Time course of the effects of epoprostenol on effective pulmonary blood flow in normal volunteers

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1 Epoprostenol (prostacyclin) has been widely used as a vasodilator, but its effects on cardiac output are controversial and the time course of its effects little studied.

2 We report its cardiovascular effects in doses of 5 and 10 ng kg⁻¹ min⁻¹ in six healthy volunteers.

3 Each of the two doses caused a mean 20% rise in effective pulmonary blood flow and a 15% rise in heart rate. These effects appeared to reach a maximum within 10 min of starting or increasing the rate of infusion, with no evidence of a rebound effect.

4 When the dose was reduced, heart rate and effective pulmonary blood flow appeared to reach a new steady state within 5 min of reducing or stopping the infusion. Only minor side-effects were encountered, and they were rapidly reversed on stopping the drug.

5 These results should be applied to the therapeutic use of epoprostenol as a vasodilator, particularly when titrating the optimum dose for a given individual.

Keywords epoprostenol prostaglandins pulmonary circulation vasodilator agents

Introduction

Epoprostenol (prostacyclin, PGI₂) has been used as a vasodilator in patients with systemic hypertension (Chaignon *et al.*, 1982), ischaemic heart disease (Bergman *et al.*, 1981), primary pulmonary hypertension (Rubin *et al.*, 1982) and congenital heart disease (Bush *et al.*, 1986a). It is known to cause a tachycardia and lower in particular the diastolic blood pressure, but its effects on cardiac output are controversial; it has been reported as doubling it (Eklund *et al.*, 1981) or having no effect (Szczeklik *et al.*, 1980; Cook *et al.*, 1983).

The cardiovascular effects of PGI₂ are reported to be fully developed within 3 min of starting an infusion and cease within 5 min of turning it off. Previous workers have relied on heart rate alone to determine the time course of its effects (O'Grady *et al.*, 1980), but this means that any changes in stroke volume caused by PGI₂ would not be detected.

We therefore carried out this study of the cardiovascular effects of PGI₂, using non-

invasive, inert gas estimations of effective pulmonary blood flow, Qp_{eff}. In this technique, the subject takes a rapid vital capacity inspiration of a gas mixture which includes two test gases, one insoluble (10% argon) and one very soluble (3.5% freon-22). He holds his breath for 1–2 s at full inspiration, and then exhales steadily over 20–30 s. The dilution volume of argon is the 'accessible lung volume', which lies within six sevenths of total lung capacity measured in the body plethysmograph in normal people. The rate of disappearance of freon-22 is proportional to that part of total pulmonary blood flow which is useful in respiratory gas exchange, 'effective pulmonary blood flow'. This amounts to more than 95% of cardiac output in normal people (Davidson *et al.*, 1972).

Methods

Six healthy normal volunteers were studied (three males, three females, mean age 31 years,

range 29–34). They had no significant history or physical signs of cardiac or pulmonary disease. The study involved a rehearsal day, during which no drug or placebo was given, and two study days. The design was for a double-blind, crossover study, with the order of infusion randomised. All subjects gave informed consent, and the protocols were approved by the Hospital Ethics Committee.

The following apparatus was used for the measurement of $\dot{V}_{E,eff}$. The subjects were seated in a chair facing the screen of an oscilloscope and the mouthpiece. The mouthpiece was attached to a Rudolph valve, which in turn was connected to two half-Haldane valves. The first half-Haldane valve connected the inspiratory limb of the Rudolph valve either to room air or to the bag of test gas (freon-22 3.5%, argon 10%, oxygen 35%, in nitrogen); the subject breathed out either into a spirometer or room air, via a second half-Haldane valve. The output from the spirometer was recorded onto a paper chart for later analysis and also displayed on the screen of the oscilloscope. The oscilloscope was set up so that an expiratory flow rate of 5 l min^{-1} caused the spot to rise along an oblique straight line drawn on the screen. The purpose of this was to ensure that the subject maintained a steady rate of expiration during the manoeuvre, and the rate remained constant throughout the study period.

The single breath manoeuvre was performed as previously described (Denison *et al.*, 1980). The subject was instructed to go onto the mouthpiece, wearing a noseclip. The subject breathed in and then out to residual volume, signalling when this point was reached. The first valve was turned, connecting the subject to the bag of test gas, and he then breathed in to total lung capacity. During the inspiration to total lung capacity, the second valve, connecting the expiratory limb of the circuit to the spirometer, was opened. The subject held his breath for 1–2 s at full inspiration, and breathed slowly out, carefully watching the oscilloscope screen. The time taken to exhale was 20–30 s, depending on the vital capacity. During exhalation, the first valve, to the inspiratory bag, was shut off. At the end of the manoeuvre, after the subject had come off the mouthpiece, the volume left in the inspiratory bag was measured by being pushed through the spirometer, so that the inspired volume could be measured accurately.

The gases were sampled just beyond the mouthpiece, using a fine nylon probe, and analysed by a mass spectrometer (MGA 200). The output signals for argon, freon-22 and oxygen were recorded on a paper chart by a 4-

channel Linseis pen-recorder (the 4th channel being for volume). The volume signal was calibrated before and after each manoeuvre with a 1 l syringe using at least three increments, and the mean of at least six 1 l steps used in the calculations. Inspired volume and rate of expiration were measured by hand from the paper chart for each manoeuvre, and the argon and freon-22 traces digitised and analysed as described elsewhere (Denison *et al.*, 1980).

Blood pressure was measured ultrasonically every 3 min using a cuff round the upper arm with the microphone applied to the brachial artery (Dinamapp vital signs monitor, Critikon Ltd, USA). There is good agreement between ultrasonically measured blood pressure and aortic pressure measured invasively (Borrow & Newburger, 1982). The heart rate was found from a single channel ECG recording and measured every 15 s, and drugs were administered via a Vickers Medical Infusion pump. PGI_2 or a vacuum packed, inert powder were freshly dissolved in the sterile glycine buffer (pH 10.5) and diluted with 0.9% sodium chloride just prior to the study. The infusion rates were adjusted so that the doses of PGI_2 used were 5 and $10 \text{ ng kg}^{-1} \text{ min}^{-1}$.

The protocols were as follows. The rehearsal run involved 15 argon/freon manoeuvres at 3 min intervals, with ultrasonic blood pressure measurements 30 s after the start of the slow expiration of each manoeuvre. No cannulae were positioned, and no drugs were given. The purpose of this run was to familiarise the subjects with the manoeuvre and study procedure, and to demonstrate that they could perform it adequately. The other purpose was to decide on the method of analysis used for the actual study days. It is possible to analyse the traces over a given fixed time interval e.g. 10–20 or 12–24 s, or to select by eye the most linear portion of the trace. In each case, the coefficient of variation was less using a fixed interval, so this was selected. The use of a fixed interval has the further advantage of eliminating at least one source of observer bias. The interval chosen was 12–24 s for all except one subject, who had a vital capacity of 2.9 l; for her 10–20 s was chosen.

The study days were separated by at least 1 week, and the same protocol was followed on each occasion. The study was performed without a break, and consisted of five stages. These were the baseline measurements ($n = 8$), and then 21 min for each of the infusion rates, that is $5 \text{ ng kg}^{-1} \text{ min}^{-1}$, then $10 \text{ ng kg}^{-1} \text{ min}^{-1}$, then reducing to $5 \text{ ng kg}^{-1} \text{ min}^{-1}$. The fifth and final stage was when the drug had been stopped, and this stage also lasted 21 min. Each stage commenced 1 min

Table 1 Coefficient of variation (%) for effective pulmonary blood flow (Qp.eff), heart rate (HR), and systolic (SBP) and diastolic (DBP) blood pressure for the rehearsal day for the six normal volunteers; the figures refer to within study variation

Subject	Sex	Qp.eff	HR	SBP	DBP
1	F	5.0	9.4	5.5	5.4
2	F	4.2	4.1	4.6	2.5
3	F	4.9	4.9	5.4	4.7
4	M	6.4	9.3	3.2	4.8
5	M	4.9	3.4	4.8	4.5
6	M	7.3	5.1	3.4	6.7

after the final measurement of Qp.eff, so that the first measurement of Qp.eff of the new step was 2 min after the change of dose.

The subjects came to the laboratory having fasted for a minimum of 2 h. The cannula was inserted, and the blood pressure cuff and ECG leads positioned. The subject then rested seated in the chair for at least 30 min. The first manoeuvre was performed at time zero. One minute after the 8th manoeuvre, the infusion of drug or placebo was commenced. We measured Qp.eff 2, 5, 8, 11, 14, 17 and 20 min after increasing or reducing the dose for each stage. Any side-effects noted by investigator or subject were recorded.

Results

The results for the rehearsal run are shown in Table 1, where the coefficient of variation ($100 \times$ standard deviation/mean) of Qp.eff, mean heart rate and systolic and diastolic blood pressure are given. These values relate to within study variation. The between study mean coefficient of variation of Qp.eff has been shown to be 6.5% (Waller, 1982). Group mean data for the study days, expressed in each case as the difference between drug and placebo, are shown graphically in Figures 1, 2, 3 and 4. For all study days, the first three single breath manoeuvres were discarded because they give artefactually high results (Waller, 1982). There were no significant changes in inspired volume, rate of expiration, or accessible lung volume at any time.

The single breath manoeuvre clearly affected the heart rate, so mean values were taken nominally at a time point 1 min before each measurement of Qp.eff, that is 1, 4, 7, 10, 13, 16 and 19 min after changing the dose. Each of these was calculated from values recorded 45 s before to 30 s after the nominal heart rate time point (six measurements). The rest of the heart rate data was discarded. The plots of mean heart

rate suggested a peak change at around 10–15 min with some possibility of a rebound effect. Since earlier work had suggested stabilisation at around three minutes, the hypothesis that effects had not stabilised by 4 min was tested by comparing the average heart rate at the second time point (4 min post-dose) with the mean (plateau) of the fourth to the sixth time point values (10–16 min post-dose). Similarly the possibility of a 'rebound' effect was tested by comparing the final (19 min) value with the plateau values. Each test was performed for increasing and decreasing dose periods separately, using analysis of variance with subject, dose level and time as factors. Since the placebo occasion showed very little change over time, values for the PGI₂ run only were used in the analysis. The readings of Qp.eff were subject to the same analysis as the heart rate values. Since there was little if any change for the group systolic and diastolic blood pressures (Figures 3 and 4) they were not analysed further. There may be a decrease in diastolic blood pressure, which the study was insufficiently powerful to detect.

The analysis of variance showed that the changes in Qp.eff and heart rate observed when the dose of PGI₂ was increased from 0 to 5 ng kg⁻¹ min⁻¹ were not significantly different from the changes observed when the dose of PGI₂ was increased from 5 to 10 ng kg⁻¹ min⁻¹. Thus alterations in these measurements described below are from a combined analysis of the changes observed with each of the two dose levels. Similarly, the changes observed when the dose of PGI₂ was decreased from 10 to 5 ng kg⁻¹ min⁻¹ were not significantly different from those observed when the infusion of PGI₂ was stopped altogether, so a combined analysis of the two dose levels is quoted. The analysis showed that increasing the dose of PGI₂ caused a 15% rise in heart rate and a 20% rise in Qp.eff.

The results also showed that the effects of PGI₂ had not stabilised by 5 min. Heart rate showed a statistically significant increase of 4.7 beats min⁻¹ from the second time point at each dose (4 min post-dose) to the mean values of the fourth to the sixth time points (10–16 min post-dose) when the infusion was increased. There was a statistically significant increase in Qp.eff of 0.4 l min⁻¹ from the second time point at each dose (5 min post-dose) to the mean values of the fourth to the sixth time points (11–17 min post-dose) on increasing the infusion. These changes amounted to about half of the total response for each stage. By contrast, when the dose was decreased, neither heart rate nor Qp.eff showed any significant changes between the second time

Figure 1 The difference between the drug and placebo study days for effective pulmonary blood flow ($Q_{p.eff}$) is plotted against time, as epoprostenol (PGI_2) is infused in increasing and then decreasing doses ($ng\ kg^{-1}\ min^{-1}$). The mean and 95% confidence intervals for this difference are shown.

Figure 2 The difference between the drug and placebo study days for heart rate is plotted against time, as epoprostenol (PGI_2) is infused in increasing and then decreasing doses ($ng\ kg^{-1}\ min^{-1}$). The mean and 95% confidence intervals for this difference are shown.

Figure 3 The difference between the drug and placebo study days for systolic blood pressure (SBP) is plotted against time, as epoprostenol (PGI_2) is infused in increasing and then decreasing doses ($\text{ng kg}^{-1} \text{min}^{-1}$). The mean and 95% confidence intervals for this difference are shown.

Figure 4 The difference between the drug and placebo study days for diastolic blood pressure (DBP) is plotted against time, as epoprostenol (PGI_2) is infused in increasing and then decreasing doses ($\text{ng kg}^{-1} \text{min}^{-1}$). The mean and 95% confidence intervals for this difference are shown.

point and the mean values of the fourth, fifth and sixth time points.

The results also did not support the suggestion of a rebound effect. There were no further significant changes between the plateau (time points 4 to 6) and the final time point at each dose for heart rate or Qp.eff on either increasing or decreasing the dose.

There were no major side-effects noted. All six subjects had facial flushing, five had headaches, and the sixth a feeling of nasal congestion. One subject had severe abdominal pain and a feeling of impending dissolution. All side-effects were rapidly reversed when the infusion rate was reduced. No subject refused the second dose of PGI₂ or asked for the infusion to be prematurely terminated. No subject became significantly hypertensive on PGI₂.

Discussion

This communication reports the application of a non-invasive, inert gas method of measuring Qp.eff to the study of the cardiovascular effects of PGI₂. The discussion centres on the methods used and the nature and timing of the drug effects.

When a subject is breathing slowly out into a spirometer, the gas within the lungs can be considered as being in a closed system. The amounts of the various gases present are altered only by uptake by lung tissue including water, and by the bloodstream. If a test gas has been added to the system, provided it is not present in mixed venous blood, and rapidly equilibrates with capillary blood, then the rate of uptake of gas is proportional to capillary flow, at least until the recirculation of blood significantly elevates the mixed venous tension of the test gas. These principles have been known for nearly 150 years. Good agreement has been found between inert gas determinations of flow and cardiac output measured by dye dilution (Ayotte *et al.*, 1970; Teichman *et al.*, 1974; Sackner *et al.*, 1975), the direct Fick principle (Becklake *et al.*, 1962; Zeidifard *et al.*, 1976) and Doppler (Mehta *et al.*, 1985).

Inert gas determinations of Qp.eff are safe and non-invasive, and thus very suitable for determining the cardiovascular effects of drugs. They have been used to study the effects of intravenous and inhaled terbutaline in asthmatics (Pierce *et al.*, 1981). This paper reports the likely variability in the measurements and the application of the technique to the study of the acute effects of intravenous PGI₂.

This study in healthy adult volunteers shows

that PGI₂ causes an increase in heart rate and Qp.eff in a dose-dependant manner. Since there is evidence that PGI₂ does not increase intrapulmonary shunting, at least in disease, (Bush *et al.*, 1986b) it is reasonable to assume that the changes in cardiac output followed those of Qp.eff. There were no significant changes in systolic, diastolic or mean blood pressure, and therefore the rise in Qp.eff was mirrored by a fall in systemic vascular resistance. The time course of these effects was also studied. When an infusion of PGI₂ is started, Qp.eff and heart rate rise rapidly, but continue to increase after 4–5 min (the second time point), reaching a plateau by 10–11 min (the fourth time point), with no evidence of a rebound effect. There is no clear evidence that Qp.eff and heart rate continue to decrease after 4–5 min when the dosage level is reduced. Examination of the confidence limits suggests that it is likely that no major rebound effect would have been missed, and that a large continued decline in heart rate and Qp.eff 4–5 min after stopping an infusion is also unlikely. However this short-term study cannot exclude the possibility of a gradual increase or decrease in the effects of PGI₂ after many hours infusion.

Although there is general agreement that PGI₂ is a vasodilator and causes tachycardia, its effects on cardiac output are controversial (Szczeklik *et al.*, 1980; Eklund *et al.*, 1981; Cook *et al.*, 1983). It is possible that in studies in which right heart catheterisation was performed, the baseline cardiac output was spuriously elevated due to anxiety (Hickam *et al.*, 1948), and a fall in cardiac output as anxiety lessened during the study masked a rise in cardiac output due to PGI₂. The reversal of the tachycardia caused by PGI₂ within 5 min of stopping an infusion has been reported before, but the time to peak effect is slower than found by others (O'Grady *et al.*, 1980). It is difficult to account for these discrepancies, other than by postulating that there are individual differences in the responses to this drug.

PGI₂ is reported to be very safe, with any side-effects rapidly reversible on stopping the infusion. All our subjects developed facial flushing and either headache or a feeling of nasal stuffiness, side-effects which have been reported before (O'Grady *et al.*, 1980; Eklund *et al.*, 1981). None persisted more than a few minutes after stopping the infusion, and no side-effect was so severe that the subject asked for the infusion to be terminated early. Although the study was double-blind, in practice the marked facial flushing meant that both subjects and investigators always correctly identified whether

drug or placebo was being infused.

PGI₂ has been widely used as a vasodilator (Bergman *et al.*, 1981; Chaignon *et al.*, 1982; Rubin *et al.*, 1982; Bush *et al.*, 1986a). The rapidity of the onset of its cardiovascular effects means that it is easy to titrate the best dose for an individual patient. Such studies have been proposed as the best way of planning pulmonary vasodilator therapy for patients with primary pulmonary hypertension (Higenbottam, 1986). Since these studies are often performed at diagnostic cardiac catheterisation, it is an advantage to make them as brief as possible. Our results suggest that the rate of infusion can be increased at 10 min intervals in such a dose-finding study. Similarly, if side-effects such as systemic hypotension are encountered, they should be completely reversible within 5 min of turning off an

infusion.

In summary, this study has shown that PGI₂ causes tachycardia and an increase in Qp.eff, that these effects reach a plateau within 10 min of starting an infusion, and that they revert to baseline within 5 min of stopping the drug. We suggest that these results should be applied to the therapeutic use of PGI₂ as a vasodilator, when it is wished to titrate the optimum dose of the drug for an individual patient as quickly as possible.

AB is supported by the British Heart Foundation. We also gratefully acknowledge helpful discussions with Mrs C. Burke, Dr J. O'Grady and Professor D. M. Denison, and financial support, including the gift of poprostenol and matched placebo, from Burroughs Wellcome Ltd.

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(Received 4 March 1987,
accepted 19 October 1987)