Prostaglandins and the cardiovascular system

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Our perception of the role of prostaglandins in the cardiovascular system changed dramatically in the 1970's with the discoveries of thromboxane A_2 and prostacyclin (for more extended reviews, see Moncada and Vane,¹ Moncada,² and Vane³). Both of these compounds are chemically unstable and share, in common with the other prostaglandins, the same precursor, arachidonic acid. This fatty acid is released from cell membrane phospholipids by chemical or mechanical perturbations and is then metabolised by a cascade of enzymes to the stable prostaglandins such as PGE_2 and $PGF_{2\alpha}$, thromboxane A_2 (TXA_2), or prostacyclin (PGI_2). On the one hand, in platelets arachidonic acid is mainly converted to thromboxane A_2 , an unstable (half life 30 seconds) vasoconstrictor and platelet aggregating substance. On the other, in the vessel wall arachidonic acid is converted to prostacyclin (PGI_2), an unstable (half life two to three minutes) vasodilator and anti-aggregating substance. We have proposed, therefore, that prostacyclin is the natural and main defence of the vessel wall against deposition of platelet aggregates. Further, prostacyclin and thromboxane A_2 represent in biological terms the opposite poles of a homeostatic mechanism for the regulation of platelet aggregability *in vivo*.⁴ Clearly, manipulation of this control mechanism is likely to affect thrombus and haemostatic plug formation.

Apart from platelets, some other tissues have also been shown to generate TXA_2 , including phagocytosing leucocytes. The role of TXA_2 in tissues other than platelets is uncertain.

Prostacyclin is the main product of arachidonic acid in all arteries and veins so far tested. Not much is known about the microcirculation but microvessels, mainly capillaries, isolated from rat cerebrum generate predominantly prostacyclin.⁵

The ability of the large vessel wall to synthesise prostacyclin is greatest at the intimal surface and progressively decreases towards the adventitia.⁶ Use of cultured cells from vessel walls additionally shows that endothelial cells are the most active producers of prostacyclin. Other cells, including myocytes in culture and mesenchymal cells (probably fibroblasts) also produce prostacyclin, as does the pericardium and the

epicardial surface of the heart. Since the release of prostaglandins is increased by any distortion of cell membranes, it is interesting to speculate that with each beat of the heart the stretching of the parietal and visceral pericardium leads to a release of prostacyclin which may act as a natural lubricant between them. In this respect, the third activity of prostacyclin (termed cytoprotection when applied to the reduction of experimentally induced ulcers in the stomach) could be important. The possibility also exists that any prostacyclin released will condition the surface coronary vessels and perhaps also be responsible for preventing the clotting of blood spilt into the pericardial sac.

Prostacyclin has been implicated in functional hyperaemia, the main evidence for which is in the gastric mucosa,⁷ where prostaglandin synthetase inhibitors such as aspirin and indomethacin reduce mucosal blood flow and cause erosions. The aspirin-like drugs, however, do not cause vasoconstriction in the normal coronary circulation either of animals or man, indicating that a continuous production of prostacyclin is not having a vasodilator activity in the normal heart. Interestingly, Friedman *et al.*⁸ found in nine patients with coronary artery disease (eight with angina) that indomethacin increased the blood pressure by an average of 20 mm, increased myocardial oxygen demand, and decreased coronary flow by 40%. The results are complicated by the fact that the patients were receiving beta-blockers and nitrates, each of which could be a source of interactions with indomethacin, but they do suggest that in coronary vascular disease the endogenous release of prostacyclin takes part in the struggle to maintain the coronary circulation.

There is also experimental evidence that exogenous prostacyclin has a beneficial effect in the acutely ischaemic heart. Infusions of prostacyclin intravenously have an antiarrhythmic effect in experimental infarction⁹ and also limit infarct size (in dogs and cats) and reduce lysosomal enzyme release. Several studies have now confirmed the original observations of Lefer *et al.*¹⁰ including that of Ribeiro *et al.*¹¹ in which they showed a substantial decrease in infarct size and mortality in dogs treated with intravenous prostacyclin for

six hours after ligating the left anterior descending coronary artery. Prostacyclin induced a reduced blood flow to the non-ischaemic myocardium and no change in the blood flow to the ischaemic myocardium, raising the possibility that this beneficial effect is connected with its "cytoprotective" activity rather than with its antiplatelet or vasodilator activity. In this context it is interesting that dogs are also protected against lethal endotoxin shock by prostacyclin infusions.¹² This protection was associated with cardiac mitochondria which were structurally and functionally normal, in contrast to the depression and disruption produced by endotoxaemia, as observed by enzymic assay and electron microscopy.¹³

The other side of the coin involves the role of platelets and thromboxane A_2 release in coronary artery disease. In man, thromboxane release into the coronary sinus blood increases after angina, but it is difficult to know whether this is cause or effect, or which cells are responsible. Artefacts resulting from the use of long catheters have been suggested, but Hirsh *et al.*¹⁴ have concluded that blood sampling across the heart through long catheters is a reliable procedure for the assessment of intracoronary thromboxane A_2 production in patients with ischaemic heart disease. Certainly, if thromboxane A_2 had a causative role in angina, aspirin should prevent its release and the consequent effects.

The discovery of prostacyclin and the possibility that a balance between prostacyclin and thromboxane formation regulates the haemostatic state of the circulation has led to intensive investigations of the role of prostacyclin in disease processes.

It has been suggested that a number of diseases are related to an imbalance in the prostacyclin- TXA_2 system, including arterial and venous thrombosis, atherosclerosis, and diabetes. It is possible that in diseases where there is a tendency for thrombosis, TXA_2 production is raised or prostacyclin production is reduced or both, while the opposite is found in some diseases associated with an increased bleeding tendency.

Synthetic prostacyclin is available as a stable freeze-dried preparation (Epoprostenol; Flolan^R, Wellcome) for administration to man. During intravenous infusion in healthy volunteers there is dose related inhibition of platelet aggregation, arteriolar vasodilatation, increase in skin temperature, and facial flushing.¹⁵⁻¹⁷ Headache is a common side effect with the higher rates of prostacyclin infusion.

Extracorporeal circulation of blood brings it into contact with artificial surfaces which cannot generate prostacyclin. In the course of such procedures thrombocytopenia and loss of platelet haemostatic function occur and make an important contribution to the bleeding problems after charcoal haemoperfusion and

prolonged cardiopulmonary bypass in man.¹⁸⁻²⁰ Formation of microemboli during cardiopulmonary bypass may also contribute to cerebral complications which sometimes follow this procedure.²¹ Animal models of these extracorporeal circulations showed²³ a platelet sparing effect of prostacyclin and this has now been confirmed in man.

In patients with fulminant hepatic failure undergoing charcoal haemoperfusion,²² prostacyclin infusion prevented the fall in platelet count and rise in beta-thromboglobulin seen in the control patients. Gimson and his colleagues²³ have now made almost 200 charcoal haemoperfusions on a daily basis using prostacyclin for platelet protection in the treatment of 76 patients with fulminant hepatic failure. Remarkable survival rates (65%) were obtained in the 31 patients who had been referred early and in whom the serial haemoperfusion was started while signs of grade III encephalopathy were still evidence (sleeping most of the time but rousable with incoherent speech and distinct confusion). In addition, cerebral oedema developed less frequently in this group than in those patients in whom haemoperfusion was started later when signs of grade IV encephalopathy were already apparent (not rousable but may or may not respond to painful stimuli). The authors thought that this was probably the major factor in their improved survival. In this latter group, 20% survived, so that the overall survival rate from the 76 patients was 38%. These results (especially those treated early) compare very favourably with a survival rate of 15% in patients under standard intensive care measures.

Several double blind clinical trials of prostacyclin in cardiopulmonary bypass have been published.²³ The treatment groups showed a preservation of platelet number and function, with a reduction in the blood loss in the first 18 hours after operation. In the trial by Longmore *et al.*²⁴ the blood loss was halved and the reduction was statistically significant. The heparin sparing effect of prostacyclin was confirmed and the vasodilator effects were not troublesome: indeed, these effects may be useful in controlling intra-bypass hypertension.²⁵

The observation in animals that during haemodialysis prostacyclin could be used without heparin to prevent platelet loss and coagulation²⁶ has also been confirmed in man. In particular, prostacyclin can be infused intravenously before dialysis and into the arterial line during dialysis.²⁷⁻²⁹ Prostacyclin safely replaced heparin as the sole antithrombotic agent during haemodialysis and could well be more advantageous when anticoagulation is contraindicated. Indeed, Turney and Weston³⁰ have safely used prostacyclin instead of heparin during dialysis in more than 50 patients.

Therapeutic assessment of prostacyclin is still in its

infancy with many trials in progress, mostly based on infusion for 72 hours intravenously or intra-arterially. Open studies and individual case reports have been reported which, though still preliminary, nevertheless point the way to conditions in which prostacyclin therapy may be useful.

In open trials, prostacyclin was of benefit to patients with peripheral vascular disease in terms of relief of ischaemic pain and ulcer healing.³¹⁻³⁵ The first double blind clinical trial of prostacyclin in 24 patients has shown significant improvements in the treated groups.^{35a} Of the 12 patients infused intravenously for four days with placebo, only one showed improvement at six months, by which time three had died and six others had received surgical intervention. Of the 15 patients who were infused with prostacyclin for four days (average 7 ng/kg per min i.v.), by one month 10 showed a substantial improvement, which was still evident in eight patients at six months. By this time, two other patients in the group had received surgical intervention and one had died. Zygulska-Mach *et al.*³⁶ infused prostacyclin into three patients with sudden blockage of central retinal veins. Improvement was observed in those two patients who were treated within the first 48 hours.

Prostacyclin also produced significant and long lasting improvements in Raynaud's phenomenon, with striking reductions in the frequency, duration, and severity of the disease in 21 of 24 patients. In all patients who responded, the improvement lasted for weeks (mean nine to 10 weeks), and in three patients subjective improvement was still reported six months after the infusion. Pain relief was a striking feature, presumably associated with the increased blood flow indicated by increased temperature of the hands and fingers.³⁷ Though this was an open trial, the authors' previous experience suggested that there was no placebo response to saline infusion in similar patients. Belch *et al.*³⁸ have also reported successful treatment in four out of five patients, and a double-blind clinical trial^{38a} has confirmed benefit in Raynaud's phenomenon, again outlasting the infusions of prostacyclin by six weeks or more.

Richard Gryglewski and his colleagues in Cracow were the first to demonstrate the beneficial effects of infusion of prostacyclin in ischaemic disease of the legs (Szczeklik *et al.*³⁹). They have now obtained dramatic improvements after prostacyclin infusion in 10 patients with ischaemic stroke. Patients with transient ischaemic attacks and haemorrhagic stroke were excluded. With prostacyclin treatment there was a reversal of symptoms strikingly sooner in all 10 patients than could have been expected and in six patients during the first six hour infusion. One patient died two weeks later of a second stroke, but the other nine have maintained return of function⁴⁰ for (so far)

up to six months.

Prostacyclin has been successfully used in a few cases of primary pulmonary hypertension⁴¹⁻⁴³ and one case of pre-eclamptic toxemia.⁴⁴ Yui *et al.*⁴⁵ described beneficial effects of intravenous infusions of prostacyclin in nine patients with severe congestive heart failure refractory to digitalis and diuretics. Mean pulmonary capillary wedge pressure, mean arterial pressure, systemic and pulmonary vascular resistance were all reduced, whereas heart rate, cardiac index, and stroke index were increased. Facial flushing was the only side effect.

Bergman *et al.*⁴⁶ gave infusions of prostacyclin to patients with coronary artery disease and were sufficiently encouraged by the acute effects in angina (similar to those of short acting nitrates) to suggest further evaluation. Szczeklik and Gryglewski³³ found a beneficial effect of intravenous prostacyclin infusions in patients with unstable angina. Hall and Dewar⁴⁷ concluded from their study of five patients with coronary artery disease that prostacyclin can safely be infused directly into diseased coronary arteries. Chierchia *et al.*⁴⁸ found intravenous administration of prostacyclin to be without effect on the number, severity, and duration of ischaemic episodes in eight of nine patients with variant angina. Consistent relief was seen on administration of prostacyclin to the ninth patient.

A prostacyclin deficiency has been reported in thrombotic thrombocytopenic purpura.⁴⁹ Infusion of prostacyclin into two patients with thrombotic thrombocytopenic purpura did not produce an increase in circulating platelet count.^{49 50} FitzGerald *et al.*,⁵¹ however, have reported an increase in platelet count and an improvement in the neurological status of one such patient during 18 days of prostacyclin infusion. They were sufficiently encouraged to conclude that the controlled evaluation of prostacyclin in thrombotic thrombocytopenic purpura was warranted.

The work of Mundy *et al.*⁵² showed that infusion of prostacyclin protected transplanted kidneys from hyperimmune rejection in dogs. Leithner *et al.*⁵³ have now shown in eight patients with chronic renal transplant rejection that intravenous infusion of prostacyclin at 5 ng/kg per min for five days resulted in less platelet consumption by the kidneys and an improvement in transplant function. Canine livers have been preserved for up to 48 hours and then successfully transplanted, using a combination of refrigeration, Sack's solution, and prostacyclin.⁵⁴

Clearly, there are many clinical conditions that may respond to prostacyclin treatment and its place (or that of stable analogues) in therapeutics will be defined in the next few years. Emphasis has rightly been placed on the potential antiplatelet and vaso-

dilator activities, but can these transient properties account for the long-lasting benefits which have been described? Other effects of prostacyclin may also be involved, including activation of fibrinolysis.⁵⁵ More work, however, is needed on the cytoprotective actions, which may account, for instance, for the limitation of infarct size. Some other instances where the cytoprotective property of prostacyclin may play a role have already been cited; others are in the protection of the lungs against injury induced by endotoxin shock in laboratory animals^{56,57} and in hypoxic damage in the cat isolated perfused liver.⁵⁸ Interestingly, the addition of prostacyclin during the separation from blood and the subsequent washing of platelets substantially improves their viability in vitro. Whereas normal platelet survival is about 10 hours, platelets prepared with the aid of prostacyclin remain functional for 72 hours.⁵⁹ All of these studies suggest a potential wider therapeutic role of prostacyclin in cell or tissue preservation.

Clearly, our knowledge of the causes and treatment of cardiovascular diseases will be substantially increased in the next few years by studies on the formation of prostacyclin in the body and by therapeutic trials of prostacyclin and its analogues in various cardiovascular diseases.

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