CENTRAL AND REGIONAL HAEMODYNAMICS DURING CONTROLLED HYPOTENSION PRODUCED BY ADENOSINE, SODIUM NITROPRUSSIDE AND NITROGLYCERIN

Studies in the Pig

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Induced hypotension during anaesthesia was introduced by Gardner in 1946 [1]. Reasons for the use of deliberate hypotension during surgery are to facilitate the surgery and to decrease blood loss [2]. However, in a retrospective series [3] there was an overall incidence of complications of more than 3%, and there is always a risk of underperfusion of vital organs—a hazard that the anaesthetist must bear in mind. Many indirect methods have been used to estimate the likelihood of ischaemia in different organs: for example, the electroencephalogram (EEG) [5], the electrocardiogram (ECG) [2] and the measurement of renal function [6]. Direct measurements have been made with flow probes [7], the hydrogen clearance method [8] and the microsphere technique [9]. The latter method has been used for many years in our laboratory [10, 11].

There are many methods for achieving controlled hypotension during clinical anaesthesia; for example, the use of the inhalation agents such as halothane, enflurane and isoflurane [2], direct vasodilators such as nitroglycerin (TNG) [7, 12, 13], sodium nitroprusside (SNP) [4, 6, 7, 13, 14] and purine nucleotides (adenosine and adenosine triphosphate) [13, 15, 16], ganglion and adrenergic receptor blocking agents [2], extradural and spinal block [17] and calcium channel blocking agents [18, 19].

The aim of the present investigation was to study and to compare, using the microsphere technique, the effects on central haemodynamics and regional blood flows of hypotension induced by adenosine nitroprusside and nitroglycerin.

SUMMARY

Controlled hypotension was induced in pigs by the infusion of adenosine, sodium nitroprusside (SNP) or nitroglycerin (TNG). Central and regional haemodynamics were studied using the microsphere technique during control and hypotensive periods. All three drugs produced decreases in mean arterial pressure (MAP), but it was very difficult to maintain stable values of hypotension with TNG, and it was necessary to increase continuously the dose of SNP to produce stable hypotension. Adenosine produced an increase in cardiac output (CO), maintained blood flow to the cerebrum, cerebellum, heart, kidneys and adrenal glands and increased blood flow to the spinal cord and splanchnic organs, except the spleen. SNP and TNG decreased CO, but blood flow to the aforementioned organs (except the spleen) was maintained. Urine flow was greatly impaired during the infusion of adenosine.

MATERIAL AND METHODS

Anaesthesia and surgical procedures

Nine pigs of both sexes of a Swedish native breed weighing between 19 and 35 kg, were used. They received no food overnight, but had free access to water.

Anaesthesia was induced with ketamine hydrochloride 500 mg (Ketalar, Parke-Davis), and...
atropine 0.5 mg was given i.v. Anaesthesia was maintained with methomidate (Hypnodil, Leo) 7.5 mg h⁻¹/kg body weight. Tracheotomy was performed and the lungs were ventilated by a volume controlled ventilator (Servo 900B, Siemens Elema). Glucose 2.5% in a balanced electrolyte solution (Rehydrex, Pharmacia) 7.5 ml h⁻¹ kg⁻¹ was administered as a continuous infusion throughout the experiment (this included the fluid in which the hypotensive agent was given). The carotid arteries and the jugular veins were prepared and polyethylene catheters were inserted with their tips lying in the left ventricle, aortic arch and right atrium. A flow-directed catheter with a thermistor was inserted with its tip positioned in the pulmonary artery. One polyethylene catheter was placed in a femoral artery. Catheters were also inserted into the ureters through an incision in the bladder.

Experimental programme (fig. 1)

After catheterization the animals were allowed to stabilize for 40 min. Measurements were made during a period of normotension and during periods of hypotension induced by adenosine, nitroglycerin (TNG) and sodium nitroprusside (SNP). Each period lasted for 30 min, and there was a 20-min recovery period in between the administration of each drug.

SNP and adenosine were given in doses sufficient to decrease MAP from 93.4 ± 11.0 mm Hg to just below 50 mm Hg. When giving TNG it was not possible to obtain a stable level below 60 mm Hg.

Mean arterial (MAP), right atrial (MRAP), pulmonary artery (MPAP) and capillary wedge (MPCWP) pressures, heart rate (HR), CO and urine output were measured at normotension and during the different periods of hypotension. One of the four different labelled microspheres was injected during each period. All the measurements mentioned above were made after 10 min of stable normotension or hypotension. Urine was collected over 20 min. Blood samples for blood-gas analyses were drawn during each period.

At the end of the observation period the animals were killed by injection of potassium chloride into the right atrium and autopsy was performed.

Measurements

MAP, MRAP, MPAP and MPCWP were measured by connecting the above catheters to transducers (EMT-33, Elema Schönander, Sweden). The signals were recorded on a multi-channel ink-jet recorder (Mingograph 81, Elema Schönander, Sweden) and the mean pressures were obtained by electronic dampening of the signals. A level of 8 cm below the sternum was used as the zero reference level. Arterial blood samples were analysed for oxygen tension (Po₂), carbon dioxide tension (Pco₂) and pH, using an automatic blood-gas analyser (ABL2, Radiometer AS, Denmark), which also computed base excess (BE).

Cardiac output (CO) was measured using the thermodilution (Cardiac Output Computer, Edwards Labs, Calif., U.S.A.) and the microsphere techniques. Regional blood flows were determined.
by the microsphere technique. According to Buckberg and colleagues [20] this produces sufficient precision in the blood flow measurements in the organs under investigation. The reference sample was drawn from a small superficial branch of the femoral artery, using a motor syringe at a rate of 1.2 ml min\(^{-1}\) (Sage Instrument Syringe, pump 352). The syringe served as a reference organ when calculating blood flows. Immediately before injection into the left ventricle, 2-3 \(\times 10^6\) microspheres were suspended in fresh pig plasma to produce a total volume of 1 ml, and agitated in a Vortex JR Mixer. The different microspheres were given sequentially to avoid systematic errors, and so that blood flow could be measured on four different occasions in the same animal.

At postmortem, samples measuring about 1 ml were collected from the heart (n = 6 pieces of tissue), lung (n = 6), kidney (n = 4), adrenal gland (n = 2), spleen (n = 2), stomach (n = 2), intestine (n = 2), liver (n = 2), pancreas (n = 2), muscle (n = 9), cerebrum (n = 3), cerebellum (n = 3) and spinal cord (n = 8). These specimens and the reference samples were analysed in a gamma-spectrophotometer (Nuclear, Chicago 1087) with respect to chromium-57, strontium-85, niobium-95 and cerium-141 activity. Correction was made for overlap between the isotopes. The total amount of radioactivity injected was obtained by comparing the activity in the injection syringe before and after the injection of the labelled microspheres.

The blood flow to the different organs \((f)\) (ml min\(^{-1}\) g\(^{-1}\)) was calculated from the following equation:

\[
f = \frac{m \cdot f_s}{m_s}\]  

where \(m\) is the radioactivity per gram of specimen, \(m_s\) the radioactivity in the reference blood sample and \(f_s\) the blood sampling rate in ml min\(^{-1}\). Cardiac output was calculated in the same way, the factor \(m\) this time equalling the amount of radioactivity injected.

**Calculations and statistics**

The systemic vascular resistance (SVR) was calculated from the formula:

\[
SVR = \frac{MAP - MRAP}{f} \cdot 10^{-6} \text{ N s m}^{-6}
\]

In the statistical analyses of results the mean, standard deviation (SD) and standard error of the

<table>
<thead>
<tr>
<th></th>
<th>Normotension</th>
<th>Adenosine hypotension</th>
<th>TNG hypotension</th>
<th>SNP hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO(_1) (litre min(^{-1}))</td>
<td>3.6 ± 0.9</td>
<td>4.0 ± 0.7</td>
<td>3.2 ± 0.6*</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>CO(_a) (litre min(^{-1}))</td>
<td>3.4 ± 0.9</td>
<td>4.1 ± 0.9*</td>
<td>3.1 ± 0.8</td>
<td>2.7 ± 0.7*</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>28.1 ± 3.2</td>
<td>36.3 ± 4.6**</td>
<td>21.6 ± 6.0*</td>
<td>18.9 ± 8.4*</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>93.4 ± 11.0</td>
<td>49.4 ± 2.4***</td>
<td>62.3 ± 11.9***</td>
<td>50.3 ± 7.0***</td>
</tr>
<tr>
<td>MRAP (mm Hg)</td>
<td>-0.11 ± 0.2</td>
<td>0.33 ± 0.1</td>
<td>-0.33 ± 0.2</td>
<td>-1.9 ± 2.4</td>
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<td>MPAP (mm Hg)</td>
<td>18.4 ± 3.9</td>
<td>17.7 ± 3.1</td>
<td>16.7 ± 5.5</td>
<td>12.7 ± 6.0**</td>
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<tr>
<td>MPCWP (mm Hg)</td>
<td>5.9 ± 4.0</td>
<td>5.4 ± 1.7</td>
<td>4.1 ± 1.9</td>
<td>2.3 ± 2.2</td>
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<tr>
<td>HR (beat min(^{-1}))</td>
<td>123 ± 32.0</td>
<td>113 ± 14.6</td>
<td>143 ± 20.4*</td>
<td>152 ± 36.0*</td>
</tr>
<tr>
<td>SVR (10^6 N s m(^{-6}))</td>
<td>228 ± 60.6</td>
<td>96 ± 21.6***</td>
<td>174 ± 46.2**</td>
<td>168 ± 48.0**</td>
</tr>
<tr>
<td>EVF (%)</td>
<td>30.9 ± 3.3</td>
<td>32.7 ± 2.7</td>
<td>32.2 ± 3.2</td>
<td>30.7 ± 4.7</td>
</tr>
<tr>
<td>Temp. (°C)</td>
<td>38.3 ± 0.6</td>
<td>38.5 ± 0.5</td>
<td>38.1 ± 0.5</td>
<td>38.4 ± 0.7</td>
</tr>
<tr>
<td>Urine (ml min(^{-1}))</td>
<td>0.39 ± 0.2</td>
<td>0.08 ± 0.1**</td>
<td>0.63 ± 0.5</td>
<td>0.28 ± 0.2</td>
</tr>
<tr>
<td>pH</td>
<td>7.46 ± 0.06</td>
<td>7.45 ± 0.04</td>
<td>7.39 ± 0.05</td>
<td>7.41 ± 0.14</td>
</tr>
<tr>
<td>Pa(_{O_2}) (kPa)</td>
<td>12.3 ± 1.9</td>
<td>11.9 ± 2.4</td>
<td>12.6 ± 1.5</td>
<td>11.1 ± 2.0</td>
</tr>
<tr>
<td>Pa(_{CO_2}) (kPa)</td>
<td>5.2 ± 0.4</td>
<td>4.6 ± 0.2</td>
<td>4.6 ± 0.5</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>Base excess (nmol litre(^{-1}))</td>
<td>2.4 ± 3.9</td>
<td>0.2 ± 2.6</td>
<td>2.7 ± 4.6</td>
<td>-0.9 ± 2.8</td>
</tr>
<tr>
<td>Standard bicarbonate (nmol litre(^{-1}))</td>
<td>26.5 ± 3.6</td>
<td>24.6 ± 2.2</td>
<td>22.2 ± 3.9</td>
<td>23.6 ± 2.4</td>
</tr>
</tbody>
</table>
CONTROLLED HYPOTENSION AND HAEMODYNAMICS

4.0 -
CD Baseline
HZ Adenosine
KXJ Sodium nitroprusside

Heart
Kidney
Adrenal gland

FIG. 2. Blood flow to the heart, kidney and adrenal gland during control conditions and during the different hypotensive periods. Values are mean ± SEM. n = 9. Significant differences between control and drug: *P < 0.05; **P < 0.01; ***P < 0.001.

mean (SEM) were calculated. Changes from baseline to each of the three treatments were tested using paired t test. There was no attempt to compare the individual treatments. A P value of < 0.05 was considered significant.

Linear regression was used in the comparison between the thermodilution and microsphere techniques.

RESULTS

All values are given as mean ± SD. The values obtained during each hypotensive period were compared with the corresponding values obtained during normotension (baseline level).

Hypotension induced by adenosine

Adenosine was given in a dose of 11.5 ± 4.3 μmol kg⁻¹ min⁻¹. MAP decreased by 47% from 93.4 ± 11.0 mm Hg to 49.4 ± 2.4 mm Hg (P < 0.001). MPAP, MPCWP and heart rate were unchanged and no arrhythmias were observed. CO increased by 18%. SVR decreased by 57% (P < 0.001). Blood-gas tensions were unchanged (table I). Blood flows to the heart, kidney, adrenal glands (fig. 2), muscles (fig. 3), cerebrum and cerebellum (fig. 4) were unchanged, whereas blood flow to the spinal cord (P < 0.001) (fig. 4), the stomach (fig. 5), the small intestine (fig. 5) and the pancreas (fig. 6) (P < 0.01) was increased. Blood flow to the spleen decreased (P < 0.001) and the blood flow to the liver was unchanged (fig. 6). The urine output decreased from 0.39 ± 0.15 to 0.08 ± 0.06 ml min⁻¹ (P < 0.01).

Hypotension induced by nitroglycerin

The mean dose of TNG was 119 ± 62 μg kg⁻¹ min⁻¹ and resulted in a 33% decrease in MAP (P < 0.001). There was no change in MRAP, MPAP or MPCWP. HR increased by 16% (P < 0.05). CO decreased by 9%. SVR decreased by 24% (P < 0.01) (table I).

There were no differences in arterial blood-gas tensions or acid-base balance (table I).

FIG. 3. Blood flow to muscle during control conditions and during the different hypotensive periods. For details see figure 2.
Blood flow to the heart, kidney, adrenal glands (fig. 2), cerebrum, cerebellum, spinal cord (fig. 4), stomach, pancreas and small intestine (figs 5, 6) was maintained. Blood flow to the spleen \((P < 0.05)\) (fig. 5) and muscle \((P < 0.05)\) (fig. 3) decreased.

The hypotension had no effect on urine output.

**Hypotension induced by sodium nitroprusside**

SNP was given in a mean dose of \(143 \pm 165 \mu g \text{ kg}^{-1} \text{ min}^{-1}\). It was necessary to increase the dose (from 13 to between 25 and 330 \(\mu g \text{ kg}^{-1} \text{ min}^{-1}\)) during the hypotensive period in order to keep the arterial pressure stable.

MAP decreased by 46% \((P < 0.001)\). MPAP decreased by 30% \((P < 0.01)\). MRAP and MPCWP were unchanged. HR increased by 24% \((P < 0.05)\). CO decreased by 21% (table I).

SVR decreased by 27% \((P < 0.01)\). There were no changes in arterial blood tensions or acid-base balance (table I). Blood flow to the various organs was unchanged except that blood flow to muscle \((P < 0.01)\) (fig. 3) and to the spleen \((P < 0.05)\)
DISCUSSION

 Previous pilot experiments have shown that CO and central pressures can be maintained stable for 8 h under the conditions of anaesthesia and fluid balance used in these investigations. This study was designed so that all three drugs were given to each animal, with a recovery period between the administrations, so that arterial pressure returned to its baseline value. Adenosine is an endogenous substance and a baseline concentration in the blood is reached within 3–9 min after stopping the infusion [16] so it was therefore given as the first drug. SNP and TNG were then given alternately as the second and third drugs, all in order to minimize the effects of the sequence of drug administration.

 Fukunaga, Flacke and Bloor [15] postulated that the actions of adenosine and SNP are of extremely short duration and arterial pressure returns quickly to control. Colley and Sivarajan [21] demonstrated equal regional blood flows before and after hypotension induced by TNG and SNP.

 In the present study it was found that it was easy to induce and maintain a stable degree of hypotension with adenosine without any signs of tachyphylaxis. It was necessary to increase the dose of SNP continuously in order to obtain stable hypotension, and this increased tolerance has been reported previously [13, 22, 23]. With TNG it was not possible to obtain a stable value of hypotension below 60 mm Hg, which is similar to findings reported by Colley and Sivarajan [13] and Lagerkranser and colleagues [21]. The difficulties with unstable hypotension when using TNG could be explained in part by the absorption of TNG by the tubing used [24].

 Cardiac output (CO) was measured using both the thermodilution and the microsphere techniques, and there was a good correlation between the two methods (correlation coefficient = 0.81). The increased cardiac output and stroke volume seen during adenosine-induced hypotension is explained by the decrease in afterload, as adenosine itself has no inotropic effect [25, 26]. TNG and SNP decrease afterload and preload [27] and there is, therefore, either no change or decreases in CO and stroke volume [28, 29], and these previous findings are in agreement with our results. Reflex tachycardia developed during SNP infusion [2], but the slowing of the heart rate during adenosine infusion described by Hoffman and co-workers [30] and Lagerkranser and colleagues [26] was not seen. The decrease in heart rate during the infusion of adenosine is presumed to be the result of impaired conduction from atrium to ventricle [31].

 One of the risks of induced hypotension is hypoperfusion of vital organs [2]. The brain is the organ of primary concern. Autoregulation in the brain can, however, maintain blood flow in spite of changes in MAP [2, 32]. Autoregulation can be eliminated when using vasodilator drugs, since they influence the vascular bed directly. In this
Blood flow to the splanchnic organs other than the spleen was maintained during SNP and TNG hypotensive periods. During adenosine infusion, blood flow to the pancreas, the stomach and the small intestine increased, and this is in accordance with the results of Lagerkranser and colleagues [26]. They found that portal venous blood flow increased during adenosine infusion, but that there was a simultaneous decrease in arterial hepatic blood flow. In our experiment arterial hepatic blood flow was not affected. This could be attributable to the use of different experimental animals.

In summary, all three drugs produced hypotension, but it was easiest to produce stable values with adenosine. CO increased during adenosine infusion, whereas it was slightly reduced during TNG and SNP infusions. Blood flow to the vital organs such as the cerebrum, cerebellum, spinal cord, heart, kidney and the splanchnic organs other than the spleen was maintained or increased. Urine flow almost ceased during adenosine hypotension, but returned to control values immediately after the infusion was stopped.

Adenosine, TNG and SNP are all easy to use and the vasodilating effect is instantaneous. The stable hypotension obtained with adenosine, without the necessity of increasing infusion speed, is a great advantage. The major disadvantage with the drug, however, is its effect on urine flow. This must be further studied before adenosine can be used clinically for hypotension of long duration.

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REFERENCES


