Effect of prostaglandin E₁ on fractional distribution of cardiac output and organ blood flow in man: a simultaneous and non-invasive determination using double dose thallium-201 scintigraphy

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SUMMARY Taking advantage of the fact that the distribution of Thallium-201 in an organ almost parallels the blood flow to the organ, we devised a non-invasive method of simultaneously determining blood flow and its distribution in human organs. With this method, we investigated the effect of exogenous prostaglandin E₁ (PGE₁) on the central and peripheral circulation. Scintigraphy was performed after two injections of ²⁰¹TI chloride, one at rest and one after the administration of PGE₁ or saline.

In eight subjects given PGE₁ (0.2 µg·kg⁻¹·min⁻¹, iv), blood pressure fell, whereas both heart rate and cardiac output rose. The fractional distribution was increased in the heart (+13.3±2.98%, mean±SD), but decreased in the liver (-10.2±1.95%) and gastro-intestinal tract (-7.09±2.65%). No significant change was observed in the kidneys or leg. The blood flow in all these organs was increased. In the six control subjects given saline, there was no change in these central and peripheral haemodynamics.

Thus, the intravenous infusion of PGE₁ in man causes uneven blood flow distribution in heart, liver, kidney, gastro-intestinal organs and leg muscles, despite increased blood flow to all these organs. The method used in this study is relatively non-invasive and useful in evaluating organ blood flow in man, and seems to be widely applicable to physiological and pharmacologic research.

Some of prostaglandins have been known to contract or relax many smooth muscles besides those of the vasculature. Responses vary with the species, type of prostaglandin and experimental conditions. Prostaglandin E₁ (PGE₁) is known to be a potent vasodilator¹⁻⁸ and is widely used as a therapeutic agent.⁹⁻¹⁶

Fractional distribution of cardiac output and simultaneous organ blood flow are difficult to evaluate in humans, and no ideal method has been reported. In animals those measurements are possible with the use of radioactive microspheres,¹⁸⁻¹⁹ but this technique is not applied to humans because of its invasive nature. We devised a technique to evaluate simultaneous blood flow and its distribution in human organs. Using this technique, we studied non-invasively the effect of PGE₁ on several vascular beds in humans.

Method

1 THEORETICAL BACKGROUND

Thallium-201 scintigraphy has been widely used in evaluating myocardial ischaemia. Like potassium-43, thallium-201 is known to be a blood flow tracer because after iv injection it is rapidly taken up in the tissues.²⁰⁻²² The initial distribution of ²⁰¹TI in an organ reflects the blood flow to that organ.²³⁻²⁵

Using this biological property, we devised a method of measuring the change of fractional distribution of cardiac output and of blood flow (double dose ²⁰¹TI scintigraphy). The principle of this technique is as follows: since ²⁰¹TI uptake in an organ, expressed as the radioactivity (C) of the organ divided by that of the ²⁰¹TI dose (D), is almost equal to the fractional
distribution (Fract) of cardiac output at the same time of 201-Tl administration (ie Fract = C/D), when 201-Tl is injected twice under different haemodynamic conditions, (1) at rest and (2) at loading condition, the change in Fract can be detected from the change in 201-Tl uptake in the organ, as in the following equation:

\[
\text{Change of Fract (d-Fract)} = \frac{\text{Fract} \ 2 - \text{Fract} \ 1}{\text{Fract} \ 2 - \text{Fract} \ 1} = \frac{\frac{C \ 2}{D \ 2} - \frac{C \ 1}{D \ 1}}{\frac{C \ 2}{D \ 2} - \frac{C \ 1}{D \ 1}} - 1
\]

where, Fract 1 is the Fract after the injection at condition 1 (ie C1/D1), and Fract 2 is that at condition 2 (ie C2/D2).

Moreover, if cardiac output is determined at the two conditions, the change of blood flow to the organ can be calculated as the product of d-Fract and d-CO:

\[
\text{Change of blood flow (d-Flow)} = (\text{d-Fract} + 1)(\text{d-CO} + 1) - 1
\]

where, d-CO is the change of cardiac output, ie d-CO = (C02-C01)/C01.

2 SCINTIGRAPHIC DATA ACQUISITION

Scintigraphy was performed with a large field gamma camera (Searle, pho/gamma LFOV) and with a scintillation detector (Shimadzu, 3 inches in diameter). The camera was equipped with a high sensitivity, parallel-hole collimator, and interfaced to an on-line digital computer. The spectrometer window of the camera was centred at 80 KeV with 20% width. The detector was interfaced to the computer through a pulse-height analyser and a ratemeter. The pulse-height analyser was adjusted to the same spectrum as the camera.

Thallium-201 chloride (2 mCi) was injected intravenously as a bolus. To avoid stagnation of 201-Tl in a peripheral vein, the right jugular vein was used, and 10 ml saline was added to flush the system.

Scintigraphic data collection was started 5 min after the first 201-Tl injection. The camera head was adjusted to the viscera (myocardium and abdominal organs) to be imaged (fig 1, left), and the scintillation detector was directed to the right thigh. Data from both camera and detector were stored in a 128 × 128 matrix with frame mode (1 frame per minute) for 20 min. Care was taken to keep the subjects from moving.

3 STUDY PROTOCOL

The first dose of 201-Tl was injected in a basal haemodynamic state (control) and the second dose during the injection of either saline (control group) or PGE1 (PGE1 group). An intravenous infusion of PGE1 (0.2 µg·kg⁻¹·min⁻¹) was started 5 min after the start of data collection and continued for 10 min. The second dose of 201-Tl was injected 5 min after the start of the PGE1 infusion (10 min after the start of data collection).

The 201-Tl dosage (D) of the two injections was prepared to have approximately equal radioactivity.
Effect of PGE₁ on human organ blood flow

The syringe containing $^{201}$Tl was placed 70 cm below the collimator centre of the other gamma camera (Searle, pho/gamma 4), and the radioactivity was counted before and after the injection, and the difference was calculated.

Blood pressure (BP) was measured in the arm by a cuff sphygmomanometer. The electrocardiogram was monitored throughout the study, and the heart rate (HR) was counted. BP and HR were recorded as often as possible throughout the study. Cardiac output (CO) was obtained by the indocyanine green dye method with a photoelectric piece applied to the ear lobe. CO was measured twice during each control and PGE₁ administration.

4 DATA ANALYSIS AND CALCULATION

Time-activity curves were generated from the regions of interest (ROI) in the images of the heart, liver, kidneys and gastro-intestinal tract (fig 1, right). The ROI of the gastro-intestinal tract was assigned to the images of the stomach, intestine and spleen and the renal ROI to both kidneys. When the image of one kidney was superimposed on the image of the gastro-intestinal tract, the other kidney which showed good delineation was representatively selected. The data from the detector on the thigh were also analysed and the time-activity curve was derived on the same CRT display. From these curves average count rates were read for 5 frames 5 min after each $^{201}$Tl injection, and the ratio of radioactivity (C₁/C₂) in these organs was calculated (fig 2).

From the ratios of radioactivity in the organ (C₁/C₂) and in the dosage (D₁/D₂), the change of fractional distribution (d-Fract) and the change of blood flow (d-Flow) were calculated by the above equations.

5 SUBJECTS

Fourteen subjects were divided into two groups. The control group (56±13 years) was composed of six patients with atypical chest pain. In these patients $^{201}$Tl scintigraphy was performed for the purpose of detecting myocardial ischaemia, but because the results were negative, they were assigned to the control group. In this group, the first and second doses were injected before and after the administration of saline, respectively, both at rest and in the same haemodynamic state.

The PGE₁ group (51±19 years) was composed of three healthy volunteers and five patients with atypical chest pain but negative test for myocardial ischaemia. In this group the first dose was injected at rest and the second after intravenous PGE₁.

![Time activity curves generated from regions of interest of heart (1), liver (2), gastro-intestinal tract (3), and right (4) and left (5) kidneys. The curve numbered 6 is from the detector on the leg. The numbers under the lowest horizontal line show the frame number, i.e. the time from the start of the computer (1 frame = 1 min). From these curves the average count rates due to the first or the second dose of $^{201}$Tl were read for 5 frames between 5 and 10 min or between 15 and 20 min, respectively.](image)
TABLE 1  Haemodynamic changes induced by intravenous prostaglandin E₂

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure syst/dia (mmHg)</th>
<th>Heart rate (beats-min⁻¹)</th>
<th>Cardiac output (litre-min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control (n=6, saline administration)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>146±21/85±12</td>
<td>74±13</td>
<td>4.8±1.6</td>
</tr>
<tr>
<td>After</td>
<td>144±19/84±10</td>
<td>72±8</td>
<td>4.5±1.5</td>
</tr>
<tr>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PGE₂ (n=8, 0.2 µg-kg⁻¹-min⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>139±19/81±14</td>
<td>82±10</td>
<td>5.3±1.6</td>
</tr>
<tr>
<td>After</td>
<td>129±18/72±15</td>
<td>91±9</td>
<td>7.1±1.8</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td></td>
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<td></td>
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<tr>
<td>NS</td>
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</tbody>
</table>

Values given are mean±1SD.
Statistical analysis was performed with a paired t test of values before and after the administration of saline or PGE₂.

TABLE 2  Changes in fractional distribution and organ blood flow induced by intravenous PGE₂

<table>
<thead>
<tr>
<th></th>
<th>Heart (%)</th>
<th>Liver (%)</th>
<th>G-I tract (%)</th>
<th>Kidney (%)</th>
<th>Leg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control (n=6, saline administration)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Fract</td>
<td>-1.60±4.43</td>
<td>-4.08±3.21</td>
<td>+1.01±1.15</td>
<td>-1.32±3.11</td>
<td>-1.73±1.56</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td><strong>PGE₂ (n=8, 0.2 µg-kg⁻¹-min⁻¹)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Fract</td>
<td>+13.3±2.98</td>
<td>-10.2±1.95</td>
<td>-7.09±2.65</td>
<td>+0.525±5.44</td>
<td>+4.33±7.28</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Flow</td>
<td>+62.5±6.93</td>
<td>+29.3±6.71</td>
<td>+37.4±8.16</td>
<td>+44.7±10.3</td>
<td>+55.6±14.3</td>
</tr>
</tbody>
</table>

Values given are mean±1SD.
Statistical analysis was performed with unpaired t test between control and PGE₂ groups. d-Fract and d-Flow are percentage change of fractional distribution and of blood flow.

Results

After PGE₂ injection, the BP decreased, but the HR and CO increased significantly, whereas no significant change occurred after saline injection (table 1). The d-Fract in the organs was slight in the control group (table 2).

In the PGE₂ group, the d-Fract increased in the heart but decreased in the liver and gastro-intestinal tract (table 2). No significant change was noted in the kidneys or leg. The d-Flow was increased in all the organs.

Discussion

For some years PGE₂ has been used as a therapeutic agent in cardiovascular disease. Since PGE₂ is a potent vasodilator and an efficient inhibitor of platelet aggregation, various uses have been reported in several clinical fields. In patients with pulmonary hypertension accompanying mitral valvular disease the intravenous infusion of PGE₂ is reported to cause a significant drop in pulmonary blood volume. Intraarterial infusion of PGE₂ has been more effective for peripheral vascular disease, and its therapeutic effectiveness has also been demonstrated after intravenous infusion. Moreover, infusion of PGE₂ has been used in patients with cardiac malformations accompanied by low partial oxygen pressure in the plasma, such as ductus arteriosus Botalli, pulmonary atresia or stenosis, Ebstein anomaly, etc.

In spite of these extensive uses in clinical practice, the information about PGE₂ is inadequate, particularly in regard to its effect on regional vascular beds in humans. The present study was undertaken to elucidate the simultaneous effect of PGE₂ on blood flow and its distribution in several organs.

Prostaglandins contract and relax many smooth muscles besides those of the vasculature. Responses may vary with the species, type of prostaglandin and experimental conditions. F-type prostaglandins are vasoconstrictors in some vascular beds, whereas E and A series prostaglandins are known to be potent vasodilators in most vascular beds.

The effects of exogenous and endogenous PGE₁ on blood pressure, heart rate and cardiac output are fairly well known, although all types of prostaglandins can exert different effects at different doses. Intravenous or intraarterial administration of PGE₁ decreases
systolic arterial pressure, but increases both heart rate and cardiac output. These effects were found in most species, including man, dog, cat, rabbit, mouse, chicken and rat. In our study in man, the continuous intravenous infusion of PGE\textsubscript{1} caused similar results.

The effects of PGE\textsubscript{1} on the peripheral circulation, especially in man, are much less well known. In the studies of Nakano \textit{et al} on the circulation of dogs, intraarterial PGE\textsubscript{1} infusion caused a significant increase of blood flow in the coronary, brachial, femoral, carotid, mesenteric and renal arteries. Pulmonary and splenic arteries also proved to be dilated by PGE\textsubscript{1}. In man, indomethacin, a cyclooxygenase inhibitor, increased renal and splanchnic vascular resistance as well as total systemic vascular resistance, and infusion of PGE\textsubscript{1} after the administration of indomethacin completely restored to normal resistance in these vascular beds. These data both in animals and in man seem to confirm that PGE\textsubscript{1} dilates nearly all peripheral arteries and increases the blood flow to the organs, although the intensity of the effect varies. Our results showed simultaneous increase in the blood flow to all the vascular beds evaluated, and seem to confirm the results of previous studies. However, in regard to the regional distribution of blood flow, PGE\textsubscript{1} caused an increase in the myocardium and a decrease in the liver and gastro-intestinal tract. Although the precise mechanism of the different effect on the several vascular beds remains unclear, this study disclosed that exogenous PGE\textsubscript{1} caused an uneven blood flow distribution in human organs.

Thallium-201 is presently the cation of choice for perfusion myocardial imaging. After intravenous injection, \(^{201}\text{Tl}\) enters rapidly and remains longer in tissues. This biological property of \(^{201}\text{Tl}\) permits us to obtain changes of blood flow distribution by two injections at a short interval under different haemodynamic conditions.

The \(^{201}\text{Tl}\) uptake by an organ depends on the presence of an active Na-K-ATP-ase transport system, organ blood flow and tissue permeability to \(^{201}\text{Tl}\). The most important factor appears to be blood flow because \(^{201}\text{Tl}\) is extracted rapidly from the blood at a high and almost uniform extraction rate. The extraction fraction for the kidneys is 85\%\textsuperscript{29} and for the heart 88\%,\textsuperscript{30} and these are not greatly affected by various interventions, such as changes of heart rate or acid-base balance or the administration of insulin, propranolol or acetylcholine. Microspheres have the advantage of being large enough to be totally extracted by organs in one passage, so that their distribution reflects only blood flow.\textsuperscript{17} Strauss \textit{et al}\textsuperscript{25} reported that the percentage dose of \(^{201}\text{Tl}\) and of microspheres was similar in the heart, kidney, thyroid and skeletal muscle in controls and even in noradrenaline-treated dogs. Redistribution occurs with time but does not play a major role if imaging is begun 10 to 20 min after injection.\textsuperscript{21,24,31-32} So initial distribution of \(^{201}\text{Tl}\) can be a true reflection of the blood flow distribution at the time of injection. To test this technique, we administered \(^{201}\text{Tl}\) twice under the same haemodynamic conditions (saline infusion might not alter haemodynamics), and the results showed a minimum change in the fractional distribution in many organs. This may be a way to prove in part the adequacy of this method since there is no other comparable or standard method to evaluate simultaneous blood flow in human organs.

In summary, we studied the effect of exogenous PGE\textsubscript{1} on several vascular beds in man by a double administration of \(^{201}\text{Tl}\), and disclosed that the intravenous infusion of PGE\textsubscript{1} causes uneven blood flow distribution in the organs, despite increased blood flow to all the organs evaluated.

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References


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