

ATP-dependent potassium channels as a key target for the treatment of myocardial and vascular dysfunction

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Purpose of review

The aim of this review is to highlight the most recent and interesting articles on the physiologic properties and functions of ATP-dependent potassium channels in the cardiovascular system and on the role of the potassium channel openers for the treatment of cardiovascular dysfunction.

Recent findings

The initial efforts in the development of potassium channel openers focused on the management of systemic hypertension. Lately, the range of possible indications for potassium channel openers has increased to include pulmonary hypertension and stable angina pectoris. The discovery of a connection between the mitochondrial ATP-dependent potassium channels and the phenomenon of cardiac preconditioning created potential new uses for potassium channel openers in myocardial ischemia, in unstable angina, in preoperative and perioperative settings, and for the preservation of organs for transplant.

Summary

The most recent data on the physiologic roles of sarcolemmal and mitochondrial ATP-dependent potassium channels and the pharmacology of potassium channel openers in the cardiovascular system are summarized and discussed. Finally, the effects of potassium channel opener drugs including minoxidil, nicorandil, pinacidil, bimakalin, and levosimendan, a dual-action potassium channel opener and calcium sensitizer with inodilator and cardioprotective activity, are discussed.

Keywords

ATP-dependent potassium channel openers, therapeutic use, vasodilation, preconditioning, cardioprotection

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Abbreviations

AMI	acute myocardial infarction
K _{ATP}	ATP-dependent potassium channels
sarcK _{ATP}	sarcolemmal ATP-dependent potassium channels
mitoK _{ATP}	mitochondrial ATP-dependent potassium channels
KCO	potassium channel opener
PCWP	pulmonary capillary wedge pressure

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Introduction

ATP-dependent potassium channels (K_{ATP}) are inward rectifying channels inhibited by physiologic intracellular ATP levels. These channels are present in tissue-specific phenotypes in several tissues in the central nervous system, heart and vasculature, lungs, pancreas, and urinary bladder. K_{ATP} activity was initially detected at the level of sarcolemmal membrane (sarcK_{ATP}) and also recently at the mitochondrial level (mitoK_{ATP}). Potassium channel openers (KCOs) are a class of chemically diverse agents sharing K_{ATP} as their common target. Their structure-activity relations and therapeutic potential were recently reviewed by Mannhold [1••], and current knowledge on their regulation has been summarized by Campbell *et al.* [2•]. Experimental studies have identified a wide range of possible clinical uses for KCOs, including roles as bronchodilators, vasodilators, and bladder relaxants [3]. The discovery of the effect of KCOs on cardiac mitochondria and the hypothesis of a connection with the phenomenon of cardiac preconditioning created further possibilities for the development of cardioprotective applications [4••]. We provide an overview of the most recent literature in the field and discuss experiences in the use of KCOs for the treatment of myocardial and vascular dysfunctions. We also discuss examples of the use of drugs such as nicorandil and pinacidil as cardiovascular therapies. Special attention is given to levosimendan, a novel inotropic drug, which, in addition to a calcium sensitizer effect *via* binding to troponin C, opens both sarcolemmal and mitochondrial K_{ATP} [5,6].

Physiologic roles of K_{ATP} in the cardiovascular system

K_{ATP} play important roles in many cellular functions. Such channel activity has been described in the vasculature muscle cells and in cardiomyocytes at both the sarcolemmal and the mitochondrial levels.

Sarcolemmal K_{ATP}

There is strong evidence that sarcK_{ATP} in the vasculature muscle cells are involved in the maintenance of the basal vascular tone in the coronary and mesenteric arteries and arterioles [7,8]. Furthermore, in conditions of hypoxia, sarcK_{ATP} contribute to the regulation of vascu-

lar tone in renal, cerebral, and pulmonary arteries [9]. These channels were rapidly recognized by researchers as physiologically important entities and possible pharmacologic targets for manipulating the function of vascular smooth muscle [10,11]. In fact, all the drugs in clinical use that are described primarily as KCOs (nicorandil, diazoxide, minoxidil, and pinacidil) have hypertension among their therapeutic uses [3].

K_{ATP} is present also on the sarcolemmal membrane of cardiomyocytes. However, 20 years after the discovery of such channels, many questions about their physiologic or pathophysiologic roles in the cardiac cells remain unresolved, despite the availability of detailed structural information and the existence of a broad consensus that they bridge bioenergetics to cellular electrical excitability [12••,13–16]. Authors generally agree that $\text{sarc}K_{ATP}$ provide a means of linking the electrical activity of the cardiomyocyte to its metabolic state. In particular, these channels modulate the duration of the cardiac action potential [17].

A brief but comprehensive commentary on recent advances in the identification and function of these channels in the cardiac tissue is available [18]. The gating mechanism of K_{ATP} and their function-to-form relation was also recently reviewed [19].

Mitochondrial K_{ATP}

Structural information is lacking for $\text{mito}K_{ATP}$, but there is ample evidence linking channel opening to protection against ischemia-reperfusion injury or apoptosis in cardiac myocytes. In their recent review, Garlid *et al.* [4••] discuss the role of the $\text{mito}K_{ATP}$ in cardiac function and cardioprotection. The authors conclude that in low-energy states, the opening of the channels triggers increased mitochondrial reactive oxygen species production, thereby amplifying a cell-signaling pathway that leads to gene transcription and cell growth. In high-energy states, the opening of $\text{mito}K_{ATP}$ prevents the matrix contraction that would otherwise occur during high rates of electron transport. $\text{Mito}K_{ATP}$ -mediated mitochondrial volume regulation, in turn, prevents disruption of mitochondrial structure and function and facilitates efficient energy transfers between mitochondria and myofibrillar ATPases.

Reperfusion of the heart after a period of ischemia leads to the opening of a nonspecific pore in the inner mitochondrial membrane, known as the mitochondrial permeability transition pore. This transition causes mitochondria to become uncoupled and capable of hydrolyzing rather than synthesizing ATP. Recent data suggest the involvement of $\text{mito}K_{ATP}$ in the indirect regulation of the pore and in ensuring that, in case of prolonged ischemia, cell death continues down an apoptotic, rather than a necrotic, pathway [20•].

Pharmacology of potassium channel openers in the cardiovascular system

The KCOs activate $\text{sarc}K_{ATP}$ on vascular smooth muscle cells and cardiac myocytes, leading to potassium ion efflux and membrane hyperpolarization, which in turn reduce calcium influx and shorten the duration of the action potential. This results in a negative inotropic effect in cardiomyocytes and vasodilatation of blood vessels [21–23].

Vasodilatation

The KCOs have an unusual chemical and structural diversity [1••,24,25•,26]. Nevertheless, all have a similar pharmacologic profile with regard to their vasorelaxant effect, as studied *in vitro* in aorta or coronary artery preparations. KCO activities *in vivo* have been reviewed comprehensively, with particular emphasis on their antihypertensive effects [24]. Members of the first generation of drugs such as cromakalim and pinacidil were intended for the treatment of hypertension but failed to show clear advantages over angiotensin-converting enzyme inhibitors or calcium antagonists.

An active drug discovery effort in the field and developments in the chemistry of KCOs led to the discovery of new cromakalin analogues and benzothiazidine derivatives, which were shown to be potent vasorelaxant agents. Studies of the vasodilation effect of the KCO minoxidil have been reviewed [25•–27].

Levosimendan, an inodilator recently introduced for acute congestive heart failure, opens $\text{sarc}K_{ATP}$ in vascular smooth muscle, among other effects. The drug has been shown to be an active vasodilator in arteries, arterioles, and veins by opening $\text{sarc}K_{ATP}$, thereby exerting an effect on systemic vascular resistance and organ microcirculation [28–33]. Interestingly, a comparison between levosimendan and pinacidil on their beneficial effect on diastolic coronary flow in isolated perfused heart showed that the two drugs are inhibited by glibenclamide but in different modes. The authors hypothesized that the two drugs do not share the same binding side on $\text{sarc}K_{ATP}$ [28].

Antiarrhythmic effects

Whether or not opening K_{ATP} (either $\text{sarc}K_{ATP}$ or $\text{mito}K_{ATP}$, selectively or otherwise) contributes to an antiarrhythmic effect in ischemia or during reperfusion remains unresolved at present. In a recent study by Fischbach *et al.* [34•], selective opening of $\text{sarc}K_{ATP}$ was associated with some potential for ventricular arrhythmia, whereas no similar hazard attached to the opening of $\text{mito}K_{ATP}$.

Separately, it has been reported that activation of $\text{mito}K_{ATP}$ by nicorandil and 3-pyridyl pinacidil was associated with an antiarrhythmic effect in an anesthetized

rabbit model of myocardial ischemia-reperfusion [35]. Horinaka *et al.* [36] have also demonstrated that nicorandil protects against lethal ischemic ventricular arrhythmias in conscious rats with acute myocardial infarction (AMI). These data were confirmed in human by Ueda *et al.* [37], who showed that intravenous nicorandil can reduce the occurrence of ventricular fibrillation and QT dispersion in AMI patients who undergo successful coronary angioplasty.

Similarly, both short-term and long-term treatment with levosimendan, which opens both sarcK_{ATP} and mitoK_{ATP}, has favorable effects on cardiac arrhythmias during coronary artery occlusion in conscious rats [38].

Preconditioning effects

There is strong evidence for an involvement of mitoK_{ATP} in ischemic or myocardial preconditioning—the phenomenon whereby brief periods of ischemia protect the myocardium against a more sustained ischemic insult. The effect of preconditioning may be manifested as a marked reduction in infarct size, amelioration of myocardial stunning, or reduced incidence of cardiac arrhythmias. A recent review has summarized the evidence that opening of mitoK_{ATP} acts as a trigger and/or downstream mediator in the phenomenon of ischemic pharmacologically induced preconditioning [39•].

Baczko *et al.* [40•] reported recently that opening cardiac sarcK_{ATP} may also protect the heart against ischemia-reperfusion injury. The basis of this effect is currently thought to be prevention of reoxygenation-induced Ca²⁺ overload *via* a mechanism linked to hyperpolarization of the membrane potential during diastole. Levosimendan opens both sarcK_{ATP} and mitoK_{ATP} [31,41–45]. This drug mitigates infarct size, myocardial stunning, ischemia, and the incidence of cardiac arrhythmias in animal models [38,46–48]. Levosimendan has been shown in controlled trials to reduce mortality in patients with severe low-output heart failure and those with left ventricular failure after AMI [49,50].

It has been proposed that a volatile anesthetic such as isoflurane may also directly activate mitoK_{ATP} or influence sarcK_{ATP} and thus induce preconditioning [51,52, 53•]. Stowe and Kevin [54••] have recently reviewed cardiac preconditioning by volatile anesthetics such as halothane, isoflurane, and sevoflurane. Although such drugs have long been known to provide protection against the effects of cardiac ischemia and reperfusion, the mechanism of action behind such cardioprotection is still unclear. In fact, in addition to the preconditioning effect, the use of volatile anesthetics may result in a cardioprotective effect by inducing coronary vasodilation, reducing contractility with corresponding decreased metabolic demand, and also by a direct decrease in myocardial Ca²⁺ entry through L-type Ca²⁺ channels [54••].

Therapeutic effects of potassium channel openers in the cardiovascular system

The value of KCOs in protecting the ischemic myocardium resides in their vasodilator effect on coronary arteries and in their property of mimicking the endogenous cardioprotective phenomenon of ischemic preconditioning. KCOs can therefore be used in several critical clinical situations such as angina and AMI and their consequences, including left ventricular dysfunction. In addition, KCOs may be increasingly used in interventional cardiology and cardiac surgery to protect organs such as the heart and the lung from ischemic injury.

Angina

The Impact of Nicorandil in Angina (IONA) study evaluated the effect of nicorandil in patients with stable angina. Nicorandil was effective in reducing the rates of the combined primary endpoint of coronary heart disease mortality, myocardial infarction, or admission for chest pain, and the secondary endpoint of coronary heart disease mortality, myocardial infarction, or unstable angina as well as the rates of cardiovascular events [55]. It has been suggested that these beneficial effects originated from the inhibition of oxidative stress-induced apoptosis in cardiac myocytes through activation of mitoK_{ATP} [56]. An update on the clinical data available on the use of nicorandil in angina was published recently [57].

By contrast, the results of a recent study of bimakalin in patients with exercise-induced angina pectoris due to coronary artery disease did not support the use of such a drug for this particular therapeutic intent [58]. The authors reported in fact that bimakalin had a dose-dependent vasodilatory activity but did not exert any anti-ischemic benefits in patients.

Myocardial ischemia (ischemic heart disease)

Recent preclinical studies show that the KCO nicorandil induces late preconditioning against myocardial infarction in conscious rabbits [59]. The early administration of nicorandil as an adjunct to reperfusion in patients with AMI proved beneficial for cardioprotection, whereas intravenous magnesium was not [60]. Furthermore, intravenous nicorandil administered in conjunction with coronary reperfusion therapy was associated with better clinical and functional outcomes in patients with AMI [37,61•]. Similarly, the inodilator levosimendan has been shown to reduce the risk of worsening heart failure and death in patients with left ventricular failure complicating AMI [50,62].

Beneficial effect on left ventricular diastolic function

Coronary hypoperfusion has been extensively known to first alter left ventricular diastolic function and therefore increase left atrial pressure and pulmonary capillary wedge pressure (PCWP). Interestingly, a significant reduction in PCWP was noted during studies of the he-

modulatory effects of hypotension induced by KRN2391 in isoflurane-anesthetized dogs [63]. A sustained decrease in PCWP has also been reported in response to nicorandil treatment of patients with congestive heart failure [64]. Similarly, the inodilator levosimendan has been shown to cause a marked reduction in PCWP in patients with severe low-output heart failure, after cardiac surgery, and in a case of peripartum cardiomyopathy [49,65,66].

Beneficial effects on pulmonary hypertension

The KCOs inhibit hypoxic pulmonary vasoconstriction and have been advocated for the management of pulmonary hypertension [67]. In a porcine model of endotoxemia, pretreatment with levosimendan substantially ameliorated pulmonary hypertension with no adverse effects on gas exchange [68].

In a recent report, an infant with myocardial infarction due to congenital stenosis of the left coronary artery and with consecutive left ventricular dysfunction and mitral regurgitation experienced refractory pulmonary hypertension and recurrent refractory pulmonary hypertension crises [69]. Catecholamines to support cardiac function, or pulmonary vasodilators such as inhaled nitric oxide, had no effect. Treatment with levosimendan improved left ventricular dysfunction, increased cardiac index, and decreased pulmonary vascular resistance. The authors suggested the use of levosimendan as a long-term inotropic agent and pulmonary vasodilator in infants with depressed cardiac function.

Perioperative cardioprotection

The benefits of percutaneous coronary intervention in AMI can be limited by reperfusion injury. Nicorandil reduces infarct size in animal models. The Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage by a KCO (J-WIND-KATP) designed a prospective, randomized, multicenter study to evaluate whether nicorandil reduced myocardial infarct size and improved regional wall motion when used as adjunctive therapy for AMI [70]. The primary endpoints were estimated infarct size and left ventricular function. The results of the study have not yet been published.

A possible additional use for KCOs is in the relief of pain related to the first inflation of an intraaortic balloon in coronary angioplasty. This hypothesis is corroborated by studies and clinical experience showing that preconditioning has an effect on the severity of cardiac pain [71,72]. For example, intracoronary administration of nicorandil has been used for the treatment of spontaneous microvascular spasm with ST segment elevation and attenuated the delayed contrast medium washout seen in right coronary angioplasty [73].

The KCOs have also been proposed for reducing the risk of ischemic adverse events after coronary artery bypass grafting [74,75••]. The potential of mitoK_{ATP} as a target in surgical cardioprotection was reviewed recently by McCully and Levitsky [76].

Effects on organ perfusion and preservation for transplant

The KCOs do not promote the “steal” phenomenon and therefore improve blood flow and oxygen availability to ischemic tissues. For instance, in a canine model, levosimendan increased blood flow to the renal medulla, decreased renal medullary and cortical vascular resistance, increased blood flow to the small intestine and liver, and reduced vascular resistance in these organs; it increased hepatic blood flow; reduced cerebral vascular resistance, and reduced skeletal muscle vascular resistance [33].

Regarding organ preservation for transplant, the addition of pinacidil to the cardioplegic solution in a heart preservation study demonstrated that hyperpolarized arrest with KCOs improves donor heart preservation when administered in a histidine-buffered lactobionate-enriched vehicle [77].

In a complementary study published recently, it was demonstrated that pinacidil protects the lungs during warm ischemia in the course of lung transplantation, thus avoiding the metabolic derangements often seen with traditional hyperkalemic preservation solutions [78]. The authors of this report recorded significantly improved graft function and reduced histologic injury with pinacidil protection compared with the warm ischemia control isolated lungs.

Conclusion

The K_{ATP} have attracted wide-ranging therapeutic interest as potential targets in a range of cardiovascular conditions. The first generation of drugs such as cromakalim and pinacidil were intended for the treatment of hypertension but failed to show clear advantages over angiotensin-converting enzyme inhibitors or calcium antagonists. Since then, however, the emergence of new chemical entities with better tissue selectivity and better pharmacokinetic and pharmacodynamic profiles has created additional possible clinical applications for this class.

In particular, the discovery of a connection between the mitoK_{ATP} and the phenomenon of cardiac preconditioning has created potential new uses for KCOs in myocardial ischemia, in unstable angina, and in preoperative and perioperative settings. Nicorandil has been tested successfully in angina.

Levosimendan may be one of the more promising compounds in this field, given that it was construed as a

dual-action KCO and calcium sensitizer that exerts at the same time positive inotropic, vasodilatory, and cardioprotective effects [79•]. This drug has been approved in 30 countries for the treatment of acute and decompensated heart failure and is currently being tested in preoperative, perioperative, and postoperative settings. The results of these studies are expected in the relatively near future.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

1 Mannhold R: KATP channel openers: structure-activity relationships and therapeutic potential. *Med Res Rev* 2004, 24:213–266.
This comprehensive review (359 references) describes the relation between the chemical structure of KCOs and their pharmacology. All chemical families of active compounds are listed.

2 Campbell JD, Sansom MS, Ashcroft FM: Potassium channel regulation. *EMBO Rep* 2003, 4:1038–1042.
This is a basic study of the relation between the structure and function of the K_{ATP} channel.

3 Jahangir A, Terzic A, Shen WK: Potassium channel openers: therapeutic potential in cardiology and medicine. *Expert Opin Pharmacother* 2001, 2:1995–2010.

4 Garlid KD, Dos Santos P, Xie ZJ, et al.: Mitochondrial potassium transport: the role of the mitochondrial ATP-sensitive $K(+)$ channel in cardiac function and cardioprotection. *Biochim Biophys Acta* 2003, 1606:1–21.
This important review discusses the current hypothesis on the role of mitochondrial K_{ATP} in preconditioning and cardioprotection.

5 Szilagyi S, Pollesello P, Levijoki J, et al.: The effects of levosimendan and OR-1896 on isolated hearts, myocyte-sized preparations and phosphodiesterase enzymes of the guinea pig. *Eur J Pharmacol* 2004, 486:67–74.

6 Sorsa T, Pollesello P, Permi P, et al.: Interaction of levosimendan with cardiac troponin C in the presence of cardiac troponin I peptides. *J Mol Cell Cardiol* 2003, 35:1055–1061.

7 Daut J, Klieber HG, Cyrus S, et al.: KATP channels and basal coronary vascular tone. *Cardiovasc Res* 1994, 28:811–817.

8 Nakajima S, Kurokawa K, Imamura N, et al.: A study on the hypotensive mechanism of pinacidil: relationship between its vasodilating effect and intracellular Ca^{2+} levels. *Jpn J Pharmacol* 1989, 49:205–213.

9 Knot HJ, Brayden JE, Nelson MT: Calcium channels and potassium channels. In *Biochemistry of Smooth Muscle Contraction*. Edited by Bárány M. San Diego: Academic Press; 1996:203–219.

10 Nielsen-Kudsk JE, Boesgaard S, Aldershvile J: K^{+} channel opening: a new drug principle in cardiovascular medicine. *Heart* 1996, 76:109–116.

11 Quayle JM, Nelson MT, Standen NB: ATP-sensitive and inwardly rectifying potassium channels in smooth muscle. *Physiol Rev* 1997, 77:1165–1232.

12 O'Rourke B: Evidence for mitochondrial K^{+} channels and their role in cardioprotection. *Circ Res* 2004, 94:420–432.
In this updated review of the recent progress in understanding the physiologic role of $mitoK_{ATP}$, outstanding questions and controversies are highlighted with the intent of stimulating additional investigation on this topic.

13 Quast U: [Structure of ATP-dependent potassium channels: SUR/Kir6 molecular complex]. *J Ann Diabetol Hotel Dieu* 2000:1–12

14 Aguilar Bryan L, Clement JP, Gonzalez G, et al.: Toward understanding the assembly and structure of KATP channels. *Physiol Rev* 1998, 78:227–245.

15 MacKinnon R: Potassium channels. *FEBS Lett* 2003, 555:62–65.

16 Dabrowski MA, Tarasov A, Ashcroft FM: Mapping the architecture of the ATP-binding site of the KATP channel subunit Kir6.2. *J Physiol* 2004, 557:347–354.

17 Riccioppo Neto F, Mesquita O Jr, Olivera GB: Antiarrhythmic and electrophysiological effects of the novel KATP channel opener, rilimakalim, in rabbit cardiac cells. *Gen Pharmacol* 1997, 29:201–205.

18 Bienengraeber M, Hodgson DM, Zingman LV, et al.: Identity and function of cardiac $K(ATP)$ channels. *J Mol Cell Cardiol* 2003, 35:433–435.

19 Enkvetchakul D, Nichols CG: Gating mechanism of KATP channels: function fits form. *J Gen Physiol* 2003, 122:471–480.

20 Halestrap AP, Clarke SJ, Javadov SA: Mitochondrial permeability transition pore opening during myocardial reperfusion: a target for cardioprotection. *Cardiovasc Res* 2004, 61:372–385.
This is an important discussion of the role of the permeability transition pore in cardioprotection and offers a proposal for alternative mechanisms.

21 Satoh H: Comparative electrophysiological and mechanical actions of ATP-sensitive potassium channel openers in canine Purkinje fibers. *Gen Pharmacol* 1993, 24:565–575.

22 Edwards G, Weston AH: Potassium channel openers and vascular smooth muscle relaxation. *Pharmacol Ther* 1990, 48:237–258.

23 Weston AH, Longmore J, Newgreen DT, et al.: The potassium channel openers: a new class of vasorelaxants. *Blood Vessels* 1990, 27:306–313.

24 Clapham JC: In vivo vascular effects of potassium channel activation in isolated blood vessels. In *Potassium Channels and Their Modulators*. Edited by Evans JM, et al. London: Taylor & Francis; 1996, 197–220.

25 Sebille S, De Tullio P, Boverie S, et al.: Recent developments in the chemistry of potassium channel activators: the cromakalim analogs. *Curr Med Chem* 2004, 11:1213–1222.
This recent review asserts that the current big effort is the drug discovery of new KCOs.

26 Cecchetti V, Calderone V, Tabarrini O, et al.: Highly potent 1,4-benzothiazine derivatives as $K(ATP)$ -channel openers. *J Med Chem* 2003, 46:3670–3679.

27 Sica DA: Minoxidil: an underused vasodilator for resistant or severe hypertension. *J Clin Hypertens (Greenwich)* 2004, 6:283–287.

28 Kaheinen P, Pollesello P, Levijoki J, et al.: Levosimendan increases diastolic coronary flow in isolated guinea-pig heart by opening ATP-sensitive potassium channels. *J Cardiovasc Pharmacol* 2001, 37:367–374.

29 Krassoi I, Pataricza J, Kun A, et al.: Calcium-dependent vasorelaxant capacity of levosimendan in porcine and human epicardial coronary artery preparations. *Cardiovasc Drugs Ther* 2000, 14:691–693.

30 Pagel PS, Hettrick DA, Wartier DC: Comparison of the effects of levosimendan, pimobendan, and milrinone on canine left ventricular-arterial coupling and mechanical efficiency. *Basic Res Cardiol* 1996, 91:296–307.

31 Pataricza J, Hohn J, Petri A, et al.: Comparison of the vasorelaxing effect of cromakalim and the new inodilator, levosimendan, in human isolated portal vein. *J Pharm Pharmacol* 2000, 52:213–217.

32 Delle-Karth G, Buberl A, Geppert A, et al.: Hemodynamic effects of a continuous infusion of levosimendan in critically ill patients with cardiogenic shock requiring catecholamines. *Acta Anaesthesiol Scand* 2003, 47:1251–1256.

33 Pagel PS, Hettrick DA, Wartier DC: Influence of levosimendan, pimobendan, and milrinone on the regional distribution of cardiac output in anaesthetized dogs. *Br J Pharmacol* 1996, 119:609–615.

34 Fischbach PS, White A, Barrett TD, et al.: Risk of ventricular proarrhythmia with selective opening of the myocardial sarcolemmal versus mitochondrial ATP-gated potassium channel. *J Pharmacol Exp Ther* 2004, 309:554–559.
This critical discussion of the roles of $sarck_{ATP}$ and $mitoK_{ATP}$ suggests that the selectivity of KCOs may be related to a proarrhythmic risk.

35 Das B, Sarkar C: Selective mitochondrial KATP channel activation by nicorandil and 3-pyridyl pinacidil results in antiarrhythmic effect in an anesthetized rabbit model of myocardial ischemia/reperfusion. *Methods Find Exp Clin Pharmacol* 2003, 25:97–110.

36 Horinaka S, Kobayashi N, Yabe A, et al.: Nicorandil protects against lethal ischemic ventricular arrhythmias and up-regulates endothelial nitric oxide synthase expression and sulfonylurea receptor 2 mRNA in conscious rats with acute myocardial infarction. *Cardiovasc Drugs Ther* 2004, 18:13–22.

37 Ueda H, Nakayama Y, Tsumura K, et al.: Intravenous nicorandil can reduce the occurrence of ventricular fibrillation and QT dispersion in patients with successful coronary angioplasty in acute myocardial infarction. *Can J Cardiol* 2004, 20:625–629.

38 Lepran I, Papp JG: Effect of long-term oral pretreatment with levosimendan on cardiac arrhythmias during coronary artery occlusion in conscious rats. *Eur J Pharmacol* 2003, 464:171–176.

39 Gross GJ, Peart JN: KATP channels and myocardial preconditioning: an update. *Am J Physiol Heart Circ Physiol* 2003, 285:H921–H930.
This review presents evidence that supports a role for both $sarck_{ATP}$ and $mitoK_{ATP}$ channels as a trigger and/or downstream mediator in the phenomenon of IPC or pharmacologically induced PC.

40 Baczko I, Giles WR, Light PE: Pharmacological activation of plasma-membrane KATP channels reduces reoxygenation-induced Ca^{2+} overload

- in cardiac myocytes via modulation of the diastolic membrane potential. *Br J Pharmacol* 2004, 141:1059–1067.
- K_{ATP} channels bridge the metabolic and electrophysiological state of the myocytes. Their role in cardioprotection is studied on the cellular level
- 41 Yokoshiki H, Katsube Y, Sunagawa M, et al.: Levosimendan, a novel Ca²⁺-sensitizer, activates the glibenclamide-sensitive K⁺ channel in rat arterial myocytes. *Eur J Pharmacol* 1997, 333:249–259.
 - 42 Yokoshiki H, Sperelakis N: Vasodilating mechanisms of levosimendan. *Cardiovasc Drugs Ther* 2003, 17:111–113.
 - 43 Pataricza J, Krassoi I, Hohn J, et al.: Functional role of potassium channels in the vasodilating mechanism of levosimendan in porcine isolated coronary artery. *Cardiovasc Drugs Ther* 2003, 17:115–121.
 - 44 Kopustinskiene DM, Pollesello P, Saris NE: Levosimendan is a mitochondrial K(ATP) channel opener. *Eur J Pharmacol* 2001, 428:311–314.
 - 45 Kopustinskiene DM, Pollesello P, Saris NE: Potassium-specific effects of levosimendan on heart mitochondria. *Biochem Pharmacol* 2004. (in press)
 - 46 Kersten JR, Montgomery MW, Pagel PS, et al.: Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K(ATP) channels. *Anesth Analg* 2000, 90:5–11.
 - 47 Jamali IN, Kersten JR, Pagel PS, et al.: Intracoronary levosimendan enhances contractile function of stunned myocardium. *Anesth Analg* 1997, 85:23–29.
 - 48 Du-Toit EF, Muller CA, McCarthy J, et al.: Levosimendan: effects of a calcium sensitizer on function and arrhythmias and cyclic nucleotide levels during ischemia/reperfusion in the Langendorff-perfused guinea pig heart. *J Pharmacol Exp Ther* 1999, 290:505–514.
 - 49 Follath F, Cleland JG, Just H, et al.: Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002, 360:196–202.
 - 50 Moiseyev VS, Poder P, Andrejevs N, et al.: Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction: a randomized, placebo-controlled, double-blind study (RUSSLAN). *Eur Heart J* 2002, 23:1422–1432.
 - 51 Nakae Y, Kohro S, Hogan QH, et al.: Intracellular mechanism of mitochondrial adenosine triphosphate-sensitive potassium channel activation with isoflurane. *Anesth Analg* 2003, 97:1025–1032.
 - 52 An J, Stadnicka A, Kwok WM, et al.: Contribution of reactive oxygen species to isoflurane-induced sensitization of cardiac sarcolemmal adenosine triphosphate-sensitive potassium channel to pinacidil. *Anesthesiology* 2004, 100:575–580.
 - 53 Tanaka K, Ludwig LM, Krolkowski JG, et al.: Isoflurane produces delayed preconditioning against myocardial ischemia and reperfusion injury: role of cyclooxygenase-2. *Anesthesiology* 2004, 100:525–531.
- This is an important study of the cardioprotective effect of the volatile anesthetic isoflurane.
- 54 Stowe DF, Kevin LG: Cardiac preconditioning by volatile anesthetic agents: a defining role for altered mitochondrial bioenergetics. *Antioxid Redox Signal* 2004, 6:439–448.
- Which is the mechanism by which volatile anesthetics exert a cardioprotection? This review summarizes the major developments in a field that is exciting to clinicians and basic scientists alike.
- 55 IONA Study Group: Effect of nicorandil on coronary events in patients with stable angina: the impact of nicorandil in angina (IONA) randomised trial. *Lancet* 2002, 359:1269–1275.
 - 56 Nagata K, Obata K, Odashima M, et al.: Nicorandil inhibits oxidative stress-induced apoptosis in cardiac myocytes through activation of mitochondrial ATP-sensitive potassium channels and a nitrate-like effect. *J Mol Cell Cardiol* 2003, 35:1505–1512.
 - 57 Anonymous: Nicorandil for angina: an update. *Drug Ther Bull* 2003, 41:86–88.
 - 58 Burian M, Piske M, Petkovic D, et al.: Lack of anti-ischemic efficacy of the potassium channel opener bimakalim in patients with stable angina pectoris. *Cardiovasc Drugs Ther* 2004, 18:37–46.
 - 59 Tang XL, Xuan YT, Zhu Y, et al.: Nicorandil induces late preconditioning against myocardial infarction in conscious rabbits. *Am J Physiol Heart Circ Physiol* 2004, 286:H1273–H1280.
 - 60 Mizuo N, Iwao I, Yoshiya M, et al.: Comparison between nicorandil and magnesium as an adjunct cardioprotective agent to percutaneous coronary intervention in acute anterior myocardial infarction. *Circ J* 2004, 68:192–197.
 - 61 Sugimoto K, Ito H, Iwakura K, et al.: Intravenous nicorandil in conjunction with coronary reperfusion therapy is associated with better clinical and functional outcomes in patients with acute myocardial infarction. *Circ J* 2003, 67:295–300.
- This retrospective clinical study shows that nicorandil treatment was associated with better myocardial perfusion and a better functional and clinical outcome than percutaneous coronary intervention alone, and this beneficial effect was maintained for a long time, particularly in patients with anterior AMI.
- 62 Sonntag S, Sundberg S, Lehtonen LA, et al.: The calcium sensitizer levosimendan improves the function of stunned myocardium after percutaneous transluminal coronary angioplasty in acute myocardial ischemia. *J Am Coll Cardiol* 2004, 43:2177–2182.
 - 63 Takeda S, Ozawa Y, Tomaru T: Haemodynamic effects of hypotension induced by KRN2391 and nicardipine in isoflurane anaesthetized dogs. *Can J Anaesth* 1997, 44:1002–1007.
 - 64 Tsutamoto T, Kinoshita M, Hisanaga T, et al.: Comparison of hemodynamic effects and plasma cyclic guanosine monophosphate of nicorandil and nitroglycerin in patients with congestive heart failure. *Am J Cardiol* 1995, 75:1162–1165.
 - 65 Labriola C, Siro Brigiani M, Carrata F, et al.: Hemodynamic effects of levosimendan in patients with low-output heart failure after cardiac surgery. *Int J Clin Pharmacol Ther* 2004, 42:204–211.
 - 66 Benlolo S, Lefoll C, Katchatouryan V, et al.: Successful use of levosimendan in a patient with peripartum cardiomyopathy. *Anesth Analg* 2004, 98:822–824.
 - 67 Dumas JP, Bardou M, Goirand F, et al.: Hypoxic pulmonary vasoconstriction. *Gen Pharmacol* 1999, 33:289–297.
 - 68 Oldner A, Konrad D, Weitzberg E, et al.: Effects of levosimendan, a novel inotropic calcium-sensitizing drug, in experimental septic shock. *Crit Care Med* 2001, 29:2185–2193.
 - 69 Luther YC, Schulze-Neick I, Stiller B, et al.: [Levosimendan-long-term inodilation in an infant with myocardial infarction.] *Z Kardiol* 2004, 93:234–239.
 - 70 Minamino T, Jiyoung K, Asakura M, et al.: Rationale and design of a large-scale trial using nicorandil as an adjunct to percutaneous coronary intervention for ST-segment elevation acute myocardial infarction: Japan-working groups of acute myocardial infarction for the reduction of necrotic damage by a K-ATP channel opener (J-WIND-KATP). *Circ J* 2004, 68:101–106.
 - 71 Leesar MA, Stoddard M, Ahmed M, et al.: Preconditioning of human myocardium with adenosine during coronary angioplasty. *Circulation* 1997, 95:2500–2507.
 - 72 Tomai F, Crea F, Gasparidone A, et al.: Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K⁺-channel blocker. *Circulation* 1994, 90:700–705.
 - 73 Satoshi K, Ichiro I, Takuji K, et al.: Intracoronary administration of nicorandil for the treatment of spontaneous microvascular spasm with ST segment elevation. *Circ J* 2004, 68:267–269.
 - 74 Yellon DM, Alkhalaf AM, Pugsley WB: Preconditioning the human myocardium. *Lancet* 1993, 342:276–277.
 - 75 Laskey WK, Beach D: Frequency and clinical significance of ischemic preconditioning during percutaneous coronary intervention. *J Am Coll Cardiol* 2003, 42:998–1003.
- The short- and long-term clinical consequences of ischemic preconditioning were assessed during percutaneous coronary intervention in a clinical study enrolling 382 patients
- 76 McCully JD, Levitsky S: Mitochondrial ATP-sensitive potassium channels in surgical cardioprotection. *Arch Biochem Biophys* 2003, 420:237–245.
 - 77 Hoenicke EM, Sun X, Strange RG, et al.: Donor heart preservation with a novel hyperpolarizing solution: superior protection compared with University of Wisconsin solution. *J Thorac Cardiovasc Surg* 2000, 120:746–754.
 - 78 Tang DG, Pavot DR, Mouria MM, et al.: Warm ischemia lung protection with pinacidil: an ATP regulated potassium channel opener. *Ann Thorac Surg* 2003, 76:385–389.
 - 79 Cleland JG, Nikitin N, McGowan J: Levosimendan: first in a new class of inodilator for acute and chronic severe heart failure. *Expert Rev Cardiovasc Ther* 2004, 2:9–19.
- In this review of the therapeutic benefits of levosimendan in patients with heart failure, the dual mechanism of action (calcium sensitization and KCO) had positive hemodynamic effects and reduction in morbidity and mortality.