Editorial

Myocardial Protection: A New Holy Grail of Contemporary Cardiology

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In the pathogenesis and evolution of heart disease loss of myocardial integrity and functional deterioration are prime determinants of cardiovascular morbidity and mortality in both primary myocardial and coronary artery disease. As a consequence, myocardial protection has acquired great significance. The last 20 years have seen a great number of observations from basic research, the "bench", being applied to the "bedside". However although an impressive array of observations has emerged from basic cardiology, their application to the bedside remains limited.

Myocardial protection

Ischaemic preconditioning, first discovered by Murry et al[1] almost 20 years ago, is a very potent protective mechanism. However, it remains limited in the clinical setting for several obvious reasons. It is difficult to quantify its severity and duration in the clinical setting. If it is too long or the episodes are too many,[2] preconditioning may be lost and stunning may occur. In our experience it can protect if applied as two short preconditioning cycles before two long ischaemic (20 min duration) cycles. However, if the preconditioning cycles are "sandwiched" between the two long ischaemic cycles they are ineffective.[3] Thus, it can reasonably be postulated that if preceding angina is too long and severe, it can lead not to preconditioning[4] but to stunning and necrosis.[5]

Another very important factor is the condition of the patient. The myocardium of aged experimental animals and patients cannot be adequately preconditioned.[6] Exercise,[7] nicorandil[8] and probably thyroid analogues (through inducing high metabolism)[9] have been found effective in reversing this condition.

Pre-existing diabetes mellitus of not too long duration produces a "preconditioned-like" state,[10] with protection of the myocardium, while diabetes of long duration inhibits preconditioning.[11] Of course, it is easy to appreciate that the length and severity of diabetes are very difficult to determine.

Hypercholesterolaemia and atherosclerosis have also been found by many[12] but not all[13] authors to blunt preconditioning. They, too, are ubiquitous disorders in the clinical setting.

Thyroid disorders present a greatly varied array. We have found that hyperthyroidism is protective against ischaemia: It increases the protective protein chaperones HSP70 and 27, decreases the noxious kinases p38 MAPK and JNK and promotes the phosphorylation of PKCδ, a cardioprotective kinase.[14,15] After an acute myocardial infarction, T3 causes normalisation of the expression of many abnormal genes and improves cardiac function[16] while ameliorating myocardial remodelling.

Chronic heart failure, characterised by a low fT3, is associated with a worse prog-

nosis[17] and a low fT3/fT4 ratio, as well as a high TSH. These are correlated with a low ejection fraction and haemodynamic deterioration.[18]

Low output after cardiac surgery can be improved by thyroid hormones or analogues,[19] since cardiopulmonary bypass is associated with marked and long-lasting depression of circulation thyroid hormones. Actually a larger prospective study (TRICC) is being planned in children.[20]

Thyroid analogues may also be expected to reverse the aging process, as already mentioned. Hypothyroidism was induced many years ago in the clinical setting with a view to ameliorating chronic intractable angina.[21] With the modern array of antianginal treatment no one would use it today, especially since it causes an elevation in plasma lipids,[22] an increased arterial resistance,[23] and attenuates flow mediated dilatation[24] and the response of the rat aorta to β2 vasodilatation.[25] Still, it produces very strong protection against global ischaemia, with recovery values up to 70% versus 40-50% seen in controls after 20 minutes of global ischaemia. Cardio-selective hypothyroidism produced by drugs such as dronedarone, which selectively inhibit the α1T3 receptor, may find clinical application.[26] It should not be forgotten that amiodarone was actually introduced many years ago as an antianginal drug.

Myocardial hypertrophy is often seen in clinical practice, since the prevalence of hypertension in patients with manifestations of coronary artery disease is around 50%. A large percentage of patients show this abnormality. Data concerning its influence on myocardial protection are scant. Both in the experimental and clinical setting the hypertrophied hearts are more sensitive to ischaemic injury.[27,28] The "stone heart" after aortic valve replacement was the fear of surgeons when the first author was training in cardiology.[29] However, both Speechly-Dick[30] and our own group[31] have shown that preconditioning is also operative in myocardial hypertrophy.

Hypertrophy may of course evolve into heart failure. Failing rat hearts and the pathological human myocardium cannot be adequately preconditioned. In papillary muscles of rabbits with heart failure ischaemic preconditioning may actually be harmful and not protective.[32] However, in normal laboratory animals in which an area of myocardial necrosis has been produced through ligation of a coronary artery, the unaffected myocardium may otherwise be completely healthy before remodelling occurs. We have found that in these hearts a better recovery of function against global ischaemia is seen. The Na^+/H^+ exchanger is inhibited, thus rendering the heart more resistant to ischaemia.[33] Moreover, thyroid a1T3 and β1T3 receptors are downgraded. We have already discussed the cardioprotective action of selective hypothyroidism. This setting is of great importance and is seen very often clinically.

It is, however, very difficult to establish when the healthy myocardium is starting to fail, thus losing its preconditioning capacity.[34] The interventions and drugs which can be employed to reverse this process will be discussed later. First, the additional clinical situations where preconditioning or other means of myocardial protection can be meaningfully employed will be enumerated.

Exercise testing

If a patient undergoes two consecutive exercise tests within approximately one hour, the second test will show less severe ischaemic manifestations and after a longer exercise time.[35] Exercise-induced ischaemia can elicit both early and delayed preconditioning, which can extend for up to 24-72 hours in animals[36] and humans.[37] It may constitute one of the beneficial effects of regular exercise training.

Angioplasty

The second or third complete balloon occlusion has been seen to produce a smaller ST elevation than the first, and less anginal pain. This has been ascribed to ischaemic preconditioning.[38] Some authors have also described preconditioning at a distance.[39] This could have applications in patients with compromised ventricular function who are undergoing multivessel interventions.

Another very important aspect of preconditioning is the obvious impracticability of its application in acute myocardial infarction as "primary angioplasty". We are all very keen on achieving opening of the occluded artery as early as possible. However, we have done very little to combat the reperfusion injury which produces most of the necrosis/apoptosis after an acute occlusion. The drugs that have shown some promise will be discussed below. What must be appreciated is that drugs are needed that are active also *after* ischaemia and during reperfusion. Luckily, many widely used drugs can be regularly expected to be administered before ischaemia in the clinical setting, as will be discussed.

Open heart operations

In this context two different situations have been seen in the clinical setting. In many studies an early post-operative deterioration has been seen and has been ascribed to stunning.[40] Obviously in these patients pre-operative protection would have been helpful. In fact, Yellon's group showed some years ago that preconditioning can be applied clinically in the operative setting.[41]

An improvement in myocardial function early after surgery has also been reported.[42] It can be postulated that in these patients an increase in coronary flow will produce an improvement of myocardial function overriding any effects of coronary stunning. Of course, the aforementioned conditions of the myocardium would be expected to play a role.

Drugs

Adenosine

Adenosine has been widely used. Apart from the experimental animal, it has been clinically tested during percutaneous transluminal coronary angioplasty,[43] in a dose of 20 mg by the intracoronary route, with prevention of the deterioration of left ventricular function. It also diminishes the no-reflow phenomenon in the setting of acute myocardial infarction,[44] and has been given successfully during aortocoronary bypass surgery.[45] However, its routine use has not become established.

K_{ATP} channel openers

Many of the drugs employed for this purpose have also been used in the clinical setting. In the experimental setting they are the prototypes of preconditioning mimickers.[46] The main drawback of these drugs is that they are effective only when given at the onset of ischaemia and not during reperfusion. However, they can produce late preconditioning,[47] which may prompt their chronic use.

Nicorandil is the most widely used drug. It has K_{ATP} channel opening and nitrate-like effects and mimicks preconditioning in the angioplasty setting.[48] It can re-instate the preconditioning effect after the time interval for its occurrence has elapsed,[49] and in elderly patients, as already mentioned.[8] However, it is still used very sparingly in chronic angina, although the encouraging findings of the IONA trial[50] would be expected to advance its use.

Although many drugs, such as sulfonylureas, inhibit their action, they have not been conclusively proven to increase mortality. Brady and Terzie[51] point out that the mortality effect of oral hypoglycaemic therapy in diabetic patients is still uncertain.

Na^+/H^+ exchanger inhibitors

These can prevent myocardial injury when given before the onset of ischaemia. However, in the ESCAMI trial cariporide, given at the time of hospital admission of patients with acute myocardial infarction, gave disappointing results.[52] Aker et al[53] very recently showed that these drugs are beneficial in experimental heart failure. Stagg and Terraciano give a pertinent outline of this modality.[54] Interestingly, hypothyroidism is also characterised by diminished Na^+/H^+ exchange activity, which is also seen in the healthy myocardium distant from myocardial infarction. All these latter states are characterised by a state of "hibernation", which by reducing oxygen needs may protect from necrosis. Preponderance of β-myosin and downregulation of thyroid a1T3 and β1T3 receptors is a common denominator. Very recently. Narolska et al[55] showed that human ventricles, in which β-myosin predominates (94.7%) manifest a five times more economical contraction than the atria (24.6%). However, it is not known for how long hibernation continues to be protective before the myocardium "sleeps to death".

Nitrates

These drugs can cause delayed preconditioning.[56] They are very widely used. However, their chronic use has not been associated with a decrease in mortality.

Hormones

Oestrogens have been shown to diminish infarct size mostly due to a Ca^{2+}-activated K_{ATP} channel opening.[57] The "synthetic" oestrogen-action product raloxifene has been found effective in the canine,[58] but not in the rabbit heart.[59] However, surprisingly, testosterone improved recovery of myocardial function after ischaemia/reperfusion injury in rats, also through a mitochondrial K_{ATP} channel opening effect.[60] However, hormone replacement in women has not found unequivocal acceptance.

ACE inhibitors, angiotensin receptor blockers (ARBs)

These drugs are currently used almost ubiquitously. Hypertension, heart failure, and recently coronary

artery disease are indeed very common indications. The administration of valsartan was found to reinstate preconditioning by preventing postinfarction remodelling at two weeks, in hearts that presumably had not failed yet,[61] while the acute administration of quinaprilat protected the post-infarction failing rat heart at 10 weeks against ischaemia.[62] Angiotensin II receptor antagonism can reduce infarct size, potentiate the infarct size-limiting effects of preconditioning, and also lower the threshold preconditioning stimulus.[63]

ACE inhibition also potentiates preconditioning through bradykinin β2-receptor activation. Leesar et al[64] showed that in man intracoronary infusion of bradykinin reproduces the cardioprotective effects of ischaemic preconditioning. β-blockers are also used in angina, heart failure and hypertension. They are potent anti-apoptotic agents, thus diminishing the effects of ischaemia-reperfusion injury.[65] It seems that not all β-blockers are created equal. Carvedilol protects against ischaemia/reperfusion to a greater degree than propranolol, probably through its additional anti-oxidant effects.[66]

Ca^{2+}-blockers have also been widely used clinically. Experimentally they are very effective.[67] They also protect against oxidant stress,[68] as will be further discussed. The very recent favorable results of nifedipine in the ACTION trial[69] thus may come as no surprise to many clinicians.

Free fatty acid oxidation

The main fuel of the myocardium is free fatty acids. However, they consume more oxygen to produce equal amounts of ATP as compared to glucose, while in large quantities they may actually be toxic. "Switch" medications cause the myocardium to preferentially use glucose. Thus they may improve energy production characteristics.

The following substances have been used in clinical practice:

Ranolazine has been protective in the isolated heart[70] and has been employed successfully clinically in the CARISA study.[71] It has also been found to have an antiarrhythmic action.

Etomoxir has given encouraging results in dilated cardiomyopathies.[72]

Trimetazine is a very widely used drug. It is equipotent to propranolol in angina pectoris,[73] and has been found to be cardioprotective in the setting of angioplasty and bypass surgery. Very recently we have found that it protects the isolated rat heart against necrosis in ischaemia/reperfusion when given *before* the onset of ischaemia, but only ameliorates stunning when given *after*.[74] The drug has consistently shown favorable results in trials of ischaemic cardiomyopathy.[75] In view of its low toxicity and lack of cardiovascular effects it may be more widely studied.

The same can be stated for *L-carnitine*, which has been used in idiopathic dilated cardiomyopathy in children[76] and adults,[77] but may also hold promise after an acute myocardial infarction.[78]

Statins are being used with greatly increasing frequence. A few years ago Bell and Yellon[79] showed that they can be effective in reducing reperfusion injury. Di Napoli et al[80] also showed that simvastatin reduces reperfusion injury in the isolated working rat heart. In addition, statins may be beneficial in reversing the lipid hydroperoxide modification of proteins—an unfavourable characteristic of ischaemia-reperfusion.[81]

It is interesting that *diltiazem* has also been found to reduce lipid peroxidation in the reperfused heart.[82] Eaton et al[81] showed that lipid peroxidation products are formed when omega-6 polyunsaturated fatty acids react with free radical species. This finding may explain the protective effect of omega 3 fatty acids against ischaemia reperfusion.[83]

Flaxseed, a rich plant source of alpha-linolenic acid also protects against ventricular fibrillation induced by ischaemia-reperfusion.[84]

Resveratrol,[85] a natural antioxidant present in red wine, has also been found to protect against ischaemia-reperfusion arrhythmias and mortality in rats. This may be another aspect of the French paradox.

The emergence of cross-tolerance has already been described. Actually, regular exercise, apart from protecting against ischaemia-reperfusion, has been found to protect against the direct oxidative injury produced by H_2O_2.[86] However, Adams et al[87] found that exercise may also induce H_2O_2 production, which in turn causes eNOS upgrade, which is protective. Thus, the variable effects of oxidant stress should be reassessed. Although too great and abrupt reactive oxygen species production, either endogenously at reperfusion injury or H_2O_2 given exogenously, can undoubtedly cause necrosis, their production in smaller amounts can be beneficial by inducing preconditioning. This aspect is extremely interesting. A few years ago Röth and Jaberansari[88] showed that antioxidants can actually inhibit preconditioning. In the clinical setting, many antioxidants have been tried but none has come into clinical prominence. n-acetylcysteine has been found to be cardioprotective,[89] as well as

beneficial in protecting against renal damage during coronary angiography/angioplasty,[90] and we have shown that vitamin C is also renoprotective.[91] It would be advisable to reexamine whether these substances are also cardioprotective in the clinical context.

It is not clear whether antioxidants can protect when given after occlusion. Thus N-(2-mercaptopropionyl)-glycine given 1 minute before reperfusion enhanced myocardial recovery, but was ineffective when given 1 minute after reperfusion.[92] Nespereira et al[93] showed that antioxidants can prevent lipid peroxidation.

Desferrioxamine has been found to be protective for the myocardium perioperatively,[94] while *allopurinol* decreases experimental infarct size by improving myocardial recovery,[95] and also increases survival in murine postischaemic cardiomyopathy, most probably by diminishing oxidative cardiac load.[96]

Other drugs which have shown promise in the experimental and clinical setting are:

Cyclosporine and its many analogues, which can be effective *after* the onset of ischaemia by reducing mitochondrial pore opening.[97]

Levosimendan, a calcium sensitiser, is being increasingly used in acute and intermittently in chronic heart failure. In the isolated rat heart it has been shown to be cardioprotective.[98] This may render it preferable to dobutamine for acute use in many aspects of heart failure, since the latter drug may through many of its actions be detrimental in the setting of ischaemia/reperfusion, as we have shown.[99]

The natriuretic peptide families have cardioprotective properties.[100] *Neseritide* is another analogue currently widely used in acute heart failure.

Two more drugs are gaining importance:

Erythropoietin, which is increasingly used in chronic heart failure. It mimicks preconditioning in the nervous and cardiac tissue.[101]

Melatonin has both cardioprotective and antioxidant properties.[102]

The ease of administration and lack of side effects of these agents suggests that they may find wide acceptance.

Preconditioning and the cardiac patient

After having enumerated all these interventions and drugs, both old and new, one should contemplate the situation of the patient with coronary artery disease and the ways through which he may be helped in his lifelong struggle against disability and death.

The patient with chronic stable angina may be encountering many episodes of ischaemia. If these are short and not too severe, they may actually precondition/protect his heart, provided that his myocardium stays healthy. The favorable effect of chronic exercise has already been mentioned. Similarly, the favorable effects of nitrates (late preconditioning), ACE inhibitors (preconditioning inducers), β-blockers (cardioprotective) have been described. Nicorandil may be another promising drug, and also trimetazidine or ranolazine, used as adjuvant therapy.

Other situations which may also abrogate preconditioning are hypercholesterolaemia/atherosclerosis, chronic long-standing diabetes mellitus, heart failure and senility. Statins, ACE inhibitors and nitrodil have been found successful in these not infrequent categories, by reversing the negative actions.

The patient with chronic angina may also need to undergo a percutaneous coronary intervention and/or revascularisation. The previously mentioned drugs, especially statins, nicorandil, nitrates and adenosine may prove helpful. Delayed preconditioning caused by exercise may be an additional consideration. Multivessel angioplasty is being increasingly employed. It may set into action the beneficial effect of remote preconditioning.

Finally, what can be done to improve the plight of the patient undergoing primary angioplasty in the always dramatic setting of acute myocardial infarction? One can hope that he has already been receiving the previously mentioned drugs, as often happens in practice in the clinical setting. It is, of course, too late to precondition him through exercise. Cyclosporine analogues can limit reperfusion injury. Statins, ACE inhibitors, antioxidants, β-blockers and glucose "switch" substances can diminish stunning and necrosis, while Na^+/H^+ exchange inhibitors, ACE inhibitors and thyroid manipulation can diminish myocardial loss. Insulin remains a candidate[103,104] despite the recent disappointing results of CREATE-ECLA.[105]

In spite of the reservations mentioned earlier concerning the deluge of reactive oxygen species after the abrupt opening of the occluded artery, hyperoxaemic reperfusion has actually been tried, without any clear-cut benefit.[106] In fact, Labruto et al recently reported that hyperoxia produces preconditioning through TNFa induction.[107] This is another expression of the yin and yang phenomenon.[108]

Inhibition of the Na/Ca^{2+} exchanger has also been tried, with a benefit reported in anterior myocardial infarction.[108] Hypothermia has been shown to preserve

myocardial function during ischaemia reperfusion.[109] Thus, it came as no surprise that an endovascular cooling catheter has also been used, with a suggestion of a reduction in infarct size.[110]

The loss of contractile function after cardiac surgery has already been mentioned, and is still being studied.[112] How to prevent this phenomenon should be the object of further studies. Pre-and postconditioning are continuously being considered.

Most of the above medications retain their value even when all primary protective mechanisms have failed and the patient goes into post-necrotic heart failure. It is very interesting however, that two currently used modalities have more than mechanical implications:

- Synchronised pacing improves glucose utilisation,[113] the beneficial effect of which has already been described.
- Progenitor cell engraftment on the infarcted myocardium has been found to be cardioprotective through a preconditioning-like mechanism.[114]

Thus, one can see that adequate cardiac protection is the holy grail of contemporary cardiology. The judicious integration of research inspiration and clinical acuity is of paramount importance if we are to claim the elusive chalice.

References

1. Murry CE, Jennings RB, Reimer KA: Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986; 75: 1124-1136.
2. Iliodromitis EK, Kremastinos DT, Katritsis DG, et al: Multiple cycles of preconditioning cause loss of protection in open-chest rabbits. J Mol Cell Cardiol 1997; 29: 915-920.
3. Cokkinos AD, Tzeis S, Moraitis P, et al: Loss of cardioprotection induced by ischemic preconditioning after an initial ischemic period in isolated rat hearts. Exp Clin Cardiol 2003; 8: 5-9.
4. Ottani F, Galvani M, Ferrini D: Angina and Cardiac adaptation, in Baxter GF, Yellon DM, (eds.): Delayed preconditioning and adaptive cardioprotection. Kluwer Academic Publishers, Dordrecht, 1998; pp. 209-224.
5. Ishihara M, Sato H, Tateishi H, et al: Implications of prodromal angina pectoris in anterior wall acute myocardial infarction: acute angiographic findings and long-term prognosis. J Am Coll Cardiol 1998; 31:1701.
6. Abete P, Ferrara N, Cioppa A, et al: Preconditioning does not prevent postischemic dysfunction in aging heart. J Am Coll Cardiol 1996; 27: 1777-1786.
7. Abete P, Calabrese C, Ferrara N, et al: Exercise training restores ischemic preconditioning in the aging heart. J Am Coll Cardiol 2000; 36:643-650.
8. Lee FM, Su SF, Chou T:F et al: Loss of preconditioning by attenuated activation of myocardial ATP-sensitive potassium channels in elderly patients undergoing coronary angioplasty. Circulation 2002; 105: 334-340.
9. Speakman JR, Talbot DA, Selman C, et al: Uncoupled and surviving: individual mice with high metabolism have greater mitochondrial uncoupling and live longer. Aging Cell 2004; 3: 87-95.
10. Hadour G, Ferrera R, Sebbag L, et al: Improved myocardial tolerance to ischaemia in the diabetic rabbit. J Mol Cell Cardiol 1998; 30: 1869-1875.
11. Ravingerova T, Neckar J, Kolar F, et al: Ventricular arrhythmias following coronary artery occlusion in rats: is the diabetic heart less or more sensitive to ischaemia? Basic Res Cardiol 2001; 96: 160-168.
12. Szekeres L, Szilvassy Z, Ferdinandy P, et al: Delayed cardiac protection against harmful consequences of stress can be induced in experimental atherosclerosis in rabbits. J Mol Cell Cardiol 1997; 29: 1977-1983.
13. Kremastinos D, Bofilis E, Karavolias G, et al: Preconditioning limits myocardial infarct size in hypercholesterolemic rabbits. Atherosclerosis 2000; 150: 81-85.
14. Pantos C, Malliopoulou V, Varonos D, et al: Thyroid hormone and phenotypes of cardioprotection. Basic Res Cardiol 2004; 99: 101-120.
15. Pantos C, Malliopoulou V, Paizis I, et al: Thyroid hormone and cardioprotection; study of p38 MAPK and JNKs during ischaemia and at reperfusion in isolated rat heart. Mol Cell Biochem 2003; 242: 173-180.
16. Ojamaa K, Kenessey A, Shenoy R, et al: Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. Am J Physiol Endocrinol Metab 2000; 279: E1319-1324.
17. Iervasi G, Pinagitore A, Landi P, et al: Low T3 syndrome. Circulation 2003; 107: 708-713.
18. Hamilton MA, Stevenson LW, Luu M, et al: Altered thyroid hormone metabolism in advanced heart failure. J Am Coll Cardiol 1990; 16: 91-95.
19. Novitzky D, Human PA, Cooper DK: Inotropic effect of triiodothyronine following myocardial ischemia and cardiopulmonary bypass: an experimental study in pigs. Ann Thorac Surg 1988; 45: 50-55.
20. Portman MA, Fearneyhough C, Karl TR, et al: The triiodothyronine for infants and children undergoing cardiopulmonary bypass (TRICC) study: Design and rationale. Am Heart J 2004; 148: 343-398.
21. Blumgart HL, Freedberg AS, Kurland GS: Radioactive iodine treatment of antina pectoris and congestive heart failure. Circulation 1957; 16: 110-118.
22. Gomberg-Maitland M, Frishman WH: Thyroid hormone and cardiovascular disease. Am Heart J 1998; 135: 187-196.
23. Klein I, Ojamaa K: Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344: 501-509.
24. Lekakis J, Papamichael C, Alevizaki M, et al: Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. Thyroid 1997; 7: 411-414.
25. Pantos CI, Tzilalis V, Giannakakis S, et al: Phenylephrine-induced aortic vasoconstriction is attenuated in hyperthyroid rats. Int J Angiol 2001; 20: 181-186.
26. Pantos C, Mourouzis I, Malliopoulou V, et al: Dronedarone administration prevents body weight gain and increases tolerance of the heart to ischemic stress: A possible involvement of thyroid hormone receptor a1. Thyroid 2005; 15: 16-23.
27. Wexler LF, Lorell BH, Momomura S, et al: Enhanced sensitivity to hypoxia-induced diastolic dysfunction in pressure-

overload left ventricular hypertrophy in the rat: role of high-energy phosphate depletion. Circ Res 1988; 62: 766-775.
28. Koyanagi S, Eastham CL, Harrison DG, et al: Increased size of myocardial infarction in dogs with chronic hypertension and left ventricular hypertrophy. Circ Res 1982; 50: 55-62.
29. Cooley DA, Reul GJ, Wukash DC: Ischemic contracture of the heart - "stone heart". Am J Cardiol 1972; 29: 575-577.
30. Speechly-Dick ME, Baxter GF, Yellon DM: Ischemic preconditioning protects hypertrophied myocardium. Cardiovasc Res 1994; 28: 1025-1029.
31. Pantos CI, Davos CH, Carageorgiou HC, et al: Ischaemic preconditioning protects against myocardial dysfunction caused by ischaemia in isolated hypertrophied rat hearts. Basic Res Cardiol 1996; 91: 444-449.
32. Dekker LR, Rademaker H, Vermeulen JT, et al: Cellular uncoupling during ischemia in hypertrophied and failing rabbit ventricular myocardium: effects of preconditioning. Circulation 1998; 97: 1724-1730.
33. Shimohama T, Suzuki Y, Noda C, et al: Decreased expression of Na^+/H^+ exchanger isoform 1 (NHE1) in non-infarcted myocardium after acute myocardial infarction. Jpn Heart J 2002; 43: 273-282.
34. Ghosh S, Standen NB, Galinanes M: Failure to precondition pathological human myocardium. J Am Coll Cardiol 2001; 37: 711-718.
35. Okazaki Y, Kodama K, Sato H, et al: Attenuation of increased regional myocardial consumption during exercise as a major cause of warm-up phenomenon. J Am Coll Cardiol 1993; 21: 1597-1604.
36. Yamashita N, Hoshida S, Otsu K, et al: Exercise provides direct biphasic cardioprotection via manganese superoxide dismutase activation. J Exp Med 1999; 189: 1699-1706.
37. Lambiase PD, Edwards RJ, Cusack MR, et al: Exercise-induced ischemia initiates the second window of protection in humans independent of collateral recruitment. J Am Coll Cardiol 2003; 41: 1174-1182.
38. Deutsch E, Berger M, Kussmaul WG, et al: Adaptation to ischemia during percutaneous transluminal coronary angioplasty. Clinical hemodynamic and metabolic features. Circulation 1990;82:2044-2051.
39. Przyklenk K, Darling CE, Dickson EW, Whittaker P: Cardioprotection "outside the box". Basic Res Cardiol 2003; 98: 149-157.
40. Gray R, Maddhai J, Berman D, et al: Scintigraphic and hemodynamic demonstration of transient left ventricular dysfunction immediately after uncomplicated coronary artery bypass grafting. J Thorac Cardiovasc Surg. 1979; 77: 504-510.
41. Yellon DM, Alkulaifi AM, Pugsley WB: Preconditioning the human myocardium. Lancet 1993; 342: 276-277.
42. Bolli R, Harley CJ, Rabinovitz RS: Clinical relevance of myocardial "stunning", in Opie LH (ed.): Stunning, hibernation, and calcium in myocardial ischemia and reperfusion. Kluwer Academic Publishers, Boston, 1992; pp 56-82.
43. Heidland UE, Heintzen MP, Schwartzkopff B, et al: Preconditioning during percutaneous transluminal coronary angioplasty by endogenous and exogenous adenosine. Am Heart J 2000; 140: 813-820.
44. Quintana M, Kahan T, Hjemdahl P: Pharmacological prevention of reperfusion injury in acute myocardial infarction. A potential role for adenosine as a therapeutic agent. Am J Cardiovasc Drugs 2004; 4: 159-167.
45. Thourani VH, Ronson RS, van Wylen DGL, et al: Adenosine-supplemented blood cardioplegia attenuates postischemic dysfunction after severe regional ischemia. Circulation 1999; 100: II 376-383.
46. Tamargo J, Caballero R, Gomez R, et al: Pharmacology of cardiac potassium channels. Cardiovasc Res 2004; 62: 9-33.
47. O'Rourke B: Mitochondrial KATP channels in preconditioning. Circ Res 2000; 87: 845-855.
48. Matsubara T, Minatoguchi S, Matsuo H, et al: Three minutes, but not one minute, ischemia and nicorandil have a preconditioning effect in patients with coronary artery disease. J Am Coll Cardiol 2000; 35: 345-351.
49. Iliodromitis EK, Cokkinos P, Zoga A, et al: Nicorandil recaptures the waned protection from preconditioning in vivo. Br J Pharmacol 2003; 138: 1101-1106.
50. The IONA, study group: Effect of nicorandil on coronary events in patients with stable angina: The Impact Of Nicorandil in Angina (IONA) randomized trial. Lancet 2002; 359: 1269-1277.
51. Brady P, Terzie A: The sulfonylurea controversy: more questions from the heart. J Am Coll Cardiol 1998; 31: 950-956.
52. Zeymer U, Suryapranata H, Monassier JP, et al: The Na^+/Ca^{2+} exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction. Results of the evaluation of the safery and cardioprotective effects of eniporide in acute myocardial infarction (ESCAMI trial). J Am Coll Cardiol 2001; 38: 645-650.
53. Aker S, Snabaitis A, Konietzke I, et al: Inhibition of the Na^+/H^+ exchanger attenuates the deterioration of ventricular function during pacing-induced heart failure in rabbits. Cardiovasc Res 2004; 63: 273-282.
54. Stagg MA, Terraciano CMN: Less Na^+/H^+-exchanger to treat heart failure: a simple solution for a complex problem? Cardiovasc Res 2005; 65: 10-12.
55. Narolska NA, van Loon RB, Boontje NM, et al: Myocardial contraction 5-fold more economical in ventricular than in atrial human tissue. Cardiovasc Res 2005; 65: 221-229.
56. Heusch G: Nitroglycerin and delayed preconditioning in humans. Circulation 2001; 103: 2876-2878.
57. Sbarouni E, Iliodromitis EK, Bofilis E, et al: Short-term estrogen reduces myocardial infarct size in oophororectomized female rabbits in a dose-dependent manner. Cardiovasc Drugs Ther 1998; 12: 457-462.
58. Ogita H, Node K, Asanuma H, et al: Amelioration of ischemia and reperfusion-induced myocardial injury by the selective estrogen receptor modulator, raloxifene, in the canine heart. J Am Coll Cardol 2002; 40: 998-1005.
59. Sbarouni E, Iliodromitis EK, Bofilis E, et al: Estrogen alone or combined with medroxyprogesterone but not raloxifene reduce myocardial infarct size. Eur J Pharmacol 2003; 467: 163-168.
60. Er F, Michels G, Gassanov N, et al: Testosterone induces cytoprotection by activating K^+ channels in the cardiac mitochondrial inner membrane. Circulation 2004; 110: 3100-3107.
61. Miki T, Miura T, Tsuchiada A, et al: Cardioprotective mechanism of ischemic preconditioning is impaired by postinfarct ventricular remodeling through angiotensin II type receptor activation. Circulation 2001; 102: 458-463.
62. Podesser BK, Schirnhofer J, Berndecker OY, et al: Optimizing ischemia/reperfusion in the failing rat heart-improved myocardial protection with acute ACE inhibition. Circulation 2002; 106: Suppl I:277-283.
63. Nozawa Y, Miura T, Tsuchida A, et al: Chronic treatment with an ACE inhibitor, temocapril, lowers the threshold for the infarct size-limiting effect of ischemic preconditioning. Cardiovasc Drugs Ther 1999; 13: 151-157.

64. Leesar M, Stoddard MF, Manchikalapudi S, et al: Bradykinin-induced preconditioning in patients undergoing coronary angioplasty. J Am Coll Cardiol 1999; 34: 639-650.
65. Veronsee CD, Lewis WR, Takla MW, et al: Protective metabolic effects of propranolol during total myocardial ischemia. J Thorac Cardiovasc Surg 1986; 92: 425-433.
66. Cargnoni A, Ceconi C, Bernocchi P, et al: Reduction of oxidative stress by carvedilol: role in maintenance of ischaemic myocardium viability. Cardiovasc Res 2000; 47:556-566.
67. Opie LH: Reperfusion injury and its pharmacological modification. Circulation 1989; 80: 1049-1062.
68. Herbaczynska-Cedro K, Gordon-Makszak W: Nisoldipine inhibits lipid peroxidation induced by coronary occlusion in pig myocardium. Cardiovasc Res 1990; 24: 683-687.
69. Lubsen J, Wagener G, Kirwan B-A, et al, on behalf of the ACTION investigators: Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with symptomatic stable angina and hypertension: the ACTION trial. J Hypertens 2005; 23: 641-648.
70. Graslinski MR, Black SC, Kilgore KS, et al: Cardioprotective effects of ranolazine (RS-43285) in the isolated perfused rabbit heart. Cardiovasc Res 1994; 28: 1231-1237.
71. Chaitman BR, Pepine CJ, Parker JO, et al, the CARISA investigators: Effects of ranolazine with atenolol, amlodipine, of diltiazem on exercise tolerance and angina frequency in patients with severe angina. A randomized controlled trial. JAMA 2004; 291: 309-316.
72. Schmidt-Schweda S, Holubarsch C: First clinical trial with etomoxir in patients with chronic congestive heart failure. Clin Sci 2999; 99: 27-35.
73. Detry JM, Sellier P, Pennaforte S, et al: Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Br J Clin Pharmacol 1994; 37: 279-288.
74. Pantos C, Bescond-Jacket A, Tzeis S, et al: Trimetazidine protects isolated rat hearts against ischemia-reperfusion injury in an experimental timing-dependent manner. Basic Res Cardiol 2004; 99: 1-7.
75. Cokkinos DV: Can metabolic manipulation reverse myocardial dysfunction? Eur Heart J 2001; 22: 2138-2139.
76. Winter S, Jue K, Prochazka J, et al: The role of L-carnitine in pediatric cardiomyopathy. J Child Neurol 1995; 10: 2S45-2S51.
77. Rizos I: Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J 2000; 139: S120-123.
78. Iliceto S, Scrutinio D, Bruzzi P, et al, on behalf of the CEDIM Investigators: Effects of L-carnitine administration on left ventricular remodeling after acute anterior myocardial infarction: The L-carnitine ecocardiografia digitalizzata infarto miocardico (CEDIM) trial. J Am Coll Cardiol 1995; 26: 380-387.
79. Bell RM, Yellon DM: Atorvastatin administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway. J Am Coll Cardiol 2003; 41: 508-515.
80. Di Napoli P, Taccardi AA, Grilli A, et al: Simvastatin reduces reperfusion injury by modulating nitric oxide synthase expression: an ex-vivo study in isolated working rat hearts. Cardiovasc Res 2001; 51: 283-293.
81. Eaton P, Hearse DJ, Shattock MJ: Lipid hydroperoxide modification of proteins during myocardial ischaemia. Cardiovasc Res 2001; 51: 294-303.
82. Koller PT, Bergmann SR: Reduction of lipid peroxidation in reperfused isolated rabbit hearts by diltiazem. Circ Res 1989; 65: 838-845.
83. Chen H, Li D, Roberts GJ, et al: Eicosipentanoic acid inhibits hypoxia-reoxygenation-induced injury by attenuating up-regulation of MMp-1 in adult rat myocytes. Cardiovasc Res 2003; 59: 7-13.
84. Ander BP, Weber AR, Rampersad PP, et al: Dietary flaxseed protects against ventricular fibrillation induced by ischemia-reperfusion in normal and hypercholesterolemic rabbits. J Nutr 2004; 134: 3250-3256.
85. Hung L-M, Chen J-K, Huang S-S Lee R-S, Su M-J: Cardioprotective effect of resveratrol, a natural antioxidant derived from grapes. Cardiovasc Res 2000; 47: 549-555.
86. Taylor RP, Ciccolo JT, Starnes JW: Effect of exercise training on the ability of the rat heart to tolerate hydrogen peroxide. Cardiovasc Res 2003; 58: 575-581.
87. Adams V, Linke A, Krankel N, et al: Impact of regular physical activity on the NAD(P)H oxidase and angiotensin receptor system in patients with coronary artery disease. Circulation 2005; 111: 555-562.
88. Roth E, Jaberansari MT: Reactive oxygen species in early and delayed cardiac adaptation. Exp Clin Cardiol 2001; 6: 81-86.
89. Cuzzocrea S, Mazzon E, Constantino G, et al: Effects of n-acetylcysteine in rat model of ischemia and reperfusion injury. Cardiovasc Res 2000; 47: 537-548.
90. Kay J, Chow WH, Chan TM, et al: Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomised controlled trial. JAMA 2003; 289: 553-558.
91. Spargias K, Alexopoulos E, Kyrzopoulos S, et al: Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. Circulation 2004; 110: 2837-2842.
92. Bolli R, Jeroudi MO, Patel BS, et al: Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion. Evidence that myocardial "stunning" is a manifestation of reperfusion injury. Circ Res 1989; 65: 607-622.
93. Nespereira B, Perez-Ilzarbe M, Fernandez P, et al: Vitamins C and E downregulate vascular VEGF and BEGFR-2 expression in apolipoprotein-E-deficient mice. Atherosclerosis 2003; 171: 667-673.
94. Paraskevaidis IA, Iliodromitis EK, Vlahakos D, et al: Deferoxamine infusion during coronary artery bypass grafting ameliorates lipid peroxidation and protects the myocardium against reperfusion injury: immediate and long-term significance. Eur Heart J 2005; 26: 263-270.
95. Werns SW, Shea MJ, Mitsos SE, et al: Reduction of the size of infarction by allopurinol in the ischemic-reperfused canine heart. Circulation 1986; 73: 518-524.
96. Stull LB, Leppo MK, Szweda L, et al: Chronic treatment with allopurinol boosts survival and cardiac contractility in murine postischemic cardiomyopathy. Circ Res 2001; 95: 1005-1011.
97. Niemann CU, Saeed M, Akbari H, et al: Close association between the reduction in myocardial energy metabolism and infarct size: dose-response assessment of cyclosporine. Pharmacol Exp Ther 2002; 302: 1123-1128.
98. 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.

99. Pantos C, Mourouzis I, Tzeis S, et al: Dobutamine administration exacerbates postischemic myocardial dysfunction in isolated rat hearts; an effect reversed by thyroxine pre-treatment. Eur J Pharmacol 2003; 460: 155-161.
100. Brar BK, Stephanou A, Liao Z, et al: Cardiotrophin-1 can protect cardiac myocytes from injury when added both prior to simulated ischemia and at reoxygenation. Cardiovasc Res 2001; 51: 265-274.
101. Bogoyevitch MA: Review: An update on the cardiac effects of erythropoietin. Cardioprotection by erythropoietin and the lessons learnt from studies in neuroprotection. Cardiovasc Res 2004; 63: 208-216.
102. Dobsak P, Siegelova J, Eicher JC, et al: Melatonin protects against ischemia-reperfusion injury and inhibits apoptosis in isolated working rat heart. Physiology 2003; 9: 179-187.
103. Van der Horst IC, Zijlstra F, van't Hof AW; the Zwolle Infarct Study Group: Glucose-insulin potassium infusion in patients treated with primary angioplasty for acute myocardial infarction: the glucose-insulin-potassium study: a randomised trial. J Am Coll Cardiol 2003; 42: 784-791.
104. Jonassen AK, Aasum E, Riemersma RA, et al: Glucose-insulin-potassium reduces infarct size when administered during reperfusion. Cardiovasc Drugs Ther 2001; 14: 615-623.
105. Mehta SR, Yusuf S, Diaz R, et al: Effects of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction. The CREATE-ECLA randomized controlled trial. JAMA 2005; 293: 437-446.
106. O'Neill WW, Dizon SR, Grines CL: The year in interventional cardiology. J Am Coll Cardiol 3005; 45: 1117-1134.
107. Labruto F, YangJ, Vaage J, et al: Role of tumor necrosis factor alpha and its receptor I in preconditioning by hyperoxia. Basic Res Cardiol 2005; 100: 198-207.
108. Cokkinos DV: Preconditioning - A paradigm of yin and yang. Hell J Cardiol 2002; 43: 179-182.
109. Ning XH, Xu CS, Song YC, et al: Hypothermia preserves function and signaling for mitochondrial biogenesis during subsequent ischemia. Am J Physiol 1998; 274: H786-793.
110. Grines CL: ICE-IT: Intravascular cooling adjunctive to percutaneous coronary intervention for acute myocardial infarction. Transcatheter Cardiovascular Therapeutics, Washington DC, September 2004.
111. Liakopoulos OJ, Muhefeld C, Koschinsky M, et al: Progressive loss of myocardial contractile function despite unimpaired coronary blood flow after cardiac surgery. Basic Res Cardiol 2005; 100: 75-83.
112. Valen G, Vaage J: Pre-and post conditioning during cardiac surgery. Basic Res Cardiol 2005; 100: 179-186.
113. Nowak B, Sinha AM, Schaefer WM, et al: Cardiac resynchronization therapy homogenizes myocardial glucose metabolism and perfusion in dilated cardiomyopathy and left bundle branch block.
114. Ii M, Nishimura H, Iwakara A, et al: Endothelial progenitor cells are rapidly recruited to myocardium and mediate protective effect of ischemic preconditioning via "imported" nitric oxide synthase activity. Circulation 2005; 111: 1114-1120.