental groups, the effect of scavenging free radicals by N-acetylcysteine alone (NAC) and on the combination of BKCa channel activator NS1619 and mPTP opener atracyloside (NS1619+ATRA+NAC) was tested. NAC was given i.p. in a concentration of 150 μg g⁻¹ 30 min before the onset of reperfusion.

**Measurement of myocardial IS**

Myocardial IS and AAR were determined using the methods described previously.²¹ Briefly, after 3 h of reperfusion, the left anterior descending coronary artery was re-occluded and 1 ml Evans Blue (0.1 g ml⁻¹, Sigma-Aldrich) was slowly injected into the carotid artery. After i.p. injection of a lethal dose of sodium pentobarbital (150 μg g⁻¹), the heart was rapidly excised. The left ventricle was separated and cut into seven to eight transversal slices of 1 mm thickness. Slices were incubated in 2,3,5-triphenyltetrazolium chloride (20 mg ml⁻¹) for 30 min at 37°C. After overnight fixation in 10% formaldehyde, slices were weighed and digitally photographed. Photographs were analysed using AdobePhotoshop CS 8.0.1 (Adobe Systems Inc., San Jose, CA, USA). Normal zone, AAR, and IS were determined gravimetrically by an investigator blinded to the experimental protocol. Animals with an AAR of <20% were excluded from the study.

**Data acquisition and statistical analysis**

The ECG, systemic haemodynamic parameters, and the body temperature were continuously recorded and analysed on a personal computer (Fujitsu Siemens, Augsburg, Germany) using a haemodynamic data acquisition and analysis software (Notocord® hem 3.5, Croissy sur Seine, France).

Based on our data from studies on the same experimental model,¹⁸ ²¹ we expected a myocardial IS of 50% (IS/AAR). Power analysis revealed a group size of n=7 to detect a reduction of 20% IS from 50% to 30% with a power of 0.8 at α-level of 0.05. All data were analysed for normal distribution using the Kolmogorov–Smirnov test. Normally distributed data were analysed by analysis of variance (ANOVA), which were based on two-tailed F-tests for comparison of components of the factors’ total deviation. Analysis for left ventricle weight, IS, IS/left ventricle weight, and AAR/left ventricle weight was performed using one-way ANOVA, including the factor treatment and post hoc Duncan’s test for significant main effects and interactions. Analysis of haemodynamic data was performed by a 15×7 ANOVA for repeated measures, including the between-factor treatment and the within-factor time point. In the case of any significant main effects or interactions, post hoc one-way ANOVAs were conducted for each group and each time point. Normally distributed data are presented as mean (±SD). Data that were not normally distributed, that is, body weight, left ventricle/body weight, and the weight of the AAR, were analysed using the χ² test. These data are presented as median, interquartile, and full range. Statistical analysis of data was performed using SPSS 17.0 software (The Apache Software Foundation, Forest Hill, MD, USA). Changes in means were considered statistically significant when P<0.05.

**Results**

A total of 115 mice were assigned to the ischaemia–reperfusion experiments to obtain 104 successful experiments. Eleven animals were excluded because of pump failure during CAO (one in the DES group, one in the NS1619 group, two in the DES+IbTx group, one in the DES+CYC A group, and one in the DES+CYC A group) or because the AAR was <20% (one in the DES+ATRA group, one in the NS1619+ATRA group, one in the CYC A group, and one in the NAC group).

**Haemodynamic parameters, AAR**

Haemodynamic parameters at baseline and AAR were similar in all groups, shown in Table 1 and Supplementary Table S1. In the NS1619+ATRA+NAC group, MAP was
myocardial IS. The administration of 1.0 MAC DES during early reperfusion and pharmacological activation of BKCa channels with NS1619 [NS1619; 20 (5)%; \(P<0.05\) vs CON] both significantly reduced myocardial IS compared with the control group (both \(P<0.05\)). The combination of DES and NS1619 did not show an additive effect regarding IS reduction (Fig. 2). The BKCa inhibitor iberiotoxin alone did not significantly affect myocardial IS but completely abolished DES-induced post-conditioning (Fig. 2).

**Role of mPTP in DES-induced post-conditioning**

The mPTP opener atracyloside alone had no effect on myocardial IS (Fig. 2). DES-induced post-conditioning was partially blocked by atracyloside (DES+ATRA; \(P<0.05\)). Pharmacological inhibition of mPTP using CYC A significantly reduced myocardial IS compared with control animals (\(P<0.05\)). The combination of CYC A with DES-induced post-conditioning significantly reduced IS compared with the control group (\(P<0.05\)), but not compared with IS reduction by DES or CYC A alone (Fig. 2).

**Interaction of BKCa and mPTP**

The combination of the BKCa activator NS1619 with the mPTP opener atracyloside resulted in a myocardial IS of 31 (7)% that was significantly larger than NS1619 alone and significantly smaller than atracyloside alone, respectively. The combination of the BKCa inhibitor iberiotoxin with the mPTP inhibitor CYC A resulted in an IS of 28 (14)% that was not different from CYC A alone but significantly smaller than iberiotoxin alone (\(P<0.05\)).
Interaction of free radicals with BK$_{Ca}$ and mPTP

NAC alone did not significantly affect myocardial IS when compared with control animals [40 (6)%]. The cardioprotective effect of the combination of NS1619 and atractyloside was abolished by the administration of NAC (Fig. 2).

**Discussion**

The current study tested the hypothesis that DES-induced post-conditioning against myocardial infarction is mediated by BK$_{Ca}$ and mPTP in mice in vivo.

An 18 min administration of 1.0 MAC DES during early reperfusion reduced myocardial IS by 61% compared with control. These results confirm findings from various other studies regarding APOST either in rabbits, rats, or mice. Furthermore, the results are in line with a previous study from our laboratory, demonstrating a profound reduction in myocardial IS by DES-induced post-conditioning in the same experimental model.

**DES-induced post-conditioning is mediated by BK$_{Ca}$**

Besides mitochondrial ATP-dependent potassium channels (mKATP) that play a role as mediators of both anaesthetic-induced preconditioning and post-conditioning, large-conductance calcium-activated potassium channels (BK$_{Ca}$) have recently been identified as important members of the cardioprotective signalling cascade. In cardiac myocytes, BK$_{Ca}$ are located at the inner mitochondrial membrane and activation of these channels has been demonstrated to protect against cardiac ischaemia/reperfusion injury. Ischaemic and helium-induced preconditioning and also cardioprotection by oestradiol, angiotensin-converting enzyme inhibition, sildenafil, and tumour necrosis factor-α are all mediated by BK$_{Ca}$. More recently, our group demonstrated that DES-induced preconditioning is mediated by BK$_{Ca}$ downstream of protein kinase A. Huhn and colleagues demonstrated a crucial role for BK$_{Ca}$ channels in cardioprotection conferred by ischaemic and morphine-induced post-conditioning in isolated rat hearts.

The current study provides evidence that DES-induced post-conditioning is mediated by BK$_{Ca}$. The BK$_{Ca}$ antagonist iberiotoxin completely abolished IS reduction by DES-induced post-conditioning, indicating that DES-induced post-conditioning is mediated by BK$_{Ca}$ in mice in vivo. Accordingly, the BK$_{Ca}$ agonist NS1619 given before the onset of reperfusion reduced IS to a similar extent as DES. Furthermore, the combination of IS and NS1619 did not further reduce myocardial IS, indicating a similar signalling pathway.

In contrast to our results, Wang and colleagues found that NS1619 given with the onset of reperfusion in the isolated mouse heart did not significantly reduce myocardial IS compared with the vehicle group. Coronary infusion of NS1619 was started with the onset of reperfusion after global ischaemia. Since the first min of reperfusion are most critical to the success of post-conditioning, this onset time of NS1619 might have been too late to achieve cardioprotective effects. In our study, NS1619 was administered 15 min before the onset of reperfusion. This might be the reason for the different results obtained.

**DES-induced post-conditioning is mediated via mPTP**

The mPTP is an unselective ion channel in the inner mitochondrial membrane. Its exact molecular composition is currently not clear and remains to be investigated. Opening of the mPTP causes dissipation of the mitochondrial membrane potential, uncoupling of oxidative phosphorylation, inhibition of ATP production, and mitochondrial swelling and rupture. Finally, mPTP opening leads to cell death by both apoptosis and necrosis.

Inhibition of mPTP opening by CYC A has been shown to reduce cardiac ischaemia/reperfusion injury in several studies in animals and humans. The present results in the murine model confirm these findings. The combination of DES and CYC A in rats in vivo. However, Krolikowski and colleagues found that the combination of two subthreshold doses of CYC A and isoflurane was additive over the effect of one drug alone in rabbits. This might indicate that post-conditioning depends on a defined threshold dose.

DES-induced post-conditioning was partially blocked by the mPTP opener atractyloside, suggesting an important role for mPTP opening in cardioprotection by DES post-conditioning. These findings add new evidence that DES-induced post-conditioning is mediated, at least in part, via mPTP and are in line with results from other studies regarding isoflurane and sevoflurane-induced post-conditioning.

**Interaction between BK$_{Ca}$ and mPTP**

In the literature, data regarding the interaction between mitochondrial K$_{ATP}$ channels and the mPTP in post-conditioning are inconsistent. It was reported that CYC A did not exert cardioprotective effects in the presence of the mKATP antagonist 5-HD. Conversely, cardioprotection by the mKATP agonist diazoxide was abolished by the mPTP opener atractyloside.

BK$_{Ca}$ were suggested to act upstream of the mPTP, since CYC A reduced myocardial IS even in the presence of the BK$_{Ca}$ antagonist paxilline in the isolated rat heart. The same group reported that cardioprotection by the BK$_{Ca}$ activator NS1619 was abolished by the mPTP opener atractyloside, again indicating that BK$_{Ca}$ act upstream of the mPTP. However, in both studies, NS1619 was given before 30 min ischaemia, but atractyloside was given during early reperfusion. The present study shows that NS1619-induced cardioprotection was only partially blocked by the mPTP opener atractyloside, indicating that cardioprotection by BK$_{Ca}$ activator NS1619 might be, at least in part, independent from the mPTP. In our study, both drugs were
given briefly before the onset of reperfusion. To our knowledge, evidence is lacking regarding the duration of the effect of NS1619 in vivo. Thus, we speculate that the results of these previous studies might be due to the fact that NS1619, when given before ischaemia, has a too short duration of action and thus only atractyloside was present during early reperfusion. In the current study, mPTP opening by atractyloside partially abolishes cardioprotection by the BKCa activator NS1619. However, it is currently not clear whether these results are due to BKCa opening or due to BKCa-independent effects of NS1619, possibly directly on the mitochondrion. Further studies are needed to clarify this issue.

### Interaction of free radicals with BKCa and mPTP

With the onset of myocardial reperfusion after ischaemic periods, oxygen returns into the cardiomyocytes and causes oxidative stress by generating reactive oxygen species (ROS). ROS cause myocardial injury. Additionally, ROS limit the availability of the cardioprotective molecule nitric oxide during early reperfusion, thereby aggravating myocardial injury. In our study, the free radical scavenger NAC alone does not affect myocardial IS but abolishes the cardioprotective effect of the combination of NS1619 and atractyloside. This indicates that cardioprotection by BKCa activator NS1619 is, at least in part, dependent on free radicals. Mechanistically, activation of BKCa channels leads to potassium influx into the mitochondria. This in turn causes swelling of the matrix and generation of ROS. One can speculate that activation of BKCa causes ROS generation that leads to cardioprotection. Thus, pharmacological blockade of ROS generation by NAC abolishes the cardioprotective effect of BKCa activation. However, whether there is a direct interaction between BKCa channel activation and ROS generation and whether this is a reason for the cardioprotective effect of BKCa activation cannot be concluded from the present data and remains to be investigated.

The results of the current study should be interpreted within the constraints of several potential limitations. The size of myocardial AAR and the amount of coronary collateral blood flow were shown to be crucial determinants of myocardial IS. However, the AAR was not different among groups. Coronary collateral blood flow was not measured in this study. However, small rodents are reported to have little if any coronary collateral blood flow. Thus, it is highly improbable that AAR and coronary collateral blood flow contribute to differences in myocardial IS. Myocardial oxygen consumption was not directly quantified in this study. Therefore, we cannot completely exclude that changes in myocardial oxygen supply/demand ratio might have contributed to our results. The pharmacological inhibitors and activators used in this study were shown to be selective for their respective targets, but we cannot exclude that other proteins, particularly ion channels, that are involved in cardioprotective signalling might have been affected by one of the drugs. However, activators and inhibitors of BKCa channels were shown not to interact with mKATP and vice versa. The BKCa activator NS1619 has been shown to act directly on the mitochondria that might account, at least in part, for its cardioprotective properties independent of BKCa. However, previous studies demonstrated that cardioprotective effects of NS1619 were blocked by the BKCa inhibitor paxilline, indicating that protective effects of NS1619 depend on BKCa. Furthermore, we did not determine BKCa activity or mPTP opening directly in this investigation.

In conclusion, the present study demonstrates that DES-induced post-conditioning against myocardial infarction is mediated via mitochondrial large-conductance calcium-activated potassium channels and the mPTP in mice in vivo. Further studies are needed to support the assumption that BKCa is acting upstream of the mPTP in the signalling cascade of APOST.

### Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

### Declaration of interest

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