tential, formation of ROS and energy production. Toyoda et al. (2000) suggested differential role of sarcolemmal and mitochondrial K_{ATP} channels in preconditioning. Reduction of myocardial infarct size is mediated largely by mitochondrial K_{ATP} channels, but functional recovery is mediated by sarcolemmal K_{ATP} channels. Mitochondrial K_{ATP} channels also play an important role in the prevention of cardiomyocyte apoptosis (Akao et al., 2001) and in late preconditioning protection (Bolli, 2001). Considerable cross-talk was reported between sarcolemmal and mitochondrial K_{ATP} channels (Sasaki et al., 2001). A lot of experimental studies indicate the mitochondrial K_{ATP} channels as the main end-effector of preconditioning, but role of sarcolemmal K_{ATP} channels cannot be dismissed totally.

Sacrolemmal K_{ATP} channels may modulate myocardial infarct size by reducing Ca^{2+} enterance into the myocytes from outside and by attenuating Ca^{2+} overload. There are three possible explanations about reduction of infarct size by mitochondrial K_{ATP} channels. First, the decreased mitochondrial Ca^{2+} overload during ischemia (Wang et al., 2001) may prevent opening of the mitochondrial permeability transition pores and guarantee optimal conditions for ATP production (Holmuhamedov et al., 1998). Second, Garlid and Pancek (2003) proposed that opening of the mitochondrial K_{ATP} channel decreases the ischemia-induced swelling of the mitochondrial interspace, which would preserve functional coupling between adenosine nucleotide translocase and mitochondrial creatine kinase (prevention of structure/function) (Kowaltowski et al., 2001; Laclau et al., 2001). This secures the transport of newly synthesized ATP from the site of production by ATP synthase on the inner mitochondrial membrane to the cytosol. Thus, high-energy phosphate substrates are supplied continuously from the mitochondria to the sites of energy consumption. Third, mitochondrial K_{ATP} channels may elicit protection in basis of the observation of increased formation of ROS (Fobes et al., 2001). ROS would stimulate the activation of multiple transcriptional factors (NF-κB, activator protein-1, protein kinases, protein phosphatase, etc.), ultimately leading to cardioprotection.

Table 1. Volatile anesthetics and opioids with mostly enhancing effects on mitochondrial and sarcolemmal K_{ATP} channels

Anesthetic agent	K_{ATP} channel	
	Mitochondrial	Sarcolemmal
Isoflurane	↑	↓/→
Sevoflurane	↑	?
Desflurane	↑	↑
Morphine	↑	?
Fentanyl	↑	→
Remifentanil	↑	→

→, no effect; ↑, increased effect; ↓, decreased effect.
K_{ATP}, ATP-sensitive potassium.

Pharmacogogical preconditioning

Preconditioning can be pharmacologically induced by anesthetics. Volatile anesthetics, opioids and other anesthetics were found to induce or enhance preconditioning in cardiac tissue.

Volatile anesthetics

Lots of studies have evaluated the cardiac preconditioning effects of isoflurane, enfrurane and halothane (Mattheussen et al., 1993; Warltier et al., 1988). Sevoflurane, the most frequently used volatile anesthetic in Japan, has also improves postischemic mechanical and coronary function, and reduces infarct size (Novalija and Stowe, 1998; Toller et al., 1999b). Desflurane, a volatile anesthetic used outside of Japan, is suggested the beneficial cardioprotection (Toller et al., 2000b). The beneficial effects of volatile anesthetics on myocardial protection by their pharmacological preconditioning have been evaluated by reduction in infarct size, postischemic contractility and coronary vasculature. Halothane, isoflurane and sevoflurane reduced the number of neutrophils sequestered in the coronary vasculature

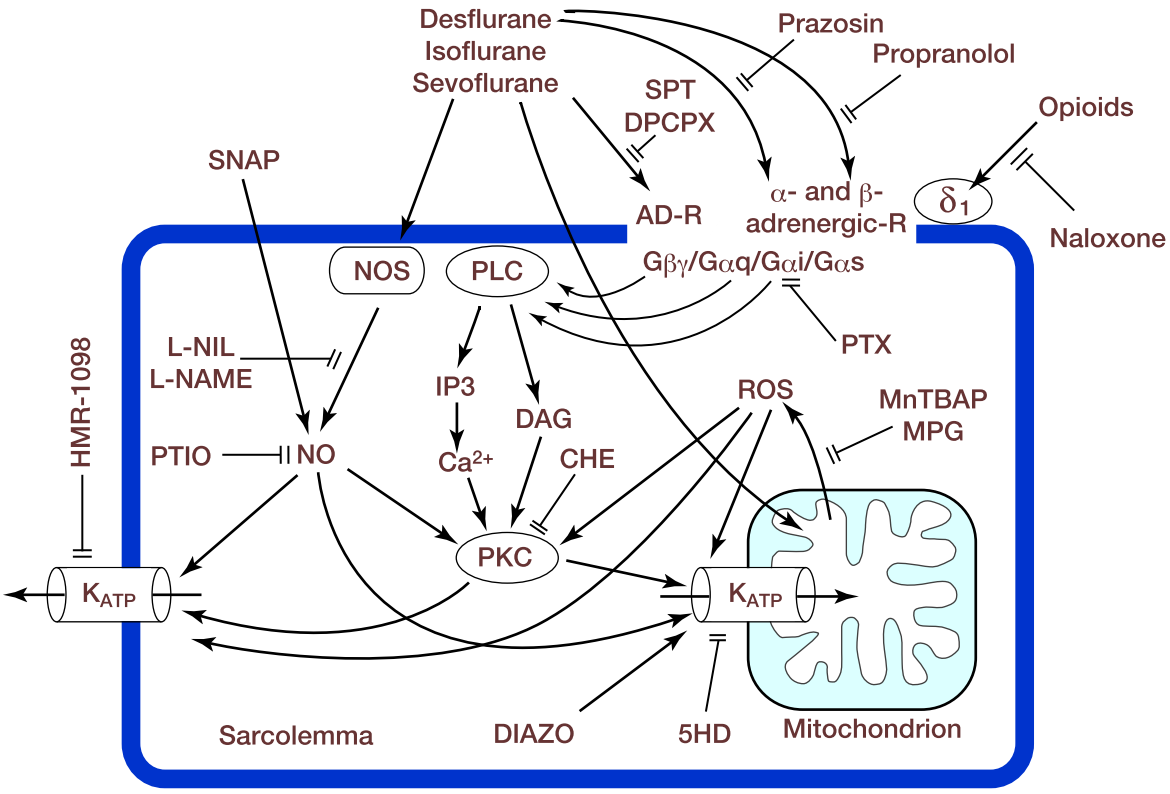

Fig. 2. Signaling pathways involved in volatile anesthetic- and opioid-induced preconditioning. Multiple signaling cascades prime the sarcolemmal and mitochondrial K_{ATP} channels, allowing rapid opening at the initiation of ischemia. This figure is changed slightly from the original figure quoted from the reference of Zaugg et al., 2003. Abbreviations of the blockers and signaling components are referred to Table 2 and the legend of Fig. 1.

after ischemia (Kowalski et al., 1997; Heindl et al., 1999a). A similar effect was also shown for platelets (Heindl et al., 1998; Heindl et al., 1999b). Reduced neutrophils/platelet entrapment by anesthetics was accompanied by enhancement of postischemic mechanical function (Heindl et al., 1999a; Heindl et al., 1999b). Novalija et al. (1999) measured coronary flow changes in response to endotherial-dependent and independent vasodilators. Sevoflurane preserved the reaction elicited by both types of vasodilators during the reperfusion period better than no treatment.

The favorable oxygen supply/demand ratio provided by volatile anesthetics is not required for preconditioning because volatile anesthetic-induced protection occurs under cardioplegic arrest (Lochner et al., 1994). Many characteristics of preconditioning by volatile anesthetics are similar to those of ischemic preconditioning. These involve activation of A_1 adenosine receptors, PKC and K_{ATP} channels. Ischemic preconditioning and anesthetic preconditioning similarly reduce Ca^{2+} loading, augment post-ischemic contractile responsiveness to Ca^{2+} and decrease infarct size (An et al., 2001). Whether volatile anesthetics induce late preconditioning is still unknown.

Key signaling components involved in preconditioning elicited by volatile anesthetics were unraveled recently by means of specific blockers for signaling steps (Fig. 2) and the specific openers and blockers for signaling steps are shown in Table 2. The main routes of activation by volatile anesthetics involve the Gai protein-coupled adenosine receptor and the production of NO, probably by modulation of NOS activity (Zaugg et al., 2002). These two signaling pathways converged at the level of PKC, although alternative routes for NO could be operative as well. Finally

Table 2. Specific openers and blockers for signaling steps of pharmacological preconditioning

Selectivity	Opener	References	Blocker	References
Adenosine receptors			SPT	Cope et al., 1997
			DPCPX	Kersten et al., 1997
PKC			CHE	Toller et al., 1999a
			Bicindolylmaleimide	Toller et al., 1999a
Gi-proteins			PTX	Toller et al., 1999a
Mitochondtrial K_{ATP} channel				
	Nicorandil	Piriou et al., 1997	5HD	Toller et al., 1999a;
	DIAZO	Sato et al., 2000		Piriou et al., 1997;
				Hanouz et al., 2002;
				Zaugg et al., 2002;
				Shimizu et al., 2001
Sarcolemmal K_{ATP} channel			HMR-1098	Hanouz et al., 2002
NOS			L-NIL, L-NAME	Müllenheim et al., 2002
NO	*S*-nitroso-*N*-acetyl-DL-penicillamine		PTIO	
ROS			MnTBAP, MPG	Müllenheim et al., 2002
α-adrenergic receptor			Phentramine, Prazosin	Hanouz et al., 2000
β-adrenergic receptor			Propranolol	Hanouz et al., 2000
δ-opioid	DADLE	McPherson and Yao, 2001	Naloxone	Tomai et al., 1999b
δ_1-selective	TAN-67	Fryer et al., 1999		

CHE, chelerythrine; DADLE, D-Ala2-D-Leu5-enkephalin; DIAZO, diazoxide; DPCPX, 8-cyclophenyl-1,3-dipropylxanthine; 5HD, 5-hydroxydecanoate; Gi, inhibitory G; L-NIL, L-*N*6-(l-iminoethyl)lysine; L-NAME, N^G-nitro-L-arginine methyl ester; MnTBAP, Mn(III)tetrakis(4-benzoic acid)porphyrine chloride; MPG, *N*-(2-mercaptopropionyl)glycine; NO, nitric oxide; NOS, NO synthase; PKC, protein kinase C; PTIO, 2-(4-carboxyphenyl)-4,4',5,5'-tetramethylimidazole-l-oxyl-3-oxide; PTX, pertussis toxin; ROS, reactive oxygen species; SPT, 8-sulfophenyl theophylline.

volatile anesthetics activate mitochondrial and sarcolemmal K_{ATP} channels, thereby providing cardioprotection. There is a question of whether the sarcolemmal K_{ATP} channel or mitochondrial K_{ATP} channel is more important in mediating volatile anesthetic-induced preconditioning. Although several experimental studies have addressed this question (Toller et al., 2000; Zaugg et al., 2002; Hara et al., 2001), it is important to note that considerable cross-talk is documented between sarcolemmal and mitochondrial K_{ATP} channels (Sasaki et al., 2001) and the importance of the individual K_{ATP} channels may vary among experimental approaches and species differences. Sato et al. (2000) proposed the concept of channel priming (including the sarcolemmal and mitochondrial K_{ATP} channels) by volatile anesthetics. The primed channel state allows easy and rapid opening at the initiation of ischemia. On the other hand, volatile anesthetics mediate their protection by selectively enhancing mitochondrial K_{ATP} channels through the triggering of multiple PKC-coupled signaling pathways, namely NO and adenosine/Gi signaling pathways (Zaugg et al., 2002). Biosynthesis of NO plays a pivotal role in reducing ischemic damage in heart tissue. Moreover, NO and cGMP may be major players in volatile anesthetic-induced cardioprotection. Both NO/cGMP signaling and basal NOS activity play a fundamental role in pacing associated-preconditioning. Volatile anesthetics may differentially modulate the activity of the various isoenzymes of NOS (nNOS, eNOS, iNOS), which are ubiquitous but heterogeneously distributed in myocytes. The observation that isoflurane-induced preconditioning is inhibited by free radical scavengers supports the concept that generation of radicals, either by means of altered NO synthesis

or by enhanced formation of ROS/NO (possibly by opening mitochondrial K_{ATP} channels), is important (Müllenheim et al., 2002). These results show that the preconditioning effects of volatile anesthetics are triggered by multiple signaling cascades and mediated mainly by mitochondrial K_{ATP} channels, but sarcolemmal K_{ATP} channels may also contribute to the protection induced by volatile anesthetics.

Volatile anesthetics can elicit coronary protection through an ischemic (pharmacological) preconditioning-like effect. Ischemic preconditioning is known to reduce ICAM-1 production and neutrophil entrapment, and to preserve the response to vasodilators (Rubino and Yellon., 2000). Treatment with volatile anesthetics decreased neutrophil adhesion on the endothelium and expression of CD11b, which forms an integrin with CD18, while the anesthetic did not affect endothelial cell actibation vis-à-vis neutrophils (Mobert et al., 1999). These findings supports that administration of volatile anesthetics prior to reperfusion maintains coronary vasculature.

Opioids

The involvement of opioid receptors in ischemic preconditioning has been demonstrated in various animal species (Schultz and Gross 2001) and humans (Bell et al., 2000). Among opioid receptor subtypes, δ-opioid receptors are responsible for ischemic preconditioning in rats and humans. Although opioid receptors are located more abundant in the central nervous system, they are also located in the heart (Bell et al., 2000). Opioid receptor subtype distribution in heart is considered to differ between species; δ- and κ-, but not μ-opioid receptors are expressed in the rat heart (Schultz and Gross, 2001), δ- and μ-opioid receptors are dominant compared with κ-opioid receptors in human atrium (Schultz and Gross, 2001). Naloxone blocked the effect of ischemic preconditioning in isolated hearts, and quaternary naloxone, which does not cross the blood-brain barrier, eliminated the protection by ischemic preconditioning in in vivo models (Chien et al., 1999). These findings suggest that it is in the heart itself that opioid receptors play a role in protection by ischemic preconditioning.

Morphine and fentanyl are capable of binding to δ- and κ-receptors although they bind dominantly with μ-receptors (Jaffe and Martin, 1990). Selective δ- (McPherson and Yao, 2001) and δ_1-(Huh et al., 2001) agonists induce cardioprotection. Conversely protection by morphine and fentanyl is abolished by δ-antagonists (McPherson and Yao, 2001). The role of κ-receptors remains controversial. Activation of opioid receptors results in a potent cardioprotection effect similar to classical and late preconditioning. Currently, it is considered that selective activation of δ_1 opioid agonists exert this protection through an interaction with Gi-proteins and activation PKC, tyrosine kinases (and possibly other kinases, such as MAPK), and ultimately K_{ATP} channels, especially mitochondrial K_{ATP} channels (Fryer et al., 1999). Morphine 1 mM induced the same protection as preconditioning with 5 min of ischemia and that protection were abolished by 5-hydroxydecanoate (a specific mitochondrial K_{ATP} channel blocker), which emphasizes the dominant role of mitochondrial K_{ATP} channels in preconditioning (Liang and Gross, 1999).

Remifentanil, a new comer of fentanyl family, induces also the pharmacological preconditioning effect as well as morphine and fentanyl through the same mechanism (Zang et al., 2004, 2005).

Conclusions: This review summarizes recent knowledge about the key cellular events involved in ischemic and pharmacological preconditioning. Many characteristics of anesthetic-induced preconditioning are similar to ischemic preconditioning. However, there may be fundamental differences in terms of signal intensity and the potential to concomitantly injured cardiac tissue. Of many anesthetics, volatile anesthetics are arguably the most promising agents as cardiopro-

tectors. They demonstrated the beneficial effect against ischemic-reperfusion injury better than any other anesthetic. Volatile anesthetics provide cardioprotection at clinically relevant concentrations and morphine has also been to be protective at clinical concentrations. Therefore, volatile anesthetic and morphine might be good choice for the patients at risk of myocardial ischemia.

References

1 Akao M, Ohler A, O'Rourke B, Marban E. Mitocondorial ATP-sensitive potassium channels inhibit apoptosis induced by oxidative stress in cardiac cells. Circ Res 2001;88:1267–1275.

2 An J, Varadarajan SG, Novalija E, Stowe DF. Ischemic and anesthetic preconditioning reduces cytosolic [Ca^{2+}] and improves Ca^{2+} responses in intact hearts. Am J Physiol Heart Circ Physiol 2001;281: H1508–H1523.

3 Bell SP, Sack MN, Patel A, Opie LH, Yellon DM. Delta opioid receptor stimulation mimics ischemic preconditioning in human heart muscle. J Am Coll Cardiol 2000;36:2296–2302.

4 Bernardo NL, Okubo S, Maaieh MM, Wood MA, Kukreja RC. Delayed preconditioning with adenosine is mediated by opening of ATP-sensitive K^+ channels in rabbit heart. Am J Physiol 1999;277: H128–H135.

5 Bolli R, Marban E. Molecular and cellular mechanisms of myocardial stunning. Physiol Rev 1999;79: 609–634.

6 Bolli R. Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: an overview of a decade of research. J Mol Cell Cardiol 2001;33: 1897-18918.

7 Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982;66:1146–1149.

8 Chien GL, Mohtadi K, Wolff RA, Van Winkle DM. Naloxone blockade of myocardial ischemic preconditioning does not require central nervous system participation. Basic Res Cardiol 1999;94:136–143.

9 Cohen MV, Yang XM, Liu GS, Heusch G, Downey JM. Acetylcholine, bradykinin, opioids, and phenylephrine, but not adenosine, trigger preconditioning by generating free radicals and opening mitochondrial K_{ATP} channels. Circ Res 2001;89:273–278.

10 Cope DK, Impastato WK, Cohen MV, Downey JM. Volatile anesthetics protect the ischemic rabbit myocardium from infarction. Anesthesiology 1997; 86:699–709.

11 Fobes RA, Steenbergen C, Murphy E. Diazoxide-induced cardioprotection requires signaling through a redox-sensitive mechanism. Circ Res 2001;88:802–809.

12 Fryer RM, Hsu AK, Eells JT, Nagase H, Gross GJ. Opioid-induced second window of cardioprotection. Potential role of mitochondrial K_{ATP} channels. Circ Res 1999;84:846–851.

13 Garlid KD, Pancek P. Mitochondrial potassium transport: the k^+ cycle. Biochim Biophys Acta 2003; 1606:23–41.

14 Guo Y, Jones WK, Xuan YT, Tang XL, Bao W, Wu WJ, et al. The late phase of ischemic preconditioning is abrogated by targeted disruption of the inducible NO synthase gene. Proc Natl Acad Sci USA 1999;96:11507–11512.

15 Hanouz J, Yvon A, Massetti M, Lepage O, Babatasi G, Khayat A, et al. Mechanisms of desflurane-induced preconditioning in isolated human right atria in vitro. Anesthesiology 2002;97:33–41.

16 Hanouz JL, Massetti M, Guesne G, Chanel S, Babatasi G, Rouet R, et al. In vitro effects of desflurane, sevoflurane, isoflurane, and halothane in isolated human right atria. Anesthesiology 2000;92:116–124.

17 Hara T, Tomiyasu S, Sungsam C, Fukusaki M, Sumikawa K. Sevoflurane protects stunned myocardium through activation of mitochondrial ATP-sensitive potassium channels. Anesth Analg 2001;92:1139–1145.

18 Heindl B, Reichle FM, Zahler S, Conzen PF, Becker BF. Sevoflurane and isoflurane protect the reperfused guinea pig heart by reducing postischemic adhesion of polymorphonuclear neutrophils. Anesthesiology 1999a;91:521–530.

19 Heindl B, Becker BF, Zahler S, Conzen PF. Volatile anaesthetics reduce adhesion of blood platelets under low-flow conditions in the coronary system of isolated guinea pig heart. Acta Anaesthesiol Scand 1998;42:995–1003.

20 Heindl B, Conzen PF, Becker BF. The volatile anesthetic sevoflurane mitigates cardiodepressive effects of platelets in reperfused hearts. Basic Res Cardiol 1999b;94:102–111.

21 Holmuhamedov EL, Jovanovic S, Dzeja PP, Jovanovic A, Terzic A. Mitochondrial ATP-sensitive potassium channels modulate cardiac mitochondrial function. Am J Physiol 1998;275:H567–H576.

22 Huh J, Gross GJ, Nagase H, Liang BT. Protection of cardiac myocytes via δ1-opioid receptors, protein kinase C, and mitochondrial K_{ATP} channels. Am J Physiol 2001;280:H377–H383.

23 Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Goodman Gillman A, Rall TW, Nies AS, Taylor P, eds. The pharmacological basis of therapeutics, 8th ed. New York: Pergamon Press; 1990. p. 485–521.

24 Jordan JE, Zhao ZQ, Vinten-Johansen J. The role of neutrophils in myocardial ischemia-reperfusion injury. Cardiovasc Res 1999;43:860–878.
25 Kawamura S, Yoshida K, Miura T, Mizukami Y, Matsuzaki M. Ischemic preconditioning translocates PKC-δ and -ε, which mediate functional protection in isolated rat heart. Am J Physiol 1998;275:H2266–H2271.
26 Kersten J, Orth KG, Pagel PS, Mei DA, Gross GJ, Warltier DC. Role of adenosine in isoflurane-induced cardioprotection. Anesthesiology 1997;86:1128–1139.
27 Kowalski C, Zahler S, Becker BF, Flaucher A, Conzen PF, Gerlach E, et al. Halothane, isoflurane, and sevoflurane reduce postischemic adhesion of neutrophils in coronary system. Anesthesiology 1997;86:188–195.
28 Kowaltowski AJ, Seetharaman S, Paucek P, Garlid KD. Bioenergetic consequences of opening the ATP-sensitive K^+ channel of the heart mitochondria. Am J Physiol Heart Circ Physiol 2001;280:H649–H657.
29 Laclau MN, Boudina S, Thambo JB, Tariosse L, Gouverneur G, Bonoron-Adele S, et al. Cardioprotection by ischemic preconditioning preserves mitochondrial function and functional coupling between adenine nucleotide translocase and creatine kinase. J Mol Cell Cardiol 2001;33:947–956.
30 Li G, Chen S, Lu E, Li Y. Ischemic preconditioning improves preservation with cold blood cardioplegia in valve replacement patients. Eur J Cardiothorac Surg 1999;15:653–657.
31 Liang BT, Gross GJ. Direct preconditioning of cardiac myocytes via opioid receptors and K_{ATP} channels. Circ Res 1999;84:1396–1400.
32 Light PE, Bladen C, Winkfein RJ, Walsh MP, French RJ. Molecular basis of protein kinase C-induced activation of ATP-sensitive potassium channels. Proc Natl Acad Sci USA 2000;97:9058–9063.
33 Lochner A, Harper IS, Salie R, Genade S, Coetzee AR. Halothane protects the isolated rat myocardium against excessive total intracellular calcium and structural damage during ischemia and reperfusion. Anesth Analg 1994;79:226–233.
34 Lu EX, Chen SX, Hu TH, Xui LM, Yuan MD. Preconditioning enhances myocardial protection in patients undergoing open heart surgery. J Thorac Cardiovasc Surg 1998;46:28–32.
35 Mattheussen M, Rusy BE, Van Aken H, Flameng W. Recovery of function and adenosine triphosphate metabolism following myocardial ischemia induced in the presence of volatile anesthetics. Anesth Analg 1993;76:69–75.
36 Maxwell SRJ, Lip GYH. Reperfusion injury: a review of the pathophysiology, clinical manifestations and therapeutic options. Int J Cardiol 1997;58:95–117.
37 McPherson BC, Yao Z. Signal transduction of opioid-induced cardioprotection in ischemia-reperfusion. Anesthesiology 2001;94:1082–1088.
38 Möbert J, Zahler S, Becker BF, Conzen PF. Inhibition of neutrophil activation by volatile anesthetics decreases adhesion to cultured human endothelial cells. Anesthesiology 1999;90:1372–1381.
39 Müllenheim J, Ebel D, Fräßdorf J, Preckel B, Thämer V, Schlack W. Isoflurane preconditions myocardium against infarction via release of free radicals. Anesthesiology 2002;96:934–940.
40 Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124–1136.
41 Nakano A, Cohen MV, Downey JM. Ischemic preconditioning. From basic mechanisms to clinical applications. Pharmacol Ther 2000;86:263–275.
42 Ninomiya H, Otani H, Lu K, Uchiyama T, Kido M, Imamura H. Enhanced IPC by activation of pertussis toxin-sensitive and -insensitive G protein-coupled purinoceptors. Am J Physiol Heart Circ Physiol 2002; 282:H1933–H1943.
43 Novalija E, Stowe DF. Prior preconditioning by ischemia or sevoflurane improves cardiac work per oxygen use in isolated guinea pig hearts after global ischemia. Adv Exp Med Biol 1998;454:533–542.
44 Novalija E, Fujita S, Kampine JP, Stowe DF. Sevoflurane mimics ischemic preconditioning effects on coronary flow and nitric oxide release in isolated hearts. Anesthesiology 1999;91:701–712
45 Okubo S, Xi L, Bernardo NL, Yoshida K, Kukreja RC. Myocardial preconditioning: basic concepts and potential mechanisms. Mol Cell Biochem 1999;196: 3–12.
46 Opie LH. Cell death: myocardial infarction. In: Opie LH, ed. The heart. Physiology, from cell to circulation, 3rd ed. Philadelphia: Lippincott-Raven Publishers; 1998a. p. 543–561.
47 Opie LH. Oxygen lack: ischemia and angina. In: Opie LH, ed. The heart. Physiology, from cell to circulation, 3rd ed. Philadelphia: Lippincott-Raven Publishers; 1998b. p. 515–541.
48 Opie LH. Myocardial reperfusion: new ischemic syndromes. In: Opie LH, ed. The heart. Physiology, from cell to circulation, 3rd ed. Philadelphia: Lippincott-Raven Publishers; 1998c. p. 563–588.
49 Piriou V, Ross S, Pigott D, Evans R, Foex P. Beneficial effects of concomitant administration of isoflurane and nicorandil. Br J Anaesth 1997;79:68–77.
50 Rubino A, Yellon DM. Ischemic preconditioning of the vasculature: an overlooked phenomenon for protecting the heart? Trends Pharmacol Sci 2000; 21:225–230.
51 Sasaki N, Sato T, Marban E, O'Rourke B. ATP consumption by uncoupled mitochondria activates sarcolemmal K_{ATP} channels in cardiac myocytes. Am J Physiol Heart Circ Physiol 2001;280:H1882–H1888.

52 Sato T, Sasaki N, O'Rourke B, Marban E. Adenosine primes the opening of mitochondrial ATP-sensitive potassium channels: a key step in ischemic preconditioning? Circulation 2000;102:800–805.
53 Schultz JEJ, Gross GJ. Opioids and cardioprotection. Pharmacol Ther 2001;89:123–137.
54 Shimizu J, Sakamoto A, Ogawa R. Activation of the adenosine triphosphate sensitive mitochondrial potassium channel is involved in the cardioprotective effect of isoflurane. J Nippon Med Sch 2001;68:238–245.
55 Strasser RH, Braun-Dullaeus R, Waldendzik H, Maruetant R. Alpha 1-receptor-independent activation of protein kinase C in acute myocardial ischemia: mechanisms for sensitization of the adenyl cyclase system. Circ Res 1992;70:1304–1312.
56 Szmagala P, Morawski W, Krejca M, Gburek T, Bochenek A. Evaluation of perioperative myocardial tissue damage in ischemically preconditioned human heart during aortocoronary bypass surgery. J Cardiovasc Surg (Torino) 1998;39:791–795.
57 Tomai F, Crea F, Chiariello L, Gioffre PA. Ischemic preconditioning in humans. Models, mediators, and clinical relevance. Circulation 1999a;100:559–563.
58 Tomai F, Crea F, Gaspardone A. Effects of naloxaone on myocardial ischemic preconditioning in humans. J Am Coll Cardiol 1999b;33:1863–1869.
59 Toyoda Y, Friehs I, Parker RA, Levitsky S, McCully JD. Differential role of sarcolemmal and mitochondrial K_{ATP} channels in adenosine-enhanced ischemic preconditioning. Am J Physiol Heart Circ Physiol 2000;279:H2694–H2703.
60 Toller WG, Montgomery MW, Pagel PS, Hettrick DA, Warltier DC, Kersten JR. Isoflurane-enhanced recovery of canine stunned myocardium: role for protein kinase C? Anesthesiology 1999a;91:713–722.
61 Toller WG, Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Sevoflurane reduces myocardial infarct size and decreases the time threshold for ischemic preconditioning in dogs. Anesthesiology 1999b;91:1437–1446.
62 Toller WG, Kersten JR, Gross ER, Pagel PS, Warltier DC. Isoflurane preconditions myocardium against infarction via activation of inhibitory guanine nucleotide binding proteins. Anesthesiology 2000a;92:1400–1407.
63 Toller WG, Gross ER, Kersten JR, Pagel PS, Gross GJ, Warltier DC. Sarcolemmmal and mitochondrial adenosine triphosphate-dependent potassium channels. Mechanism of desflurane-induced cardioprotection. Anesthesiology 2000b;92:1731–1739.
64 Vahlhaus C, Schulz R, Post H, Onallah R, Heusch G. No prevention of ischemic preconditioning by the protein kinase C inhibitor staurosporine in swine. Circ Res 1996;79:407–414.
65 Wang L, Cherednichenko G, Hernandez L, Halow J, Camacho SA, Figueredo V, et al. Preconditioning limits mitochondrial Ca^{2+} during ischemia in rat hearts: role of K_{ATP} channels. Am J Physiol Heart Circ Physiol 2001;280:H2321–H2328.
66 Warltier DC, al Wathiui MH, Kampine JP, Schmeling WT. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. Anesthesiology 1988;69:552–565.
67 Zang Y, Irwin MB, Wong TM. Remifentanil preconditioning protects against ischemic injury in the intact rat heart. Anesthesiology 2004;101:918–925.
68 Zang Y, Irwin MB, Wong TM, Chen M, Cao CM. Remifentanil preconditioning confers cardioprotection via cardiac κ- and δ-opioid receptors. Anesthesiology 2005;102:371–378.
69 Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K_{ATP} channels via multiple signaling pathways. Anesthesiology 2002;97:4–14.
70 Zaugg M, Lucchinetti E, Uecker M, Pasch T, Schaub MC. Anaesthetics and preconditioning. Part I. Signalling and cytoprotective mechanisms. Br J Anaesth 2003;91:551–565.

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