HEART

Editorial

Delayed protection against ventricular arrhythmias by cardiac pacing

Although heavy physical exercise, and psychological stress that produces similar physiological responses, may trigger a cardiac event in the immediate (within one hour) postexertion period,[1 2] there is prospective evidence that the relative risk of sudden cardiac death and non-fatal myocardial infarction occurring during this period is reduced in individuals who exercise regularly.[2 3] The intensity of the exercise required to induce this protection, as well as the time course of this protection, are subjects of ongoing debate[3 4]; the conclusion that "the protective effect of exercise requires continued exertion"[3] implies that the duration of the protection is relatively short lived. The mechanisms of this risk reduction remain unclear but include an increase in baroreflex sensitivity (and increased vagal activity that is antifibrillatory[5]) and favourable effects on other risk factors.[6]

Both exercise training[7] and right ventricular pacing[8 9] confer significant protection against coronary artery occlusion induced ventricular fibrillation in conscious[7] and anaesthetised[8 9] dogs. Similar to the protection associated with ischaemic preconditioning (defined as the protective effect of brief coronary artery occlusions against the consequences of a subsequent more prolonged period of ischaemia), the protection is demonstrable immediately after, or even during,[7] the pacing or exercise period but is lost shortly afterwards.[9] Of potential clinical interest is the more recent finding that the protection associated with both ischaemic preconditioning and cardiac pacing, returns 20–24 hours after the initial stimulus, a phenomenon that has been described as the second window of protection[10] or delayed myocardial protection.[11] In pacing studies, protection is again lost 48 hours after the stimulus[8] but can be regained if the pacing stimulus is repeated.[12] Under these conditions, the protection now lasts for at least 48 hours (fig 1). Whether protection against ischaemia induced arrhythmias can be maintained indefinitely by repeated periods of pacing is presently being investigated.

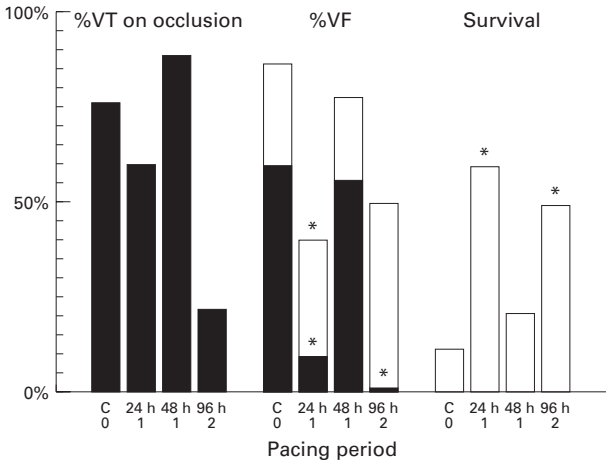

Figure 1 The incidence of ventricular fibrillation (VF) during coronary artery occlusion and reperfusion, ventricular tachycardia (VT) on occlusion, and survival rate following a combined ischaemia–reperfusion insult in anaesthetised dogs subjected to occlusion of the left anterior descending coronary artery at various times after right ventricular pacing (4 × 5 min at 220 beat/min). The incidence of VF was significantly reduced ($p < 0.05$) 24 hours after pacing compared with unpaced controls (C) but this protection was lost 48 hours after the initial pacing stimulus. However, if dogs were repaced at this time protection was still apparent a further 48 hours later (at 96 hours). Filled columns, incidence of VF and VT during occlusion; Open columns, incidence of VF during reperfusion following a 25 minute period of coronary artery occlusion.*

A number of suggestions have been made[10] to explain certain manifestations of the second window of protection of the heart, such as the reduction in the extent of myocardial necrosis. These include the induction of cytoprotective heat shock (stress) proteins, or of potentially protective enzymes such as nitric oxide synthase, and increased myocardial anti-oxidant status. There is evidence for the initial participation of endogenous myocardial protective substances[13] such as adenosine as triggers for this protection, and for the involvement of signal transduction processes that include the early activation of tyrosine kinase and protein kinase C.[10] It is not known whether pacing or exercise triggers similar mechanisms to those involved in ischaemic preconditioning and other possibilities have been suggested to explain the delayed antiarrhythmic effect of pacing and exercise. These include a change, as a result of the tachycardia, in cardiac autonomic balance producing an increase, or a relative dominance, of the vagal component.[5] The release from coronary vascular endothelial cells of a variety of diffusible mediators, which include prostacyclin, bradykinin and, of especial importance, nitric oxide has also been suggested as important for this protection.[14]

Role of endothelium derived mediators in the antiarrhythmic effects of ischaemic preconditioning and cardiac pacing

The hypothesis that coronary vascular endothelial cells contribute to arrhythmia suppression through the increased generation of diffusible mediators is illustrated in fig 2. It implies that endothelial cells not only modulate platelet function (adhesion, aggregation) and vascular smooth muscle activity (vasodilatation, vasoconstriction) but communicate directly with cardiac myocytes through the release of the same or similar mediators. This regulation of myocyte function by endothelial cells takes two forms, modulation of contractility[15] and protection of the myocyte against some of the consequences of ischaemia.[14] Most of the evidence for this hypothesis comes from studies involving the effects of coronary vascular endothelial denudation[16] and of ischaemic preconditioning. It includes the results from studies indicating the early release of bradykinin following occlusion and reperfusion

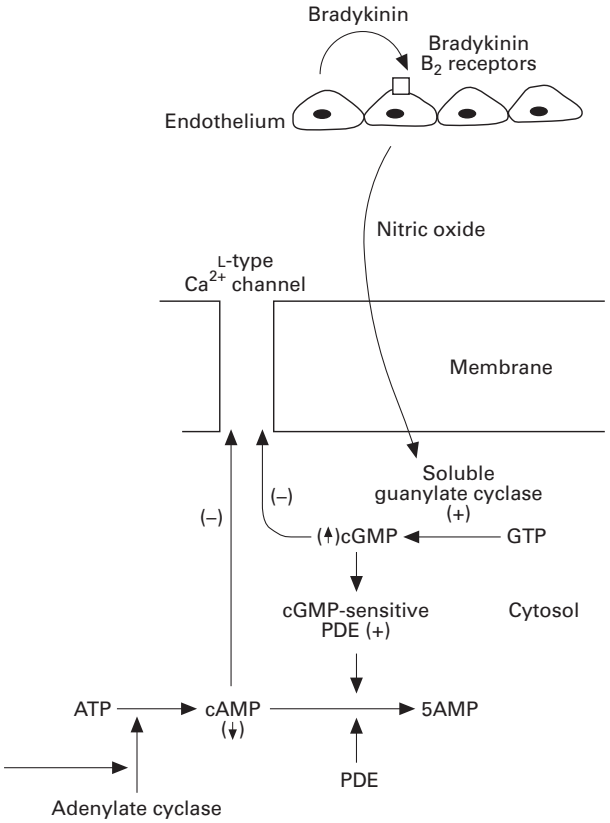

Figure 2 The role of endothelium derived endogenous protective mediators in ischaemic preconditioning and in cardiac pacing. Bradykinin is released, probably from endothelial cells (which have the mechanisms for generating and releasing kinins), which then acts on B_2 receptors on the endothelial surface to increase the calcium transient within these cells and hence activate the L-arginine nitric oxide pathway. Nitric oxide then communicates with the cardiac myocyte, stimulates soluble guanylyl cyclase, and raises cGMP. This reduces cAMP and calcium entry through L-type calcium channels as well as suppressing myocardial oxygen consumption.

in both experimental animals, as well as in patients following balloon inflation (angioplasty),[17] and the abolition of the antiarrhythmic effects of ischaemic preconditioning (and of cardiac pacing[18]) by blockade of the relevant (B_2) bradykinin receptor. Further, there is evidence for the cardiac generation of nitrosyl-haem products, implying a bradykinin mediated generation of nitric oxide. Nitric oxide involvement is also suggested by the attenuation of the antiarrhythmic effects of ischaemic preconditioning following inhibition of nitric oxide generation through the L-arginine pathway, and by inhibition of the nitric oxide target organ, soluble guanylyl cyclase.[19]

NITRIC OXIDE

Figure 2 also illustrates how nitric oxide, generated in coronary vascular endothelial cells as a result of activation of the kallikrein–kinin pathway, might reduce arrhythmia severity. There is evidence that cGMP concentrations are raised following rapid cardiac pacing[20] and this would lead to reduced calcium influx and increased cAMP breakdown through stimulation of a cGMP sensitive cAMP phosphodiesterase.[19] Nitric oxide so generated might also reduce the oxygen deficit of myocytes during ischaemia, in part through its ability to reduce myocardial contractility. Indeed, nitric oxide has been described as an "endogenous suppressor of myocardial oxygen consumption".[21] There is experimental evidence that cell nitric oxide synthase (NOS) in cardiovascular endothelial cells is upregulated by exercise[22] and by pacing, resulting in a nitric oxide mediated increase in the calibre of epicardial arteries.[23] In dogs preconditioned by a single brief coronary artery occlusion there are increased coronary vascular responses to endothelium dependent vasodilators, such as bradykinin, and this is associated with increased (doubled) amounts of nitric oxide breakdown products such as nitrite and nitrate.[24] Whether this is caused by upregulation of endothelial (constitutive NOS (NOS-3)) or to induction of iNOS (NOS-2) has not been clarified but the time course (a peak effect one to two days after ischaemia) suggests the latter. What triggers this increased ability of coronary vascular endothelial cells to generate nitric oxide is not known but may involve changes in shear stress resulting from increased coronary blood flow during tachycardia. How long this induction, or upregulation, lasts after cessation of the exercise or pacing stimulus is also not known, nor to what extent, if at all, it occurs in endothelial cells in atherosclerotic vessels.

Clinical implications

What are the implications of these findings? Presumably, under known conditions where endothelial dysfunction is evident (hypertension, atherosclerosis, hypercholesterolaemia) the ability to generate such endogenous myocardial protective substances may be impaired. This would lead to the attenuation of a major pathway for protection and may explain, in part, the increased susceptibility of such patients to the arrhythmic consequences of acute ischaemia. If bradykinin indeed proves to be an important trigger for this cardioprotective process then one might expect arrhythmias to be less severe in patients on angiotensin converting enzyme (ACE) inhibitors, as ACE is also one of a family of enzymes (kininases) destroying kinins. As has been recently reviewed in this journal,[25] there is some evidence that these drugs may offer protection against the important arrhythmias that complicate cardiac failure. Similarly, one might expect that inhibition of neutral endopeptidase (NEP), enzymes present in cardiac tissue, would also be cardioprotective. Inhibition of kinin metabolism using NEP inhibitors increases nitric oxide production from local coronary microvessels, suggesting that this enzyme also plays an important role in local kinin modulated vascular nitric oxide production.[26] Another possible implication is that the beneficial effects of exercise may be partly explained by increased endothelial NOS gene expression leading to increased nitric oxide production, reduced platelet and leucocyte adherence to the vascular endothelium, inhibition of cardiac sympathetic transmission, and modulation of the cAMP:cGMP balance in cardiac myocytes.

JAMES R PARRATT

Department of Physiology and Pharmacology,
University of Strathclyde,
Royal College,
Glasgow G1 1XW, UK

AGNES VEGH

Department of Pharmacology,
Albert Szent-Gyorgyi Medical University,
Szeged, Hungary

1 Willich SN, Lewis M, Löwel H, Arntz H-R, Schubert F, Schröder R. Physical exertion as a trigger of acute myocardial infarction. *N Engl J Med* 1993;**329**:1684–90.
2 Mittleman MA, Maelurf M, Toffler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. *N Engl J Med* 1993;**329**: 1677–83.
3 Tofler GH, Mittleman MA, Muller JE. Physical activity and the triggering of myocardial infarction: the case for regular exercise [editorial]. *Heart* 1996; **75**:323–5.
4 Lee IM, Hsieh CC, Paffenbarger RS. Exercise intensity and longevity in men. The Harvard Alumni Health Study. *JAMA* 1995;**273**:1179–84.
5 Vanoli E, De Ferrar GM, Stramba-Badiale M, Hull SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in

conscious dogs with a healed myocardial infarction. *Circulation Res* 1991;**68**:1417–18.
6 Rauamaa R, Salonen JT, Kukkonen-Harjula K, Seppanen K, Seppala E, Vapaatalo H, *et al*. Effects of mild exercise on serum lipoproteins and metabolites of arachidonic acid: a controlled trial in middle aged men. *BMJ* 1984;**288**:603–6.
7 Hull SS, Vanoli E, Adamson TB, Verrier RL, Foreman RD, Schwartz PJ. Exercise training confers anticipatory protection from sudden death during acute myocardial ischemia. *Circulation* 1994;**89**:548–52.
8 Kaszala K, Vegh A, Papp JGy, Parratt JR. Time course of the protection against ischaemia and reperfusion-induced ventricular arrhythmias resulting from brief periods of cardiac pacing. *J Mol Cell Cardiol* 1996;**28**:2085–95.
9 Parratt JR, Vegh A, Kaszala K, Papp J Gy. Protection by preconditioning and cardiac pacing against ventricular arrhythmias resulting from ischacmia and reperfusion. *Ann NY Acad Sci* 1996;**793**:98–107.
10 Baxter GF, Yellon DM. The "second window of protection" associated with ischaemic preconditioning. In: Marber MS, Yellon DM, eds. *Ischaemia, preconditioning and adaptation*. Oxford: Bios Scientific Publishers, 1996:113–30.
11 Parratt JR, Szekeres L. Delayed protection of the heart against ischaemia. *Trends Pharmacol Sci* 1995;**16**:351–5.
12 Kis A, Vegh A, Papp JGy, Parratt JR. Repeated pacing widens the time window of delayed protection against ventricular arrhythmias in dogs [abstract]. *J Mol Cell Cardiol* 1996;**28**:A229.
13 Parratt JR. Endogenous myocardial protective substances. *Cardiovasc Res* 1993;**27**:693–702.
14 Parratt JR, Vegh A. Endothelial cells, nitric oxide and ischaemic preconditioning. *Basic Res Cardiol* 1996;**91**:27–30.
15 Winegrad S. Endothelial cell regulation of contractility of the heart. *Ann Rev Physiol* 1997;**59**:505–25.
16 Fatehi-Hassanabad Z, Furman BL, Parratt JR. Endothelium and ischaemic preconditioning in rat isolated perfused hearts. *J Physiol* 1996;**494**:112–13P.
17 Parratt JR, Vegh A, Zeitlin IJ, Ahmad M, Oldroyd K, Kaszala K, Papp J Gy. Bradykinin and endothelial-cardiac myocyte interactions in ischaemic preconditioning—a review. *Am J Cardiol.* [In press.]
18 Kaszala K, Vegh A, Papp J Gy, Parratt JR. Modification by bradykinin B_2 receptor blockade of protection by pacing against ischaemia-induced arrhythmias. *Eur J Pharmacol* 1997;**328**:51–60.
19 Parratt, JR, Vegh A, Kaszala K, Papp J Gy. Suppression of life-threatening ventricular arrhythmias by brief periods of ischaemia and by cardiac pacing with particular reference to delayed myocardial protection. In: Marber MS, Yellon DM, eds. *Ischaemia, preconditioning and adaptation*. Oxford: Bios Scientific Publishers, 1996:85–111.
20 Szilvassy Z, Jakab I, Lonovics J, Papp J Gy. Is rapid pacing-induced preconditioning related to changes in myocardial cyclic nucleotide content? [abstract]. *J Mol Cell Cardiol* 1996;**28**:A70.
21 Burnstein RD, Forfia PR, Ochoa M, Xu X, Hintze TH. Endogenous nitric oxide reduces myocardial oxygen consumption during calcium chloride infusions in conscious dogs [abstract]. *Circulation* 1996;**94(suppl)**:I–63.
22 Sessa WC, Pritchard K, Seyedi N, Wang J, Hintze TH. Exercise-induced shear stress upregulates endothelial cell nitric oxide synthase gene expression. In: Moncada S, Feelish M, Busse R, Higgs EA, eds. *The biology of nitric oxide part III, physiological and clinical aspects*. London: Portland Press, 1994:1–3.
23 Egeshira K, Katsuda Y, Mohri M, Kuga T, Tagawa T, Kubota T, *et al*. Role of endothelium-derived nitric oxide in coronary vasodilatation induced by pacing tachycardia in humans. *Circulation Res* 1996;**79**:331–5.
24 Kim S-J, Gahleh B, Kudej RK, Hintze TH, Vatner SF. Delayed enhanced nitric oxide-mediated coronary vasodilation following brief ischemia and prolonged reperfusion in conscious dogs. *Circ Res* 1997;**81**:53–9.
25 Campbell RWF. ACE inhibitors and arrhythmias. *Heart* 1996;**76(suppl 3)**:79–82.
26 Zhang X, Xu X, Forfia PR, Nasjletti A, Hintze TH. Neutral endopeptidase (NEP) and angiotensin convertinig enzyme (ACE) modulate nitric oxide (NO) via local kinin formation production from canine coronary microvessels [abstract]. *Circulation* 1996;**94(suppl)**:349.

STAMPS IN CARDIOLOGY

Karl Freiherr von Rokitansky (1804–78)

This Austrian stamp is part of the Welfare Funds issue from 1937 featuring famous Austrian doctors. Other stamps in the set of nine feature among others Auenbrugger, Skoda, van Swieten, and Billroth. Rokitansky appeared on Austrian postage stamps again in 1954 to commemorate the 150th anniversary of his birth.

Karl Freiherr von Rokitansky was professor of pathological anatomy at Vienna and with Joseph Skoda was a founder of the New Vienna School. Not only was he the leading figure in pathological anatomy in Europe but he also made significant contributions to the understanding of congenital heart disease. In his illustrated book of 1875, *Die Defecte der Scheidewande des Herzens,* he gave accurate details of the anatomy of atrial and ventricular septal defects and was the first to delineate the differences between ostium primum and ostium secundum atrial septal defects.

He believed that abnormalities in the chemical constitution of the blood were the pathological basis for disease and he developed the thrombogenic or encrustation theory for atherosclerosis.

M K DAVIES
A HOLLMAN