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Myocardial protection: The role of the K_{ATP} channel

R. Carroll, J. M. Walker, D. M. Yellon

Ischaemic preconditioning provides powerful protection to the ischaemic myocardium. The clinical problem has always been how to trigger that protection in a non-injurious way. Good evidence now suggests the mitochondrial K_{ATP} channel may be the end effector of preconditioning, and this protection can be mimicked by pharmacological opening of the K_{ATP} channel in a variety of experimental situations. Clinical data exist that suggest the K_{ATP} channel is involved in human preconditioning, but more extensive evidence will be needed before the true potential of preconditioning by K_{ATP} openers can be realised. *J. Clin Basic Cardiol* 1999; 2: 8–11.

Key words: myocardial protection, K_{ATP}-channels, preconditioning

Ischaemic heart disease and its clinical correlate of acute myocardial infarction (AMI) remains the largest cause of death in developed countries. Despite the great benefits seen in major trials of the use of thrombolytic therapy and various adjunctive treatments such as β -blocker therapy and ACE inhibitors, which result in potentially important benefits for patients with AMI, there remains an important clinical burden of disease and premature death [1]. Of the 180,000 patients admitted with AMI in the United Kingdom, 10–15 % die during hospitalisation and a further 15–20 % die in the following year. For those with impairment of left ventricular performance, even with ACE inhibitor therapy, the outlook remains guarded [2].

Similarly, in patients with Unstable Angina (UA), despite improvements in diagnosis and more aggressive management, UA is still associated with significant morbidity and mortality. More than 10 % of these patients die or go on to experience myocardial infarction within six months [3]. Newer anti-thrombin and antiplatelet agents offer hope for considerable improvement, but again their impact on the burden of disease remains to be shown.

It is clear therefore that there is scope for agents capable of directly protecting the myocardium during severe ischaemia and thus lengthening the time available for rescue of myocardium by reperfusion.

The Preconditioning Phenomenon

Background

It is now apparent that the heart possesses important innate powers of adaptation capable of generating significant protection against lethal ischaemia. This phenomenon, originally identified by Murry and co-workers has been termed ischaemic preconditioning [4]. In a canine model of myocardial infarction, they discovered that, prior to a normally lethal ischaemic insult, preceding short cycles of sublethal ischaemia with intermittent reperfusion resulted in a 75 % reduction in infarct size. Since this landmark paper, it has become clear that other than direct reperfusion, ischaemic preconditioning is the most potent and reproducible mode of cardioprotection investigated to date, and has been demonstrated in every species studied, including man (for review see [5]). The preconditioned heart, when exposed to a subsequent prolonged and potentially lethal ischaemia and reperfusion stress has a markedly reduced infarct size, less ultrastructural damage, higher ATP reserves, better recovery of mechanical function and

fewer episodes of reperfusion arrhythmia (for review see [5]).

Classical Preconditioning versus the Second Window of Protection

The initial protection provided by ischaemic preconditioning, although powerful, is short lived with the protection lasting a few hours in most of the species studied. Protection is apparent immediately after the preconditioning stimulus but disappears after one or two hours [6, 7]. However, 12 to 24 hours later a return of myocardial protection is observed [8, 9]. Although not as powerful as the early phase, this second window of protection (SWOP) [10] is more prolonged and lasts up to 72 hours [11]. It is likely that these two forms of adaptation have different underlying mechanisms although they share the same triggers, that are mediated via G-proteins coupled to protein kinase C (PKC) [5]. For example, sublethal ischaemia, adenosine A₁ receptor agonism, bradykinin B₂ receptor stimulation and opioid agonists all are capable of triggering preconditioning. In classical preconditioning, a variety of end effectors have been proposed, such as hyperphosphorylation of the small heat shock protein Hsp27 [12] or opening of the mitochondrial K_{ATP} channel [13]. In the second window of protection, enhanced functional activity of the antioxidant enzyme superoxide dismutase [14], increased levels of the inducible 70 kDa heat shock protein, Hsp72i [8], hyperphosphorylation of Hsp27 [15], induction of nitric oxide synthetase [16], and indeed opening the K_{ATP} channel [17], have been implicated. As can be seen, the K_{ATP} channel looks to be an increasingly attractive candidate as the target or end-effector for both forms of preconditioning.

The K_{ATP} Channel

What is it?

The K_{ATP} channel is a member of a family of membrane spanning proteins. The channel was first identified in cardiac tissue by Noma in 1983 [18] who found it to be an intermediate conduction channel gated by ATP. In the sarcolemma it acts as an inward rectifier, existing as octamers of four pore-forming subunits of the Kir6 family, coupled to four sulphonylurea receptors (SUR) [19]. The probability of open state configuration is dependent on intracellular ATP concentration, such that with normal ATP levels, the channel is quiescent, but as ATP levels fall, open probability is greatly increased [20]. SUR is a member of the ATP binding cassette superfamily

[21] and appears to gate K_{ATP} by direct secretion of ATP, which modulates the channel via a local purinergic receptor effect. This complex is inhibited by ATP and sulphonylurea drugs and activated by agents such as diazoxide, cromakalim, pinacidil and nicorandil. Normally, in vivo, the probability of K_{ATP} channel opening is regulated by ATP concentrations in the 25–200 micromole range. Activated PKC isoforms can change the ATP sensitivity threshold for K_{ATP} opening to the concentrations of ATP seen in early ischaemia (1–2 millimole), by changing the stoichiometry of the ATP binding site [22]. Other mediators are thought to gate this channel such as adenosine, pH and lactate, all of which show significant changes during ischaemia. Cardioprotection produced by the PKC activator dioctanoyl glycerol is abolished by glibenclamide in human muscle, indicating that the K_{ATP} channel is likely to be an end effector of the preconditioning response [23]. The K_{ATP} channel has also been identified in the mitochondrion [24], but again, in the cardiocyte, its precise role is unclear (see below). The sarcolemmal K_{ATP} channel has been cloned and work is currently underway to sequence the mitochondrial channel.

Initial experiments

Opening the sarcolemmal K_{ATP} channel results in a repolarising current that reduces the length of the cardiac action potential duration (APD), causing reduced calcium entry to the myocyte [25]. Cardiac workload is reduced and myocardial viability enhanced, in effect, generating a pharmacological cardioplegia in ischaemic cells. The majority of data supporting the role for the K_{ATP} channel comes from animal studies in which blockade of these channels by sulphonylurea compounds abolished the protective effect of preconditioning, whereas pharmacologic activation of these channels clearly mimics the protection (for review see [26] and [27]). Protection by K_{ATP} channel opening drugs can occur at doses that do not cause shortening of the action potential duration, indicating that the protective effect exists independent of any postulated “cardioplegic” effect. In one such study, Yao and Gross showed that the K_{ATP} opener bimakalim provided protection against infarction in the dog with minimal shortening of APD [28]. Subsequently, Grover and colleagues demonstrated that the class III antiarrhythmic agent dofetilide administered at a dose that prevented the shortening of APD, could not abolish the protective effects of ischaemic preconditioning [29]. Similarly, other agents that affect inward potassium currents other than those of the K_{ATP} channel, such as the inward rectifier potassium channel (KIR) blocker terikalant do not abolish the protection mediated by preconditioning, in keeping with a protective function specific to the K_{ATP} channel [30]. In a recent study, co-transfection of the genes coding for the K_{ATP} channel combined with the SUR receptor (Kir6.2/SUR2A) into native COS-7 cells (which do not possess an indigenous K_{ATP} channel) transformed the cells from an ischaemia sensitive phenotype to one which, in the presence of low dose diazoxide, was profoundly resistant to ischaemia [31]. This points strongly to the fact that the K_{ATP} channel complex may possess inherent cytoprotective properties. However, not all data support activation of the K_{ATP} channel as being protective. Recently, in a study using paced strips of perfused, guinea-pig ventricular myocardium, Picard and colleagues measured labelled arachidonic acid release as an index of lipid membrane damage. Briefly, they found not only that cromakalim, 10uM, increased membrane damage, but that glyburide significantly decreased it compared to controls. Of particular note in this study, was a significant proarrhythmic effect of cromakalim [32].

Mitochondrial K_{ATP} channels

The K_{ATP} channel in the inner mitochondrial membrane was first identified in 1991, but its functional significance is unclear although it clearly allows K⁺ cycling across the inner mitochondrial membrane. Regulation of mitochondrial volume and or membrane potential would seem likely roles, and it is attractive to imagine the K_{ATP} channel as a link between a cell's metabolic status and contractile function [33]. One of the most striking features of the mitochondrial K_{ATP} channel compared to the sarcolemmal channel is its remarkable sensitivity to the K_{ATP} channel opener diazoxide, which exceeds the sensitivity of the sarcolemmal channel 2000-fold [34]. Administration of the K_{ATP} channel opener diazoxide at a concentration that does not open sarcolemmal but only mitochondrial K_{ATP} channels is highly protective against injury. In the working rat heart, Garlid and colleagues showed prior administration of diazoxide at a mitochondrial specific concentration conferred strong protection against infarction, and that this protection was abolished by either glyburide (glibenclamide) or 5-hydroxydecanoate sodium [13]. Although the exact roles of the K_{ATP} channel in physiological states and during ischaemia are unclear, opening of the mitochondrial K_{ATP} channel will dissipate the electrochemical gradient established across the inner mitochondrial membrane by the proton pump. Feedback will therefore accelerate electron transfer by the respiratory chain and lead to net oxidation of the mitochondria. Mitochondrial redox state can be measured by recording the fluorescence of FAD-linked enzyme systems in the mitochondria, and would allow an indirect measurement of electrochemical gradient if all other factors remained constant. Using this technique, in a study on isolated rat cardiomyocytes, Liu and colleagues demonstrated that diazoxide reduced cardiomyocyte death by 50 % in a simulated model of ischaemia, which involved pelleting cardiomyocytes beneath a layer of mineral oil to produce an anoxic environment. More importantly, they clearly showed that this occurred at a concentration that did not activate the sarcolemmal K_{ATP} channel. They also demonstrated localisation of the effect of diazoxide to the mitochondrion using confocal imaging of fluorescence arising from oxidised flavoproteins and the mitochondrial fluorophore tetramethyl rhodamine ester (TMRE), which localises to negatively charged areas in organelles such as the mitochondrial inner membrane [35]. Once again, they showed that both the protection and the redox changes conferred were abolished by 5-hydroxydecanoate sodium. A number of studies have now reported the effects of K_{ATP} channel opening on isolated mitochondria. This technique has the advantage of allowing control of the ion concentrations in the mitochondrial buffer and using the tetraphenylphosphonium (TPP⁺) electrode effectively to derive an absolute value for mitochondrial membrane potential. In one such recent study, Holmuhamedov and colleagues studied the relationship between cardiac mitochondrial membrane potential, respiration, calcium loading, volume and integrity. Using the K_{ATP} channel openers pinacidil, cromakalim and levromakalim, they demonstrated that these agents caused depolarisation of the membrane, acceleration of respiration, decreased ATP production, release of preloaded calcium and swelling of the mitochondrion. It is worth noting that in the same study, the K_{ATP} channel openers also induced a net efflux of mitochondrial proteins including cytochrome-c. However, the functional significance of these changes remains unclear, and may even be argued to be deleterious in the case of increased cytochrome-c release, a known trigger of apoptosis [36]. As discussed earlier, PKC isoforms seem to be key mediator in the signal transduction of the preconditioning stimu-

lus. It also appears that PKC may specifically enhance the effects of K_{ATP} channel opening. Using the PKC activator phorbol 12-myristate 13-acetate, Sato showed a synergistic enhancement of the protective and redox-potential effects of diazoxide in cultured non-beating adult rabbit myocytes [37].

It may be reasonable then, to suppose that the effector is in fact the mitochondrial K_{ATP} channel, independent of the status of the sarcolemmal channel, although how opening this channel directly protects the myocyte is at present unknown. Many possibilities exist, for example, dissipation of the mitochondrial membrane potential decreases calcium influx through the calcium uniporter. It is well established that inhibition of the uniporter by agents such as ruthenium red is highly protective, and this appears an attractive hypothesis. Secondly, it has been shown that dissipation of the mitochondrial membrane potential enhances the binding of the F₀F₁ ATPase inhibitor, IF₁, helping to conserve ATP during ischaemia [38].

Examining the role of K_{ATP} in human models of preconditioning

There is good laboratory evidence that the human myocardium is amenable to preconditioning [39]. Clinical correlates include "warm up angina" [40] and a survival benefit seen in studies on pre-infarct angina in myocardial infarction [41]. Furthermore, preconditioning activity in patients can be inferred during coronary angioplasty and open heart surgery [42]. It is therefore likely that classical preconditioning and SWOP occur in man, as it has been shown in every other animal species studied to date.

Basic science

Studies in isolated superfused human atrial trabeculae suggest that simulated ischaemia can produce classical preconditioning and that this effect may be modulated by signalling pathways involving PKC and the K_{ATP} channel as the effector [23]. More recently it appears that other agents which couple to the PKC signalling pathway such as the delta opioid receptor may also be involved in the initiation of the stimulus [43]. Interestingly, the beneficial effects of opioid receptor agonism can be attenuated with 5-hydroxydecanoate sodium, yet again implying a role for the K_{ATP} channel in the protection observed. Similarly, isolated, cultured human ventricular myocytes have been shown to be able to be preconditioned with ischaemia [44, 45]. Furthermore, using a human cardiocyte cell line, we have been able to demonstrate the SWOP, protection seeming to be mediated by the K_{ATP} channel [46].

Angioplasty studies

In the setting of PTCA, it is possible to subject regions of the ventricular myocardium to controlled ischaemia and reperfusion in a repetitive way using specific balloon inflation protocols. Myocardial ischaemia can be measured in a semi quantitative manner using clinical, electrocardiographic, metabolic or haemodynamic measurements. It has been shown that when the duration of the initial inflation is beyond a certain threshold of between 60 and 90 seconds, subsequent balloon inflations produce less myocardial ischaemia as measured by the above markers [47–49]. This effect appears independent of recruitment of collaterals in the acute setting, even though this is a difficult confounding factor to account for [47, 48]. Most importantly, preconditioning in the setting of balloon inflation appears to be mediated by the K_{ATP} channel [50] via stimulation of the adenosine A₁ receptor [51].

Studies during open heart surgery

We have studied the possibility that the human heart could be protected against the ischaemia induced by aortic cross clamp fibrillation during coronary artery surgery. To achieve this, the heart was preconditioned with two cycles of global ischaemia consisting of 3 minutes cross clamping and pacing at 90 beats per minute interspersed with 2 minutes of reperfusion prior to a 10 minute episode of global ischaemia and ventricular fibrillation. At various points during the protocol needle biopsies were taken and analysed for ATP content. The preconditioned group showed much improved preservation of myocardial ATP than the control group [52]. A subsequent study using the same protocol demonstrated decreased release of Troponin-T measured in serum in the preconditioned group [53].

Clinical correlates

Unstable angina

The only K_{ATP} channel opener in current clinical use is nicorandil, the nitrate ester of nicotinamide. As such, nicorandil possesses both nitrovenodilator properties and the ability to open K_{ATP} channels. It has a proven track record in the management of both stable and variant angina and as such would seem to be a logical choice in the clinical study of the myocardial effects of K_{ATP} channel opening. Two important studies have been reported in the setting of unstable angina. Firstly, in a double blind manner, Kato studied the effects of intravenous nicorandil [54] versus intravenous isosorbide dinitrate on patients with unstable angina. The treatment group showed a trend to fewer episodes of anginal rest pain. More interestingly, in a recently reported study, Patel and colleagues [55], have analysed the effects of nicorandil when administered orally to patients with unstable angina. All patients were treated with an aggressive, standardised antianginal therapy, which included a beta-blocker, calcium channel blocker, nitrates and heparin. The trial compared the group receiving oral nicorandil versus placebo added to the therapy. The nicorandil treated group had significantly less episodes of silent myocardial ischaemia than the control group. More importantly, the nicorandil treated group had significantly less arrhythmic events, allaying initial fears that opening the K_{ATP} channel may be pro-arrhythmic.

Myocardial infarction

Limited data exist on the effects of nicorandil during early myocardial infarction and are confounded by the potential of coronary or collateral vasodilator effects. In one small study, the administration of intracoronary nicorandil following reperfusion by either thrombolysis or primary angioplasty showed significant improvements in regional wall motion scoring at one month; but this must be tempered by the fact that the treatment group also showed improved myocardial blood flow in the area in jeopardy on contrast echo [56]. Similarly, when oral nicorandil was administered to patients early after AMI, a reduction in arrhythmia was seen as well as a trend against the development of Q-waves in the non-Q MI group [57]. Clearly the mechanisms here are not those of preconditioning per se, but these two studies, and those evaluating unstable angina refute proarrhythmia due to opening the K_{ATP} channel in the setting of ischaemia/reperfusion injury, and strongly underline the need for further clinical evaluation of nicorandil or other, novel K_{ATP} channel openers in the setting of acute coronary syndromes.

References

- Gershlik AH, More RS. Treatment of myocardial infarction. *Br Med J* 1998; 316: 280–4.
- Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. *Acute Infarction Ramipril Efficacy. Lancet* 1997; 349: 1493–7.
- Yusuf S. For the OASIS Registry Investigators. Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. *Lancet* 1998; 352: 507–14.
- Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74: 1124–36.
- Yellon DM, Baxter GF, Garcia-Dorado D, Heusch G, Sumeray MS. Ischaemic preconditioning: present position and future directions. *Cardiovasc Res* 1998; 37: 21–33.
- Li YW, Whittaker P, Kloner RA. The transient nature of the effect of ischemic preconditioning on myocardial infarct size and ventricular arrhythmia. *Am Heart J* 1992; 123: 346–53.
- Murry CE, Richard VJ, Jennings RB, Reimer KA. Myocardial protection is lost before contractile function recovers from ischemic preconditioning. *Am J Physiol* 1991; 260: H796–H804.
- Marber MS, Latchman DS, Walker JM, Yellon DM. Cardiac stress protein elevation 24 hours after brief ischemia or heat stress is associated with resistance to myocardial infarction. *Circulation* 1993; 88: 1264–72.
- Kuzuya T, Hoshida S, Yamashita N, et al. Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. *Circ Res* 1993; 72: 1293–9.
- Yellon DM, Baxter GF. A “second window of protection” or delayed preconditioning phenomenon: future horizons for myocardial protection? *J Mol Cell Cardiol* 1995; 27: 1023–34.
- Baxter G, Goma F, Yellon D. Characterisation of the infarct-limiting effect of delayed preconditioning: time course and dose-dependency studies in rabbit myocardium. *Basic Res Cardiol* 1997; 92: 159–67.
- Armstrong S, Delacey M, Hoover D, Ganote C. Hsp27 phosphorylation after protein phosphatase inhibition and ischaemic preconditioning. *J Mol Cell Cardiol* 1998; 30: A20(abstract).
- Garlid KD, Paucek P, Yarov-Yarovoy V, et al. Cardioprotective effect of diazoxide and its interaction with mitochondrial ATP-sensitive K⁺ channels. Possible mechanism of cardioprotection. *Circ Res* 1997; 81: 1072–82.
- Yamashita N, Nishida M, Hoshida S, et al. Induction of manganese superoxide dismutase in rat cardiac myocytes increases tolerance to hypoxia 24 hours after preconditioning. *J Clin Invest* 1994; 94: 2193–9.
- Dana A, Yellon DM. Adenosine A1 receptor induced delayed cardioprotection: investigation into time course and cellular mechanisms. *Heart* 1999; (abstract in press).
- Takano H, Manchikalapudi S, Tang XL, et al. Nitric oxide synthase is the mediator of late preconditioning against myocardial infarction in conscious rabbits. *Circulation* 1998; 98: 441–9.
- Pell TJ, Yellon DM, Goodwin RW, Baxter GF. Myocardial ischemic tolerance following heat stress is abolished by ATP-sensitive potassium channel blockade. *Cardiovasc Drugs Ther* 1997; 11: 679–86.
- Noma A. ATP-regulated K⁺ channels in cardiac muscle. *Nature* 1983; 305: 147–8.
- Inagaki N, Gonoi T, Seino S. Subunit stoichiometry of the pancreatic B-cell ATP sensitive K-channel. *FEBS Lett* 1997; 409: 232–6.
- Edwards G, Weston AH. The pharmacology of ATP-sensitive potassium channels. *Annu Rev Pharmacol Toxicol* 1993; 33: 597–637.
- Philipson LH, Steiner DF. Pas de deux or more: the sulphonylurea receptor and K-channels. *Science* 1995; 268: 372–3.
- Light P, Sabir A, Allen B, Walsh M, French R. Protein kinase C-induced changes in the stoichiometry of ATP binding activate cardiac ATP-sensitive K⁺ channels. *Circ Res* 1996; 79: 399–406.
- Speechly Dick ME, Grover GJ, Yellon DM. Does ischemic preconditioning in the human involve protein kinase C and the ATP-dependent K⁺ channel? Studies of contractile function after simulated ischemia in an atrial in vitro model. *Circ Res* 1995; 77: 1030–5.
- Inoue I, Nagase H, Kishi K, Higuti T. ATP-sensitive K-channel in the mitochondrial inner membrane. *Nature* 1991; 352: 244–7.
- Schulz R, Rose J, Heusch G. Involvement of activation of ATP-dependent potassium channels in ischemic preconditioning in swine. *Am J Physiol* 1994; 267: H1341–H1352.
- Grover GJ. Pharmacology of ATP-sensitive potassium channel openers in models of myocardial ischaemia and reperfusion. *Can J Physiol Pharmacol* 1997; 75: 309–15.
- Gross GJ, Mei DA, Schultz JJ, Mizumura T. Criteria for a mediator or effector of myocardial preconditioning: do K_{ATP} channels meet the requirements? *Basic Res Cardiol* 1996; 91: 31–4.
- Yao Z, Gross G. Effects of KATP channel opener bimakalim on coronary blood flow, monophasic action potential duration, and infarct size in dogs. *Circulation* 1994; 89: 1769–75.
- Grover GJ, Dalonzo AJ, Dzwonczyk S, Parham CS, Darbenzio RB. Preconditioning is not abolished by the delayed rectifier K⁺ blocker dofetilide. *Am J Physiol* 1996; 40: H1207–H1214.
- Schultz JE, Kwok WM, Hsu AK, Gross GJ. Terikalant, an inward-rectifier potassium channel blocker, does not abolish the cardioprotection induced by ischemic preconditioning in the rat. *J Mol Cell Cardiol* 1998; 30: 1817–25.
- Jovanovic A, Jovanovic S, Lorenz E, Terzic A. Recombinant cardiac ATP-sensitive K channel subunits confer resistance to chemical hypoxia-reoxygenation injury. *Circulation* 1998; 98: 1548–55.
- Picard S, Rouet R, Duval D, Chesnay F, Gerard J. KATP channel modulators and myocardial damage induced by ischaemia-reperfusion: membrane lipids injury and arrhythmias. *J Mol Cell Cardiol* 1998; 30: 2613–21.
- Garlid KD. Cation transport in mitochondria – the potassium cycle. *Biochim Biophys Acta* 1996; 1275: 123–6.
- Garlid KD, Paucek P, Yarov-Yarovoy V, Sun X, Schindler PA. The mitochondrial KATP channel as a receptor for potassium channel openers. *J Biol Chem* 1996; 271: 8796–9.
- Liu Y, Sato T, B OR, Marban E. Mitochondrial ATP-dependent potassium channels: novel effectors of cardioprotection? *Circulation* 1998; 97: 2463–9.
- Holmuhamedov EL, Jovanovic S, Dzeja PP, Jovanovic A, Terzic A. Mitochondrial ATP-sensitive K⁺ channels modulate cardiac mitochondrial function. *Am J Physiol* 1998; 275 (5 Pt 2): H1567–H1576.
- Sato T, O'Rourke B, Marban E. Modulation of mitochondrial ATP-dependent K⁺ channels by protein kinase C. *Circ Res* 1998; 83: 110–4.
- Rouslin W. Regulation of the mitochondrial ATPase in situ in cardiac muscle: role of the inhibitor subunit. *J Bioenerg Biomembr* 1991; 23: 873–88.
- Walker DM, Walker JM, Pugsley WB, Pattison CW, Yellon DM. Preconditioning in isolated superfused human muscle. *J Moll Cell Cardiol* 1995; 27: 1349–57.
- Marber MS, Joy MD, Yellon DM. Is warm-up in angina ischaemic preconditioning? *Br Heart J* 1994; 72: 213–5.
- Kloner RA, Shook T, Przyklenk K, et al. Previous angina alters in-hospital outcome in TIMI 4. A clinical correlate to preconditioning? *Circulation* 1995; 91: 37–45.
- Van Der Laarse A, Manger Cats V, Brushke AVG. Preconditioning of the Heart. *Eur Heart J* 1996; 17: 490–1.
- Bell S, Sack M, Patel A, Opie L, Yellon D. Delta opioid receptor stimulation mimics ischaemic preconditioning in human heart muscle. *Circulation* 1998; 98 (17): 1-486 (abstract).
- Ikonomidis JS, Tumati LC, Weisel RD, Mickle DA, Li RK. Preconditioning human ventricular cardiomyocytes with brief periods of simulated ischaemia. *Cardiovasc Res* 1994; 28: 1285–91.
- Ikonomidis JS, Toshizumi S, Weisel RD, et al. Preconditioning cultured human pediatric myocytes requires adenosine and protein kinase C. *Am J Physiol* 1997; 272: H1220–H1230.
- Carroll R, Yellon DM. Mechanisms of delayed cardioprotection in human cardiocytes. *Heart* 1999; (abstract in press).
- Deutsch E, Berger M, Kusmaul WG, Hirshfeld JW, Herrmann HC, Laskey WK. Adaptation to ischemia during percutaneous transluminal coronary angioplasty: Clinical, hemodynamic, and metabolic features. *Circulation* 1990; 82: 2044–51.
- Cribier A, Korsatz L, Koning R, et al. Improved myocardial ischemic response and enhanced collateral circulation with long repetitive coronary occlusion during angioplasty: a prospective study. *J Am Coll Cardiol* 1992; 20: 578–86.
- Tomai F, Crea F, Gaspardone A, et al. Mechanisms of cardiac pain during coronary angioplasty. *J Am Coll Cardiol* 1993; 22: 1892–6.
- Tomai F, Crea F, Gaspardone A, et al. Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K⁺ channel blocker. *Circulation* 1994; 90: 700–5.
- Tomai F, Crea F, Gaspardone F, et al. Effects of A₁ adenosine receptor blockade by bamiphylline on ischaemic preconditioning during coronary angioplasty. *Eur Heart J* 1996; 17: 846–53.
- Yellon DM, Alkhulaifi AM, Pugsley WB. Preconditioning the human myocardium. *Lancet* 1993; 342: 276–7.
- Jenkins DP, Pugsley WB, Alkhulaifi AM, Kemp M, Hooper J, Yellon DM. Ischaemic preconditioning reduces Troponin-T release in patients undergoing cardiac surgery. *Heart* 1997; 77: 314–8.
- Kato K. Haemodynamic and clinical effects of an intravenous potassium channel opener – a review. *Eur Heart J* 1993; 14 (Suppl B): 40–7.
- Patel DJ, Purcell HJ, Fox KM. Cardioprotection by opening of the K_{ATP} channel in unstable angina. *Eur Heart J* 1999; 20: 51–7.
- Sakata Y, Kodama K, Komamura K. Salutary effect of adjunctive intracoronary nicorandil administration on restoration of myocardial blood flow and functional improvement in patients with acute myocardial infarction. *Am Heart J* 1997; 133: 616–21.
- Sen S, Neuss H, Berg G, Nitsche K, Goddemeier T, Doring G. Beneficial effects of nicorandil in acute myocardial infarction. *Br J Cardiol* 1998; 5: 208–20.

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