Hemodynamic and Cardiometabolic Studies in Patients with Distributive Circulatory Dysfunctions — with Special Reference to the Effects of the Beta-1-adrenoreceptor Agonist Prenalterol

av

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Sammanfattningen baseras på följande delarbeten.


ABSTRACT


A total of 49 patients were studied, using invasive hemodynamic techniques with systemic arterial, pulmonary artery and right atrial pressure recordings together with thermodilution cardiac output determinations. Sixteen of the patients were also subjected to cardiometabolic studies, using measurement of coronary sinus blood flow by the continuous thermodilution technique and analyses of oxygen content and lactate concentration in the systemic and coronary circulation. A common denominator in the five investigations was, that a distributive cardiovascular dys-equilibrium was either induced (for surgical or anaesthesiological reasons) or already present due to a pathological condition.

Thoracic epidural block from T1 to T12 induced marked decrease in systemic blood pressure due to vasodilation and impairment of cardiac performance. Prenalterol administration effectively abolished the low blood pressure by its marked inotropic action, having no effect on systemic vascular resistance. Myocardial oxygen consumption changed in parallel with the changes in cardiac work following both thoracic epidural block and prenalterol. Coronary vascular resistance was markedly decreased by the block and was not affected by prenalterol. It is suggested, that the critically low perfusion pressure is the main cause of the coronary vasodilation and that alpha-blockade induced by the thoracic epidural block is of less importance.

The combination of a thoracic epidural block from T1 to T12 and selective β1-stimulation with prenalterol was an effective way to modify the cardiovascular response to infrarenal aortic cross clamping. This treatment transferred the patients to a more favourable cardiac function curve and possibly facilitated the redistribution of blood flow in association with clamping.

In association with declamping of the infrarenal aorta or the common iliac arteries, volume loading to a slightly elevated left ventricular filling pressure shortly before declamping was an effective way to counteract the expected blood pressure drop. A normal left ventricular filling pressure prior to declamping did not prevent the blood pressure drop following declamping. It is suggested, that mismatching between vascular volume and blood volume is the main cause of declamping hypotension.

In patients with low resistance, distributive septic shock caused by gram negative bacteremias and signs of impaired cardiac function, prenalterol effectively reversed the hypotension and improved tissue perfusion by selectively increasing cardiac output. In parallel to the increased cardiac work, an increase in myocardial metabolic demand was demonstrated.

Key words:

aortic aneurysm surgery; gram negative septic shock; hemodynamics; myocardial metabolism; thoracic epidural block; volume loading; thermodilution; prenalterol

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This thesis is based on the following papers, referred to in the text by their Roman numerals:


II. Reiz, S., Nath, S., Rais, O. (1979):


IV. Reiz, S., Peter, T., Rais, O. (1979):

V. Reiz, S., Friedman, A. (1979):
Hemodynamic and cardiometabolic effects of prenalterol in patients with gram negative septic shock. Acta Anaesth. Scand. Accepted for publication.
Introduction

The term "distributive defect" was defined by WEIL and SHUBIN (1972) in their revision of the classical shock definitions. Their reclassification of different types of shock was based upon a simple working model of the circulatory system consisting of the following components:

1) the transport system for the blood to the capillary bed, i.e. the arteries and arterioles.
2) the capillary exchange system.
3) the capacitance vessels, in which up to 70% of the blood volume is located (GREEN, 1950).
4) the blood volume.
5) the heart.

Hence, a dysfunction of any single or a combination of these components will induce a distributive circulatory defect, the treatment of which must be based upon the primary site(s) of the disturbance(s) and the physiology involved in the regulation of the particular system(s). In the present investigations, dysfunctions in all five major components of the circulatory model can be identified.

Thoracic epidural block (I,II,III)

A thoracic epidural block will induce a sympathetic block to the region supplied by the blocked segments with vasodilation of both resistance and capacitance vessels (BROMAGE, 1951, BONICA 1957). If the block affects the upper part of the thoracic region (T1 to T5) the cardiac sympathetic supply is affected and cardiac function is impaired (RANDALL et al, 1957,
When extending from T4 to L2 the block will affect splanchnic circulation (Lund, 1966) and possibly also the release of adrenaline and noradrenaline from the adrenal medulla (Bromage, 1978). Hence, the block in the present investigations, extending from T1 to T12 will affect the control of both cardiac performance and vascular tone in the region.

Abdominal aortic aneurysm surgery (III, IV)

In reconstructive surgery on the abdominal aorta there are two major causes for serious intraoperative complications besides bleeding, namely aortic cross clamping hypertension and declamping hypotension (Campbell, 1967, Perry, 1968, Thomas, 1971, Imparato et al, 1972, Attia et al, 1976, Meloche et al, 1977). Infra-renal aortic cross clamping induces an abrupt reduction in arterial flow to the lower part of the body and redistribution of blood flow occurs only slowly. The rapid increase in afterload will often induce left ventricular failure (Attia et al, 1976) as these patients often have a significant degree of overt or covert cardiac disease. During the clamping period about 3% of cardiac output only is directed to the lower extremities (Rutherford, 1977), leading to tissue dysoxia and vasodilation. When declamping is performed, the blood flow directed to the lower extremities increases to approximately 21% of cardiac output. This increase occurs at the expense of mesenteric, hepatic and renal flow. In addition, cardiac output decreases by approximately 25% (Rutherford, 1977) due to peripheral pooling of blood which may be potentiated if the intraoperative bleeding is extensive and the patient is not adequately volume substituted. Aortic declamping may therefore induce severe hypotension unless optimal blood volume is maintained.
Gram negative septic shock (V)

Peritonitis is frequently associated with gram negative septicemia. Characteristically there is an inflammatory vasodilation with decreased arterial resistance and arteriovenous shunting (GUMP et al, 1970, ARCHIE, 1977). Cardiac output is often normal or may even be increased and peripheral tissue perfusion is impaired as demonstrated by lactacidemia (WEIL et al, 1975, WEIL, 1977). In spite of normal or high measured cardiac output, cardiac function is frequently impaired (LOEB et al, 1967, WEISEL et al, 1977, BRUNI et al 1978, CERRA et al 1978).

Aim of the investigations

The present investigations deal with disturbances in the main compartments of the circulatory system. The studies are focused on the treatment of these disturbances with interventions influencing vascular volume, blood volume and/or cardiac performance. The aim was a well defined therapeutic strategy where interventions with target effects should be preferred to those with more general actions on the cardiovascular system. In this respect, the use of the cardioselective $\beta_1$-adrenoreceptor agonist prenalterol (CARLSSON et al, 1977, JOHNSON et al, 1978, KNAUS et al, 1978, RÖNN et al, 1979 a and b) for increasing cardiac performance has been of particular interest in four of the investigations (I, II, III, V).

Material

Hemodynamic studies were performed in 49 patients who had given their informed consent. Sixteen of the patients were also subjected to cardiometabolic investigations. The studies were approved by the Ethics Committee.
of the University of Umeå. In the investigations where pernalterol was used, beta blockers were withdrawn at least 48 hours prior to the study.

Study I

Eight patients scheduled for abdominal aortic aneurysm resection and grafting were investigated. These patients also took part in study III and their relevant clinical data is outlined under the headline of that study (Table 2, group I).

Study II

Four patients scheduled for abdominal aortic aneurysm resection and grafting were included in the study. These patients all suffered from coronary artery disease, diagnosed by a history of previous myocardial infarction(s) and/or angina pectoris with positive bicycle ergometer test. Their relevant clinical data is outlined in Table 1.

Table 1. Clinical data of the four patients in study II.

<table>
<thead>
<tr>
<th>PAT.</th>
<th>AGE</th>
<th>SEX</th>
<th>PREVIOUS AMI</th>
<th>PREVIOUS CHF</th>
<th>ANGINA PECTORIS</th>
<th>DIURETICS</th>
<th>DIGITALIS</th>
<th>BETA-BLOCKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+*</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>F</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+*</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction  CHF = congestive heart failure
* = beta blocker discontinued 48 hours before the study
Study III

Sixteen patients scheduled for abdominal aortic aneurysm resection and grafting were randomly assigned to two groups to study the cardiovascular effects of infrarenal aortic cross clamping. Group I received a thoracic epidural block from T1 to T12 with plain prilocain followed by the β₁-adrenoreceptor agonist prenalterol before general anaesthesia was induced. Group II was not given any treatment before general anaesthesia. The clinical data is outlined in Table 2.

Table 2. Clinical data of the sixteen patients in study III. The patients in group I also took part in study I.

<table>
<thead>
<tr>
<th></th>
<th>AGE (RANGE)</th>
<th>SEX</th>
<th>PREVIOUS AMI</th>
<th>ANGINA PECTORIS</th>
<th>DIURE-TICS</th>
<th>BETA-BLOCKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=8)</td>
<td>67</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>GROUP II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=8)</td>
<td>66</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction

* = beta blockers discontinued 48 hours before the study

Study IV

Nineteen patients undergoing abdominal aortic aneurysm surgery were randomly assigned to two groups to elucidate the mechanisms of declamping hypotension. None of the patients had taken part in any of the other studies. The control patients in group I (9) in this study were kept at an average mean pulmonary artery occlusion pressure (MPAOP) of approxima-
tely 11 mm Hg (1.5 kPa) before declamping. The patients in group II (10) were volume loaded to an MPAOP around 16 mm Hg (2.1 kPa) shortly before declamping. The relevant clinical data of the patients is outlined in Table 3.

Table 3. Clinical data of the 19 patients in study IV.

<table>
<thead>
<tr>
<th>AGE (RANGE)</th>
<th>SEX</th>
<th>ANGINA</th>
<th>PREVIOUS HYPERTENSION</th>
<th>DIURETICS</th>
<th>DIGITS</th>
<th>BETA-BLOCKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROUP I</td>
<td>67</td>
<td>3 6 8</td>
<td>2 4 5 2 6*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
<td></td>
<td>(61-76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP II</td>
<td>67</td>
<td>3 7 8</td>
<td>4 3 3 3 5**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=10)</td>
<td></td>
<td></td>
<td>(62-74)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHF = congestive heart failure
* = beta blockers discontinued in 2 patients 48 hours before the study.
** = beta blocker discontinued in 1 patient 48 hours before the study.

Study V

Ten patients with low resistance, distributive septic shock diagnosed by invasive hemodynamic studies and positive blood cultures for gram negative bacteremias were included in the study. Besides hypotension, all patients had clinical signs of shock with oliguria and impaired tissue perfusion with lactacidemia. The criteria to treat the patients with prenalterol was a systolic blood pressure of 90 mm Hg (12 kPa) or less for at least 60 min after initial volume loading with 5% albumine, human plasma and/or crystalloids to a stable mean pulmonary artery occlusion pressure around 12 mm Hg (1.6 kPa). The relevant clinical patient data is outlined in Table 4.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Disease</th>
<th>Causative microorganism(s)</th>
<th>Duration of hypotension (hours)</th>
<th>Additional disease</th>
<th>Additional drugs employed</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>52</td>
<td>M</td>
<td>hemorrh.pancr. e.coli</td>
<td></td>
<td>3.5</td>
<td>chron.alc.</td>
<td>none</td>
<td>survived</td>
</tr>
<tr>
<td>2*</td>
<td>38</td>
<td>M</td>
<td>hemorrh.pancr. klebs.ent.</td>
<td></td>
<td>5</td>
<td>chron.alc. liver failure</td>
<td>furosemide</td>
<td>dead after 23 days</td>
</tr>
<tr>
<td>3*</td>
<td>48</td>
<td>F</td>
<td>gangr.gallbl. pseudomonas</td>
<td></td>
<td>3</td>
<td>none</td>
<td>none</td>
<td>survived</td>
</tr>
<tr>
<td>4*</td>
<td>62</td>
<td>M</td>
<td>gangr.gallbl. pseudomonas</td>
<td></td>
<td>2.5</td>
<td>hypertension diabetes mell.</td>
<td>furosemide aldactone</td>
<td>survived</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>post gastrect. pseudomonas</td>
<td></td>
<td>7</td>
<td>coronary art. disease</td>
<td>none</td>
<td>survived</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>F</td>
<td>gangr.gallbl. pseudomonas</td>
<td></td>
<td>3</td>
<td>none</td>
<td>none</td>
<td>survived</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>M</td>
<td>post gastrect. e.coli, serratia pseudomonas</td>
<td></td>
<td>16</td>
<td>diabetes</td>
<td>digitalis</td>
<td>dead after 29 days</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>M</td>
<td>traumatic intestinal rupture</td>
<td>e.coli, klebs.ent.</td>
<td>3.5</td>
<td>none</td>
<td>none</td>
<td>survived</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>F</td>
<td>hemorrh.pancr. pseudomonas</td>
<td>gangr.gallbl.</td>
<td>3</td>
<td>none</td>
<td>none</td>
<td>survived</td>
</tr>
<tr>
<td>10</td>
<td>53</td>
<td>M</td>
<td>post gastrect. klebs.ent.</td>
<td></td>
<td>5</td>
<td>coronary art. disease</td>
<td>digitalis</td>
<td>survived</td>
</tr>
</tbody>
</table>

* participant in the cardiometabolic study
Methods & procedures

Hemodynamic studies

All patients were catheterized in the operating room (I - IV) or at the bedside (V). The arterial cannulations were done percutaneously under local anaesthesia with a 60 mm long, 1.2 mm internal diameter teflon catheter (VIGGO) in studies I - IV. The radial or brachial artery on the nondominant arm was used. In study V, a 170 mm long, 1.4 mm internal diameter teflon central venous catheter (VIGGO) was introduced percutaneously under local anaesthesia into the right common iliac artery via the right femoral artery to get accurate pressure readings during the hypotension. In all patients (49), a calibrated 7F balloon tipped thermodilution catheter was introduced percutaneously under local anaesthesia into the right internal jugular vein and placed in good occlusion position in the pulmonary artery under close monitoring of the pressure curve. Occlusion of the catheter balloon in the right lower segment artery was obtained in all patients where fluoroscopic control could be performed (26). In 16 of the 49 patients, a calibrated 7F Webster coronary sinus catheter was introduced under local anaesthesia into the left (14) or right (2) internal jugular vein and then placed in the coronary sinus under fluoroscopy and close monitoring of the pressure curve. Special care was taken of the accurate positioning of the catheter not to get interference from the blood stream through the right atrium at the level of the proximal thermistor of the catheter. This was checked by a bolus infusion of cold normal saline through the proximal orifice of the pulmonary artery catheter. Perfect sampling from the coronary sinus was also controlled before the catheter was secured by sutures to the skin. All intravascular catheters were flushed with normal saline using the Intraflo CFS® at 3 ml/h.
Arterial, pulmonary artery and right atrial pressures were recorded continuously throughout the investigations using Siemens-Elema's pressure transducers 746/51 positioned at midchest (0-level). Calibration with electric and normal saline standards were done regularly before and after scheduled pressure registrations. A Mingograf 62 or 82 recorder was used for the pressure recordings. In studies I and III no pressure gradient between the pulmonary artery diastolic pressure \( (P_{Ad}) \) and the mean pulmonary artery occlusion pressure was noted in any of the patients. Subsequently, \( P_{Ad} \) was regarded as a representative reflection of the left atrial pressure variations (FORRESTER et al., 1971). In the other investigations, mean pulmonary artery occlusion pressure was registered after balloon inflation during periods scheduled for hemodynamic calculations (see flow charts for the different investigations, Figures 1 - 4). Cardiac output was determined by the thermodilution method (GANZ et al., 1971, 1972, FORRESTER et al., 1972). The means of two measurements not differing more than 10\% were used in studies I - IV and of three measurements not differing more than 10\% in study V. To standardize the indicator injection technique, a pneumatic infusion pump (U-LAB, ATI - 1), synchronized to the cardiac output computer (CARDIOVASCULAR INSTRUMENTS, CV 600 or 3750) and delivering 10 ml of 5.5\% glucose at room temperature in 1.2 s was used. All catheters were thoroughly calibrated at 37 and 40\(^\circ\)C before insertion. The thermodilution curves were recorded on the Mingograf and judged before the results were accepted or rejected.

Coronary sinus blood flow (CSF) was determined by the continuous thermodilution technique described by GANZ et al (1971). The method requires a stable position of the catheter within the coronary sinus and even if the placement and securing is perfect, softening of the teflon catheter may affect the thermistor positions (WEISSE and REGAN, 1974). Furthermore, the
position of the proximal thermistor in relation to the posterior descending arterial drainage will determine to what extent coronary sinus blood flow is reflecting total myocardial blood flow. With knowledge of the problems of the catheter positioning and other limitations mainly due to anatomical variations the method will still give reproducible values (GANZ, 1977). In the present investigations (II, IV, V), double measurements within 5 min in the 16 patients were analyzed. The standard deviation of a single measurement was 5 ml/min and the coefficient of variation was 3%. A detailed review of the method has been published by KLOCKE (1976).

The thermistors of the CSF catheter were thoroughly calibrated before usage and the resistance/temperature relation was found to be linear within 0.1°C from 20 to 40°C. Glucose (5.5%) at room temperature was used as the indicator and infused by a calibrated constant rate infusion pump (SAGE 355) at a rate of 40 ml/min during approximately 20 s for each measurement. A Wheatstone bridge (WEBSTER INSTRUMENTS) was used for balancing the thermistor resistances and recordings of the resistance changes were done on the Mingograf 82.

ECG (lead V₅) was registered continuously throughout the investigations on the Mingograf. A paper speed of 10 mm/s was used except during the scheduled hemodynamic measurement periods when 25 mm/s was used. Heart rate was calculated from the ECG recordings.

**Measured & derived hemodynamic variables**

SAP  systolic arterial pressure (mm Hg, kPa)
DAP  diastolic arterial pressure (mm Hg, kPa)
MAP  mean arterial pressure (mm Hg, kPa)
PA_D pulmonary artery diastolic pressure (mm Hg, kPa)
MPAOP mean pulmonary artery occlusion pressure (mm Hg, kPa)
also called mean pulmonary artery wedge pressure (PAW) in studies I and III.
MRAP mean right atrial pressure (mm Hg, kPa)
also shown as RAP in studies I and III
CO cardiac output (L.min\(^{-1}\))
HR heart rate (bpm)
BSA body surface area - \(
\frac{L + W - 160}{100} + 1\) (m\(^2\)), where L = length in cm and W = weight in kg
T_b blood temperature, measured in the coronary sinus (°K)
T_i coronary sinus blood flow indicator temperature, measured in the coronary sinus (°K)
T_m temperature of the mixed indicator-coronary sinus blood (°K)
V_{inj} coronary sinus blood flow indicator infusion rate (ml.min\(^{-1}\))
SV stroke volume - CO/HR (ml)
SVI stroke volume index - SV/BSA (ml.m\(^{-2}\))
LVSWI left ventricular stroke work index - SVI x (MAP - MPAOP) x 0.0144* (g-m.m\(^{-2}\))
CI cardiac index - CO/BSA (L.min\(^{-1}.m\^{-2}\))
SVR systemic vascular resistance - (MAP - MRAP)/CI (mm Hg.l\(^{-1}.min.\m^{-2}\), kPa.l\(^{-1}.min.m^{-2}\))
CSF coronary sinus blood flow - V_{inj} x 1.08 x (\frac{T_b - T_i}{T_b - T_m} - 1) (ml.min\(^{-1}\))
CVR coronary vascular resistance - (DAP - MPAOP)/(CSF x 10\(^{-3}\)) (mm Hg.l\(^{-1}.min, kPa.l^{-1}.min\))

Methods for blood gas & lactate analyzes

For the metabolic studies (16 patients) arterial, pulmonary artery and coronary sinus blood was sampled simultaneously and anaerobically in heparinized glass syringes and immediately analyzed on a Radiometer ABL-2 (KOKHOLM and van SCHAICK, 1976) blood gas analyzer for $pO_2$, $pCO_2$ and pH and on a Radiometer OSM-2 (SIGGARD-ANDERSEN, 1976) for hemoglobin concentration and oxygen saturation. $pO_2$- and $pCO_2$- values were corrected for body temperature according to SEVERINGHAUS (1958) and pH was corrected according to ROSENTHAL (1948). Lactate was analyzed in simultaneously sampled arterial and coronary sinus blood according to the enzymatic method described by MARBACH and WEIL (1967). The oxygen content was calculated from the formula:

$$C_{O_2} = 10 \times ((Hb \times 1.39 \times S_{O_2} \times 10^{-2}) + 0.0031 \times pO_2) \text{ (ml } O_2.l^{-1})$$

where $S_{O_2}$ is the saturation of oxygen (%) and the hemoglobin concentration (Hb) is expressed in g.(100 ml)$^{-1}$.

The following variables were derived:

- $(a - \nu)D_{O_2}$ arterio-mixed venous oxygen difference (ml $O_2.l^{-1}$)
- $(a - cs)D_{O_2}$ arterio-coronary sinus oxygen difference (ml $O_2.l^{-1}$)
- $(a - cs)L_{L}$ arterio-coronary sinus lactate difference (mmole.$l^{-1}$)
- $V_{O_2\text{tot}}$ total body oxygen consumption - CO x $(a - \nu)D_{O_2}$ (ml $O_2.min^{-1}$)
- $V_{O_2\text{myoc}}$ myocardial oxygen consumption - CSF x $(a - cs)D_{O_2}$ x $10^{-3}$ (ml $O_2.min^{-1}$)
- myocardial lactate extraction - CSF x $(a - cs)L_{L}$ (micromole.$l^{-1}$)
Thoracic epidural block

No premedication had been given prior to the investigations. A thoracic epidural block was induced and kept stable in 12 patients by a continuous infusion (IVAC 530) of prilocain, (10 mg/ml), without vasoconstrictor through a Portex epidural catheter. This was inserted by the paramedian and loss of resistance techniques through the thoracic 8 - 9 interspace. The tip of the catheter was at the T6 to T7 level. The spread of the block was followed by the pin prick method and within 15 min a block from T1 to T12 was obtained in all but one patient, in whom the extension of the block was from T1 to T11.

General anaesthesia

No premedication had been given prior to the investigations. A balanced format of anaesthesia was used. It consisted of 0.5 mg of atropine followed by thiopentone sodium 4 - 6 mg/kg. Intubation was performed under suxamethonium 1 - 1.5 mg/kg followed by pancuronium bromide 0.1 mg/kg. In study III an average of 0.3 ± 0.1 mg of fentanyl and 7.5 ± 2.5 mg of droperidol had been given in the two groups prior to aortic cross clamping. In study IV, an average of 0.7 ± 0.3 mg of fentanyl and 7.5 ± 2.5 mg of droperidol had been given in group I (control). The corresponding figures for the volume loaded group (II) were 0.8 ± 0.2 mg of fentanyl and 7.5 ± 2.5 mg of droperidol. The patients were all ventilated with N_2O/O_2 (75/25) by an Engström 2000 ventilator and p_{aCO_2} maintained around 4.2 kPa.
Surgical procedures

In study III, infrarenal aortic cross clamping was performed on an average 35 min (range 23 - 47 min) after induction of general anaesthesia in group I (thoracic epidural block + prenalterol pre-treatment). For group II (control) aortic cross clamping occurred on an average 33 min (range 29 - 39 min) after induction of general anaesthesia. All the patients in study III were operated on for fusiform aortoiliac aneurysms with insertion of a bifurcation graft.

In study IV, 16 of the 19 patients had resection of a fusiform aortoiliac aneurysm and three had a saccular aortic aneurysm. The patients with fusiform aneurysms had a bifurcation graft inserted, while the patients with saccular aneurysms had a tube graft. Seven patients with fusiform and 2 with saccular aneurysms were assigned to group I (control) and 9 patients with fusiform and 1 with a saccular aneurysm were assigned to group II. In the patients operated on for an aortoiliac aneurysm, the right common iliac artery was always declamped first, an average of 23 min (range 15 - 46 min) prior to the declamping of the left common iliac artery. The average clamping time for group I was 62 min (range 55 to 81 min) and for group II 67 min (range 48 - 80 min).

Fluid administration

In study I and II no fluid besides the 5.5% glucose for measuring cardiac output and coronary sinus blood flow was administered. In study III no fluid besides the 5.5% glucose for measuring cardiac output was given prior to the operation. After induction of general anaesthesia, isotonic sodium chloride acetate and/or sodium chloride glucose was administered
at a rate of 20 ml/kg/h to all patients. In study IV the patients in group I (control) were given an isotonic sodium chloride glucose infusion besides the necessary transfusions to maintain a stable MPAOP around 10 mm Hg (1.3 kPa) prior to declamping. The patients in group II were volume loaded with 5% albumine or human plasma from approximately 10 min prior to declamping to reach an MPAOP around 16 mm Hg (2.1 kPa) when declamping was performed. In addition, these patients had the same treatment as the patients in the control group, including 5.5% glucose for measuring cardiac output and coronary sinus blood flow. In study V volume loading with 5% albumine, human plasma and/or isotonic crystalloids to an MPAOP around 12 mm Hg (1.6 kPa) was used as the primary treatment of the hypotension. As none of the patients increased cardiac output at higher levels of left ventricular filling pressure or improved clinically, no further fluid challenge was tried during the 160 min investigation period. Besides the 5.5% glucose for measuring cardiac output and coronary sinus blood flow, isotonic sodium chloride glucose was administered at 100 ml/h to all patients.

Prenalterol

Prenalterol \(^1\) (and the racemic form H 80/62) is a selective \(\beta_1\)-adrenoreceptor agonist. Compared to isoprenaline it has a more pronounced inotropic than chronotropic effect (CARLSSON et al, 1977). It was also noted that the drug had no effect on the vascular resistance. JOHNSSON et al (1978) and KNAUS et al (1978) confirmed the findings in animals in human pharmacological studies. ARINIEGO et al (1979) could show that H 80/62 was a highly specific antidote to cardioselective \(\beta\)-blockers and in this

\(^1\) H 80/62 = C.50.005/ABa - racemic form
Prenalterol - levo isomer of H 80/62
respect superior to isoprenaline. RÖNN et al (1979) have shown that pre-
nalterol also counteracts the effects of β-blockers. The elimination half
life of prenalterol in man is approximately 120 min (RÖNN et al, 1979).
Prenalterol was administered intravenously over a period of 15 min in a
total dose of 10 mg in study I and III. In study II and V the drug was
given intravenously over a 10 min period in a total dose of 150 microgram
/kg.

Flowcharts of all measurements, samples and interventions in the five in-
vestigations are presented in Figures 1 to 4.

Statistics

The paired and unpaired t-tests were used for statistical analysis of the
results, which are presented as means ± S.D. A p-value less than 0.05 was
considered statistically significant.
Figure 1. Flowchart of measurements, blood samples and interventions in study II.

Figure 2. Flowchart of measurements and interventions in study III. The patients in study I are presented in group I from 0 to 70 min.
<table>
<thead>
<tr>
<th>GROUP I</th>
<th>RIGHT LIMB</th>
<th>LEFT LIMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRESSURES AND ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDIAC OUTPUT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORONARY SINUS FLOW</td>
<td>[\cdots]</td>
<td>[\cdot\cdot\cdot]</td>
</tr>
<tr>
<td>VOLUME LOADING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART AND C.S BLOOD GAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART LACTATE AND pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORONARY SIN LACTATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRESSURES AND ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDIAC OUTPUT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORONARY SINUS FLOW</td>
<td>[\cdots]</td>
<td>[\cdot\cdot\cdot]</td>
</tr>
<tr>
<td>VOLUME LOADING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART AND C.S BLOOD GAS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART LACTATE AND pH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORONARY SIN LACTATE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIME (MIN)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLAMPING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Flowchart of measurements, blood samples and interventions in study IV.

<table>
<thead>
<tr>
<th>ECQ &amp; PRESSURES</th>
<th>CARDIAC OUTPUT</th>
<th>CORONARY SINUS FLOW</th>
<th>ARTERIAL MIXED VENOUS AND CORONARY SINUS BLOOD GASES</th>
<th>ARTERIAL AND CORONARY SINUS LACTATE</th>
<th>VOLUME LOADING</th>
<th>PRENALTETROL INFUSION</th>
<th>URINARY OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[\cdots]</td>
<td>[\cdot\cdot\cdot]</td>
<td>[\cdot\cdot\cdot]</td>
<td>[\cdot\cdot\cdot]</td>
<td>[\cdots]</td>
<td>[\cdots]</td>
<td>[\cdots]</td>
</tr>
</tbody>
</table>

| TIME (MIN) | 0 | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | 110 | 120 | 130 | 140 | 150 | 160 | 170 |
|------------|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|

Figure 4. Flowchart of measurements, samples and interventions in study V.
Results

Hemodynamic effects of thoracic epidural block & prenalterol (1)

Thoracic epidural block from T1 to T12 induced a marked reduction in mean arterial pressure due to a decrease of both systemic vascular resistance and cardiac output. There was no significant change in heart rate, mean right atrial pressure or pulmonary artery diastolic pressure, nor were any arrhythmias recorded. On individual analysis it was found that 3 patients had a moderate decrease in heart rate, 3 remained unchanged and 2 had a moderate increase following the block.

After administration of prenalterol mean arterial pressure increased almost to pre-epidural control level due to marked increase in cardiac output. No significant changes in heart rate, systemic vascular resistance or pulmonary artery diastolic pressure were seen, nor were any arrhythmias recorded. The hemodynamic effects are summarized in Table 5.

Table 5. Hemodynamic effects of thoracic epidural block from T1 to T12 (ED) followed by intravenous administration of 10 mg prenalterol (P). C-control value before epidural block. Results are means ± S.D., n= 8.

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>MPAOP (mm Hg)</th>
<th>HR (bpm)</th>
<th>CI (l.min⁻¹.m⁻²)</th>
<th>SVR (mm Hg.l⁻¹.min.m⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>98 ± 14</td>
<td>8 ± 2</td>
<td>68 ± 6</td>
<td>3.1 ± 0.5</td>
<td>31 ± 8</td>
</tr>
<tr>
<td>ED</td>
<td>58 ± 9**</td>
<td>7 ± 3</td>
<td>77 ± 13</td>
<td>2.6 ± 0.6**</td>
<td>22 ± 8*</td>
</tr>
<tr>
<td>P</td>
<td>88 ± 13**</td>
<td>8 ± 2</td>
<td>75 ± 10</td>
<td>3.7 ± 0.5***</td>
<td>23 ± 5</td>
</tr>
</tbody>
</table>

* = p<0.05      ** = p<0.01      *** = p<0.001
Cardiometabolic effects of thoracic epidural block & prenalterol (II)

The hemodynamic effects in the four patients in this study were about the same as for the patients in study I, both after thoracic epidural block and prenalterol. However, there was a more uniform response in heart rate as all the patients had a 5 – 10 bpm decrease following the block and then increased their heart rate to slightly above pre-epidural control value after administration of prenalterol.

Following the epidural block there was only a moderate decrease in coronary sinus blood flow in spite of the marked reduction in coronary artery perfusion pressure. Subsequently, calculated coronary vascular resistance decreased substantially. Myocardial oxygen consumption decreased by approximately 30% and myocardial lactate extraction by approximately 55%. An increased coronary sinus lactate concentration was measured. Total body oxygen consumption decreased by about 20% in all patients.

Following prenalterol coronary sinus blood flow increased to above pre-epidural control value but coronary vascular resistance was not affected. Myocardial oxygen consumption and lactate extraction returned to control values and total body oxygen consumption increased to above pre-epidural control value. The cardiometabolic effects are shown in Table 6.

Table 6. Cardiometabolic effects of thoracic epidural block from T1 to T12 in 3 patients and from T1 to T11 in one (no 4) (ED) followed by prenalterol (P) as compared to pre-epidural control situation (C). The results are given for the individual patients.

<table>
<thead>
<tr>
<th>PAT.</th>
<th>CSF</th>
<th>CVR</th>
<th>( \dot{V}_{O2,myoc} )</th>
<th>MYOC. LACT. EXTR.</th>
<th>( \dot{V}_{O2,tot} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(ml.min(^{-1}))</td>
<td>(mmHg.l(^{-1}).min)</td>
<td>(ml.min(^{-1}))</td>
<td>(micromole.min(^{-1}))</td>
<td>(ml.min(^{-1}))</td>
</tr>
<tr>
<td>C</td>
<td>ED</td>
<td>P</td>
<td>C</td>
<td>ED</td>
<td>P</td>
</tr>
<tr>
<td>1</td>
<td>156/131/195</td>
<td>600/290/290</td>
<td>14.8/ 9.5/13.3</td>
<td>32.0/14.2/44.0</td>
<td>218/171/267</td>
</tr>
<tr>
<td>2</td>
<td>133/112/168</td>
<td>530/330/370</td>
<td>12.9/ 8.6/15.0</td>
<td>29.9/11.8/32.3</td>
<td>229/198/295</td>
</tr>
<tr>
<td>3</td>
<td>148/123/189</td>
<td>460/290/290</td>
<td>12.4/10.9/12.7</td>
<td>31.8/15.1/30.9</td>
<td>241/212/304</td>
</tr>
<tr>
<td>4</td>
<td>151/119/209</td>
<td>490/270/310</td>
<td>13.2/10.1/14.3</td>
<td>38.6/17.0/36.9</td>
<td>241/203/304</td>
</tr>
</tbody>
</table>
Hemodynamic effects of aortic clamping (III)

Before any intervention, the only hemodynamic difference between the two groups was a slightly lower (8 versus 11 mm Hg) pulmonary artery diastolic pressure in group I (thoracic epidural block + prenalterol). The epidural block and prenalterol induced the hemodynamic changes shown in study I (Table 5). Subsequently, group I had a significantly lower pulmonary artery diastolic pressure and systemic vascular resistance but higher cardiac and stroke volume indices than group II (control) before general anaesthesia. These differences were maintained during general anaesthesia and persisted till immediately before cross clamping as shown in Figure 5.

In group I aortic cross clamping induced an immediate rise (within 30 s) in mean arterial pressure, pulmonary artery diastolic pressure and cardiac and stroke volume indices. Systemic vascular resistance did not rise significantly until 2 min after clamping. Mean right atrial pressure and heart rate did not change and no arrhythmias were recorded in any patient.

In group II aortic cross clamping induced a rise within 30 s in mean arterial pressure, pulmonary artery diastolic pressure and systemic vascular resistance. In contrast to group I, cardiac and stroke volume indices decreased. Mean right atrial pressure decreased from 3.2 ± 0.4 to 0.8 ± 0.3 mm Hg, (0.43 ± 0.05 to 0.11 ± 0.04 kPa), (p < 0.01). There was no change in heart rate after clamping but frequent supraventricular and ventricular ectopic beats were recorded in 7 of the 8 patients in group II from 1 min after cross clamping throughout the 5 min post clamping observation period. The hemodynamic effects of aortic cross clamping in the two groups are shown in Figure 5.
Figure 5. Cardiovascular effects of infrarenal aortic clamping in group I (thoracic epidural block + prenalterol) and group II (control). Significant differences in systemic vascular resistance, pulmonary artery diastolic pressure, cardiac and stroke volume indices are seen before cross-clamping.

In the control group, cross-clamping is followed by a sharp increase in systemic vascular resistance, mean arterial pressure and pulmonary artery diastolic pressure in parallel to a drop in cardiac and stroke volume indices.

Group I shows the same increases in mean arterial and pulmonary artery diastolic pressures, but in contrast to the control group, a very slow increase in systemic vascular resistance in parallel to an increase in stroke volume and cardiac indices, suggesting an increase in venous return and myocardial performance. Results shown are means ± S.D. (n = 8).
Declamping hypotension (IV)

In the patients who were operated on with insertion of a bifurcation graft there was no difference between the hemodynamic or cardiometabolic responses to declamping of the right or left common iliac artery. Therefore, only the results from the right common iliac artery declamping which always occurred first are presented.

The only hemodynamic and cardiometabolic difference between the two groups before declamping was the higher mean pulmonary artery occlusion pressure in group II induced by the volume loading. In group I (control), declamping induced decreases in mean arterial pressure, mean pulmonary artery occlusion pressure, cardiac and stroke volume indices and left ventricular stroke work index. Heart rate and systemic vascular resistance did not change, nor were any arrhythmias recorded. In group II, there was an equal drop in mean pulmonary artery occlusion pressure following declamping while the decreases in mean arterial pressure and left ventricular stroke work index were significantly less than in group I. In contrast to group I, systemic vascular resistance decreased while cardiac and stroke volume indices did not change. Like in group I there was no change in heart rate, nor were any arrhythmias recorded in any patient. The hemodynamic effects of declamping in the two groups are shown in Figure 6.

Declamping in group I induced decreases in coronary sinus blood flow and myocardial oxygen consumption and lactate extraction. Total body oxygen consumption also decreased significantly. In group II, none of these variables changed significantly after declamping. There was an equal rise in arterial lactate concentration 2 min after declamping in both groups. Five min after declamping, arterial lactate had returned to about the
Figure 6. Maximal hemodynamic changes 2 min after declamping in the individual control patients (x) and the volume loaded patients (o). Note the significant difference in the reduction of MAP, (p < 0.01), SVI, (p < 0.01) and LVSWI, (p < 0.001) between the two groups of patients.

same level as before declamping. A slight but insignificant decrease in arterial pH paralleling the increase in lactate concentration was seen. The cardiometabolic effects of declamping in the two groups are shown in Figure 7.
Figure 7. Myocardial substrate utilization, total body oxygen consumption and arterial lactate concentration in the control group (x-x) and the volume loaded group (o-o) before (C) and 2 and 5 minutes after declamping. Significant decreases in myocardial oxygen and lactate extraction rates (p < 0.001, p < 0.01) as well as total body oxygen consumption, (p < 0.01), are seen in the control group. There is no significant change in these variables in the volume loaded patients. A transient increase in arterial lactate concentration is seen 2 minutes after declamping in both groups. Results shown are means ± S.D., n = 4.

Gram negative septic shock (V)

All patients responded rapidly to prenalterol administration with increases in mean arterial pressure and cardiac output within 2 min after termination of prenalterol infusion. Fifteen min after completion of the drug infusion, all patients were hemodynamically improved and stable and remained so for the remaining 60 min of the observation period. The hemodynamic effects of prenalterol are shown during steady state before administration of the drug and 15 min after the termination of prenalterol infusion in Table 7.
Table 7. Hemodynamic effects of prenalterol (P), 150 microgram/kg i.v. in 10 patients with low resistance, distributive septic shock. C-control value before prenalterol. Results are given as means ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>MPAOP (mm Hg)</th>
<th>CI (l.min⁻¹.m⁻²)</th>
<th>SVR (mm Hg.l⁻¹.min.m²)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>57 ± 11</td>
<td>12.8 ± 4.3</td>
<td>2.65 ± 0.40</td>
<td>18 ± 5</td>
<td>125 ± 16</td>
</tr>
<tr>
<td>P</td>
<td>75 ± 20**</td>
<td>12.0 ± 3.0</td>
<td>3.80 ± 0.47***</td>
<td>19 ± 5</td>
<td>119 ± 14</td>
</tr>
</tbody>
</table>

**p < 0.01   ***p < 0.001

Coronary sinus blood flow, myocardial oxygen consumption and lactate extraction increased significantly following prenalterol. Arterial lactate concentration decreased and total body oxygen consumption increased after the drug. The metabolic effects of prenalterol are summarized in Table 8.

Table 8. Cardiometabolic effects of prenalterol (P) in four patients with gram negative septic shock. Results are means ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>CSF (ml.ml⁻¹)</th>
<th>C_lact (mmole.l⁻¹)</th>
<th>( \dot{V}_{O_2, tot} ) (ml.min⁻¹)</th>
<th>( \dot{V}_{O_2, myoc} ) (ml.min⁻¹)</th>
<th>Myoc.lactate extraction (micromole.min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>185 ± 14</td>
<td>5.51 ± 0.55</td>
<td>287 ± 13</td>
<td>19.8 ± 2.1</td>
<td>33.2 ± 2.3</td>
</tr>
<tr>
<td>P</td>
<td>246 ± 14***</td>
<td>3.94 ± 0.16**</td>
<td>348 ± 23**</td>
<td>26.6 ± 2.1***</td>
<td>44.7 ± 2.1***</td>
</tr>
</tbody>
</table>

**p < 0.01   ***p < 0.001
Discussion

The major function of the cardiovascular system is to deliver sufficient oxygenated blood to meet the metabolic requirements of the tissues. As these are variable within and between different organs there is a close interplay between cardiac output and vascular tone. The determinants of cardiac output are heart rate and stroke volume. Heart rate is regulated by intrinsic rhythmicity and neurohumoral activity, whereas stroke volume is depending mainly on preload, contractility and afterload (BRAUNWALD 1974). Vascular tone is regulated by intrinsic myogenic and metabolic mechanisms (BAYLISS 1902, GUYTON 1973) as well as by neurohumoral factors (FOLKOW & NEIL, 1971, WHITE et al 1971). The following discussion will be focused on how different interventions such as high thoracic epidural block and aortic clamping and declamping or base pathophysiology during gram negative septic shock may affect these regulatory mechanisms. Possible treatments of the circulatory dysequilibriums will also be discussed.

Hemodynamic & cardiometabolic effects of thoracic epidural block & prenalterol (I,II)

In the present investigations (I and II), a substantial drop in blood pressure was recorded after thoracic epidural block from T1 to T12 with plain prilocain. The fall in blood pressure was due to a vasodilation and a decreased cardiac output. These results are in agreement with earlier reports on the hemodynamic effects of an epidural block in the thoracic region (BROMAGE 1951, BONICA 1957, OTTON & WILSON 1966, McLEAN et al 1967, OTTESEN et al 1978). After a widespread epidural
block there is a pronounced vasodilation inducing a marked decrease in blood pressure. The effect on the blood pressure is to a certain extent counteracted by a compensatory vasoconstriction within non-blocked areas (BONICA et al 1970, SJÖGREN & WRIGHT 1972). A contributory factor to the decrease of the arterial blood pressure after high thoracic epidural block is the presynaptic block of the cardiac sympathetic nerve supply (T1 to T5) (RANDALL et al 1957) with a concomitant decrease of cardiac output (OTTON & WILSON 1966, McLEAN et al 1967). The findings of a decreased cardiac output and vascular resistance together with unchanged pulmonary artery diastolic pressure in the present investigations indicate a depressed cardiac function following the epidural block. Normally, a falling blood pressure is accompanied by a reflexogenic increase in heart rate. In the present investigations there was however a varying heart rate response. Six of the patients decreased, three increased and three had unchanged heart rate following the block. The reason for this varying effect on the heart rate might be an incomplete sympathetic block due to the use of an anaesthetic solution of low concentration without vasoconstrictor agent (BROMAGE 1978). Furthermore, the vagal influence on the heart was intact and there was still a minor and unaffected supply of cardiac sympathetic nerve fibres from the C5 to C8 segments (WIESMAN et al 1966), which might modify the cardiovascular effects of the thoracic epidural block.

Different treatments to avoid arterial hypotension after thoracic epidural block have been tried. Volume expansion is an effective way to counteract hypotension following lumbar epidural block (BROMAGE 1967) but is not effective by itself in high thoracic epidural block.
(ENGBERG 1977). By administrating ephedrine prior to the thoracic epidural block and using a local anaesthetic with adrenaline, ENGBERG & WIKLUND (1978) were able to prevent arterial hypotension. In the present investigations, the effect of the cardioselective $\beta_1$-adreno-receptor agonist prenalterol (CARLSSON et al 1977) on the induced hypotension was studied. This drug normalized the systemic blood pressure almost completely due to an increase in cardiac output to above pre-epidural control values. The increase in cardiac output was mainly due to increased stroke volume and in some patients to a moderately increased heart rate. The effect on heart rate varied: in 10 of the 12 patients there was an unchanged or only slightly increased heart rate and in the remaining two, there was a marked decrease (more than 20 bpm). The unchanged pulmonary artery diastolic pressure (reflecting left ventricular filling pressure) together with an increase of the stroke volume indicate that prenalterol had a direct positive inotropic effect and could abolish the negative inotropic effect induced by the thoracic epidural block.

The effects of high thoracic epidural block on myocardial metabolism and coronary hemodynamics have not been studied in man before. OTTESEN et al (1978) investigated the cardiovascular effects of cardioselective thoracic epidural block in sheep and found a reduction in myocardial blood flow measured by the hydrogen washout technique and a decreased myocardial oxygen consumption. The changes of these variables in the present investigation were of the same magnitude. In addition, myocardial lactate extraction decreased secondary to a decreased coronary sinus blood flow and increased coronary sinus lactate admixture.
The major determinants of myocardial oxygen consumption are heart rate, wall tension and myocardial contractility (BRAUNWALD 1971, PARMLEY & TYBERG 1976). Coronary blood flow is largely determined by the coronary arteriolar tone which is regulated by myocardial metabolic rate (FOLKOW & NEIL 1971, BERNE & RUBIO 1974, KLOCKE 1976). The direct autonomic nerve control of the coronary vascular tone which seems to be of much less importance is regulated by alpha- and beta\textsubscript{2}-adrenoreceptors (BERNE et al 1965, GRANATA et al 1965, KLOCKE et al 1965, PITT et al 1966, FEIGL 1967). The decrease in calculated coronary vascular resistance in the present investigation is probably due to a critically low perfusion pressure as the diastolic arterial pressure decreased to below 50 mm Hg. In support of regional myocardial ischemia during the hypotensive period is also the increased coronary sinus lactate admixture. It is also possible, that part of the coronary vasodilation following the thoracic epidural block was due to alpha adrenoreceptor blockade.

Administration of prenalterol increased coronary sinus blood flow in parallel to the increase in coronary perfusion pressure. Subsequently, coronary vascular resistance was not affected. This is probably due to the increased metabolic rate induced by the drug as demonstrated by increased myocardial oxygen and lactate extractions. It is apparent, that prenalterol had no direct effect on coronary vascular smooth muscle.
Hemodynamic effects of aortic clamping (III)

Patients operated on for abdominal aortic aneurysms constitute a high intra- and postoperative risk group. Almost all these patients have overt or covert cardiac disease, thus making them vulnerable to rapid changes in afterload as seen in association with cross clamping (PERRY et al 1968, CARROLL et al 1976) or long hypotensive periods associated with extensive bleeding or declamping of the aorta (CAMPBELL 1967, THOMAS 1971, IMPARATO et al 1972, BUSH et al 1977). Following infrarenal aortic cross clamping an extensive rise in systemic blood pressure accompanied by left ventricular failure has been reported by several workers (ATTIA et al 1976, MELOCHE et al 1977, BUSH et al 1977). Pharmacological interventions to modify these negative cardiovascular changes have mainly been focused on reduction of after-load (POTTECHER & MELOCHE 1977). However, systemically administered drugs will affect the total vascular system. A thoracic epidural block from T1 to the level of cross-clamping (approximately T12) is from a theoretical point of view a more interesting intervention, as the block will induce a decreased resistance in the vascular bed central to the clamping level. However, to counteract the negative inotropic action of the block itself the combined treatment with a drug with positive inotropic action without vascular effects would be justified.

The cardiovascular response to infrarenal aortic cross clamping in a group of patients pre-treated with thoracic epidural block and pre-alterol and then given general anaesthesia (group I) was compared to that of a group of patients who had general anaesthesia only (group II).
Clinically, the two groups were comparable, but group I started the investigation with a slightly lower pulmonary artery diastolic pressure than group II (8 versus 11 mm Hg, 1.1 versus 1.5 kPa) before any intervention. This difference was somewhat increased after the epidural block and prenalterol. The pre-treatment also induced a lower systemic vascular resistance but higher cardiac output than seen in the control group. There were no significant differences in systemic blood pressure and heart rate between the two groups. These hemodynamic differences persisted during general anaesthesia until the aortic cross clamping procedure (Figure 6).

Following cross clamping in group II (control) the cardiovascular response did not differ from that reported by other workers (ATTIA et al 1976, MELOCHE et al 1977). Within 30 s there was a marked increase in brachial artery and pulmonary artery diastolic pressures in parallel to a sharp increase in calculated systemic vascular resistance. In addition, mean right atrial pressure and cardiac output decreased. Heart rate did not change but premature supraventricular and ventricular contractions were recorded in 7 of the 8 patients. These changes indicate that aortic cross clamping induced decreased venous return and severe impairment of cardiac function. Furthermore, the appearance of supraventricular and ventricular arrhythmias is strongly suggestive of myocardial dysoxia.

Compared to the control patients, the patients in group I had an equal rise in brachial artery pressure and pulmonary artery diastolic pressure without change in heart rate 30 s after cross clamping. In contrast to group II, cardiac output increased significantly. Calculated systemic
vascular resistance did not increase significantly until 2 min after cross clamping and was also at this time significantly lower than that calculated for the control group. No arrhythmias were recorded in any patient. The results indicate that venous return increased and cardiac performance improved in association with cross clamping. The mechanisms for the increased venous return are not perfectly clear. BAYLISS (1902) demonstrated that vascular distention induced by an elevation of arterial pressure increased the tone of vascular smooth muscle. This mechanism is also active in denervated blood vessels (BRAUNWALD 1974b). It is possible that the epidural block might create opening of physiological arterio-venous shunts within the splanchnic area and thereby could facilitate redistribution of blood flow and increase venous return in association with cross clamping.

When left ventricular stroke work index (LVSWI) is plotted against pulmonary artery diastolic pressure (PA_D) for the individual patients in the two groups (Figure 8) it is apparent, that the control patients (group II) are on the flat part of the function curve, whereas the patients treated with thoracic epidural block and prenalterol (group I) are capable of increasing cardiac performance in association with the rapid increase in afterload induced by the aortic cross clamping.

Figure 8. Effects of infrarenal aortic clamping for the individual patients in groups I and II. The patients with thoracic epidural block and prenalterol (group I) are on the upward slope of the function curve whereas the control patients (group II) are on the horizontal part. Note the difference in PA_D scale between the groups.
Declamping hypotension (IV)

From studies with microspheres in dogs it is known that about 3% of cardiac output only, is directed to the lower extremities during the clamping period (RUTHERFORD 1977). This will result in dysoxia and accumulation of acid metabolites in the lower limbs. When aortic declamping is performed, the proportion of cardiac output directed to the lower extremities increases to about 21%. This occurs at the expense of renal, hepatic and mesenteric blood flow and in parallel to a decrease in cardiac output by 25% (RUTHERFORD 1977). "Central hypovolemia" suggested by STRANDNESS et al (1961), FRY et al (1963) and BAUE & McCLERKIN (1965) seems to be by far the most important mechanism for the development of the declamping hypotension. Other mechanisms, like release of myocardial depressant factors from the post ischemic lower limbs (SELBY et al 1964, BRANT et al 1970, RITTENHOUSE et al 1976) or the presence of acid metabolites in the systemic circulation (MAUSBERGER et al 1966, LIM et al 1969) have not been adequately proven. BUSH et al (1977) who were also in favour of central hypovolemia as the major cause of declamping hypotension reported that a left ventricular filling pressure around 10 mm Hg (1.3 kPa) completely abolished the blood pressure drop following declamping of the infrarenal aorta. As this was not our experience, we wanted to investigate the use of higher left ventricular filling pressure to prevent declamping hypotension.

Nineteen patients operated on for abdominal aortic aneurysm under general anaesthesia only, were therefore randomly assigned to two groups. The control patients (group I) were kept at a stable mean pulmonary artery occlusion pressure around 11 mm Hg (1.5 kPa) till
immediately before declamping. The patients in group II were volume loaded during the last 10 min before declamping to a mean pulmonary artery occlusion pressure around 16 mm Hg (2.1 kPa). Besides this there were no clinical or hemodynamic differences between the two groups. Following declamping however, striking differences between the groups became apparent:

In contrast to what was postulated by BUSH et al (1977) the patients in the control group had a substantial decrease in systemic blood pressure coinciding with a 3 mm Hg drop in mean pulmonary artery occlusion pressure which was of the same magnitude as reported by BUSH et al. The volume loaded patients had an equal reduction in filling pressure following declamping, but the reduction in systemic blood pressure was significantly smaller than that recorded in the control patients. In the control group, cardiac output decreased. In contrast, cardiac output did not change in the volume loaded patients. Heart rate was not affected by declamping in any of the groups, nor were arrythmias recorded in any patient. During deep general anaesthesia it is common that a decrease in stroke volume is not followed by a reflexogenic increase in heart rate. Furthermore, eight of the 19 patients were under influence of beta-blockers which may also explain the absence of heart rate response.

In Figure 9, left ventricular stroke work index (LVSWI) has been plotted against mean pulmonary artery occlusion pressure (MPAOP) for the two groups. It is apparent, that the volume expansion has transferred the patients in group II to the horizontal part of the function curve, where a moderate reduction of pre-load does not affect cardiac per-
formance, whereas the same reduction of pre-load in the control patients will induce a substantial drop in cardiac performance.

In the volume loaded patients the systemic vascular resistance decreased, which is regarded as an effect of decreased vascular tone in the reperfused lower extremity(ies) and may well explain the moderate decrease in systemic blood pressure in these patients as cardiac output was unchanged. In contrast, systemic vascular resistance did not change in the control patients suggesting vasoconstriction in central vascular beds to compensate for reduction in central blood volume.

When comparing the two groups, no difference in myocardial oxygen or lactate extraction was found before declamping implying that the volume loading did not affect cardiac work. In parallel to the decrease in afterload and preload and thereby cardiac work in the control patients, there was a decreased myocardial oxygen and lactate utilization. Myocardial ischemia could not be demonstrated following declamping despite a reduced coronary artery perfusion pressure. In group II no
significant changes in myocardial substrate utilization could be demonstrated after declamping.

It is apparent from the findings in the present study, that the results from animal studies by RUTHERFORD are also relevant in the clinical situation. Even with a normal left ventricular filling pressure immediately before aortic declamping, venous return and thereby cardiac output and systemic blood pressure cannot be adequately maintained after declamping. However, a compensatory vasoconstriction, probably in the splanchnic area, will prevent a profound blood pressure drop and thereby preserve coronary perfusion. Volume expansion to slightly supra-normal left ventricular filling pressure shortly before declamping did not induce any adverse cardiometabolic changes and almost completely abolished the negative cardiovascular effects of declamping seen in the control patients.

From the present investigations it is obvious, that the cardiovascular system can be extensively manipulated and that the hazardous intra-operative events of abdominal aortic aneurysm surgery can be effectively eliminated. Thoracic epidural blockade from T1 to T12 supported by cardioselective beta1-receptor stimulation with prenalterol transferred the patients to a more favourable myocardial function curve and probably also facilitated redistribution of blood flow in association with infrarenal aortic cross clamping. However, the local anaesthetic used for the thoracic epidural block has to be short acting not to interfere with the declamping. Apparently, declamping hypotension is induced by a mismatching between vascular volume and blood volume, where well preserved venous return is essential for cardiovascular equilibrium. A
thoracic epidural block, still effective, in association with declamping, might therefore potentiate the hypotension by its effect on vascular volume and also block a compensatory splanchnic vasoconstrictor response to central hypovolemia. It would therefore appear, that the beneficial effects of a thoracic epidural block are restricted to modify the adverse cardiovascular response to cross clamping but should ideally be over at the time of declamping.

Gram negative septic shock (V)

Acute peritonitis associated with gram negative bacteremia, is characterized by an inflammatory vasodilation with increased blood flow within the infected tissues (SHAL’KOV et al 1975, SILL 1976, ARCHIE 1977, WEIL 1977, LUTSENKO 1978). Vascular resistance is decreased and a large portion of cardiac output is directed to the peritoneal cavity which could lead to tissue dysoxia in other organs. To meet the basal peripheral demand, cardiac output must increase, which occurs mainly by an increase in heart rate (WEIL 1977). In circulatory shock associated with gram negative peritonitis there is, subsequently, a critical perfusion deficit demonstrated by lactacidemia (WEIL et al 1975). The primary treatment of the hypotension thus consists of volume expansion in order to increase cardiac output further (LOEB et al 1971, GOLDBERG 1971, WEIL 1977). However, volume expansion is often not followed by further increase in cardiac output, indicating impaired cardiac function (LOEB et al 1967). Under these circumstances, pharmacological intervention with inotropic drugs can be used to increase cardiac output (WINSLOW et al 1973).
The endogenous catecholamine, dopamine, is the most commonly used drug for this purpose today, due to its inotropic and renal cortical vasodilating action which tends to maintain urinary output (GOLDBERG 1972). The drug exerts a mixed, dose dependent action on the cardiovascular system. In dosages from 1 to 10 microgram/kg/min the drug is a dopamine- and beta$_1$-receptor agonist, whereas it predominantly will stimulate beta$_2$- and alpha-adrenoreceptors at higher dose levels (GOLDBERG 1977). As unwanted effects like tachycardia and arrhythmias can be seen during dopamine infusion at high dose levels, we wanted to investigate the effects of a selective beta$_1$-adrenoreceptor agonist, prenalterol, in patients with low resistance, distributive shock caused by gram negative bacteremias. A criteria in the present investigation to institute this treatment was that the patients had been adequately volume loaded and did not increase cardiac output further at higher levels of left ventricular filling pressure, indicating the need for inotropic support.

Ten patients with peritonitis and gram negative bacteremia(s) associated with clinical, metabolic and hemodynamic signs of circulatory shock were included. In all but one patient the time from onset of shock till prenalterol treatment was less than 8 hours (Table 4). Prenalterol administration increased systemic blood pressure by 30% and cardiac output by 44% within 15 minutes from termination of the infusion of the drug. These effects persisted throughout the rest of the investigation period. Systemic vascular resistance and heart rate did not change significantly during the 60 min observation period after prenalterol. Mean pulmonary artery occlusion pressure declined slowly to reach a level of significance 60 min after the drug administration. The hemodynamic changes in the present study were of the same magnitude as reported for dopamine
in septic shock by REGNIER et al (1977) and support previous observations that prenalterol is a selective \( \beta_1 \)-adrenoreceptor agonist which compared with for instance isoprenaline has a higher inotropic than chronotropic action (CARLSSON et al 1977). In parallel to the increased cardiac work an increase in myocardial oxygen consumption and lactate extraction was demonstrated. Total body oxygen consumption increased after prenalterol concomitant with a decrease in arterial lactate concentration, suggesting improved tissue perfusion. The increase in total oxygen consumption might in part be due to increased lipolysis and metabolic rate after administration of prenalterol (RÖNN et al 1979). Urinary output increased significantly after prenalterol. There is as yet no evidence that the drug exerts any action on the dopaminergic receptors in the kidney and we therefore regard the increased urinary output as an effect of improved renal perfusion pressure.

The mortality in the present investigation was considerably lower than that reported in most other studies of septic shock (LOEB et al 1967, WINSLOW et al 1973, DRUECK et al 1978). There are probably several reasons for this. Early, correct diagnosis and classification of the shock state by the use of invasive hemodynamic studies, aggressive treatment of the hypotension together with early surgical intervention and appropriate treatment with antibiotics, was the combined beneficial therapy for most of these patients.
Conclusions

Thoracic epidural block from T1 to T12 induced marked decrease in systemic blood pressure due to vasodilation and impairment of cardiac performance. Prenalterol administration effectively abolished the low blood pressure by its marked inotropic action, having no effect on systemic vascular resistance. Myocardial oxygen consumption changed in parallel with the changes in cardiac work following both thoracic epidural block and prenalterol. Coronary vascular resistance was markedly decreased by the block and was not affected by prenalterol. It is suggested, that the critically low perfusion pressure is the main cause of the coronary vasodilation and that alpha-blockade induced by the thoracic epidural block is of less importance.

The combination of a thoracic epidural block from T1 to T12 and selective $\beta_1$-stimulation with prenalterol was an effective way to modify the cardiovascular response to infrarenal aortic cross clamping. This treatment transferred the patients to a more favourable cardiac function curve and possibly facilitated the redistribution of blood flow in association with clamping.

In association with declamping of the infrarenal aorta or the common iliac arteries, volume loading to a slightly elevated left ventricular filling pressure shortly before declamping was an effective way to counteract the expected blood pressure drop. A normal left ventricular filling pressure prior to declamping did not prevent the blood pressure drop following declamping. It is suggested, that mismatching between vascular volume and blood volume is the main cause of declamping hypo-
tension.

In patients with low resistance, distributive septic shock caused by gram negative bacteremias and signs of impaired cardiac function, pre-nalterol effectively reversed the hypotension and improved tissue perfusion by selectively increasing cardiac output. In parallel to the increased cardiac work, an increase in myocardial metabolic demand was demonstrated.
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References

Anatomic arterial-venous shunting in endotoxic and septic shock in dogs.

Ariniego, R., Waagstein, F., Mombay, B., Hjalmarson, A. (1979):
Hemodynamic effects of a new beta1-receptor agonist in acute myocardial
infarction. A useful antidote to unwanted cardiac effects of beta
blocking agents.

Attia, R.R., Murphy, J.D., Snider, M., Lappas, D.G., Darling, R.C.,
Lowenstein, E. (1976):
Myocardial ischemia due to infrarenal aortic cross-clamping during
aortic surgery in patients with severe coronary artery disease.
Circulation 53, 961.

A study of shock: acidosis and the declamping phenomenon.

Bayliss, W.M. (1902):
On the local reactions of the arterial wall to changes of internal
pressure.
J. Physiol. (London) 28, 220.

Influence of the cardiac nerves on coronary resistance.
Am. J. Physiol. 208, 763.

Regulation of coronary blood flow.
Adv. Cardiol. 12, 303.

Bonica, J.J., Backup, P.H., Anderson, C.E., Hadfield, D., Crepps, W.F.,
Monk, B.F. (1957):
Peridural block: Analysis of 3637 cases and a review.
Anesthesiology 18, 723.

Circulatory effects of peridural block: I. Effects of level of
analgesia and dose of lidocaine.
Anesthesiology 33, 619.

Vasodepressor factor in declamp shock production.
Surgery 67, 650.

Control of myocardial oxygen consumption.
Am. J. Cardiol. 27, 416.

Regulation of the circulation, part 1.


Engberg, G., Wiklund, L. (1978):  
The use of ephedrine during epidural analgesia.  

Feigl, E.O. (1967):  
Sympathetic control of coronary circulation.  
Circ. Res. 20, 262.

Circulation.  

Filling pressures in the right and left sides of the heart in acute myocardial infarction. A reappraisal of central-venous-pressure monitoring.  

Forrester, J., Ganz, W., Swan, H.J.C. (1972):  
Thermodilution cardiac output determination with a single flow-directed catheter.  

Prevention of hypotension due to aortic release.  

A new technique for measurement of cardiac output by thermodilution in man.  
Am. J. Cardiol. 27, 392.

Measurement of coronary sinus blood flow by continuous thermodilution in man.  
Circulation 44, 181.

Ganz, W., Swan, H.J.C. (1972):  
Measurement of blood flow by thermodilution.  
Am. J. Cardiol. 29, 241.

Personal communications.

Current therapy of shock.  

Goldberg, L.I. (1972):  
Cardiovascular and renal actions of dopamine: potential clinical applications.  


Metabolic and tissue blood flow changes resulting from aortic cross clamping.
Surgery 65, 304.

Loeb, H.S., Cruz, A., Teng, C.Y. (1967):
Hemodynamic studies in shock associated with infection.

Lund, P.C. (1966):
Peridural analgesia and anesthesia.

Lutsenko, S.M. (1978):
Hemodynamics of regional blood circulation in peritonitis.
Khirurgiia (Mosk) 5, 116.

Rapid enzymatic measurement of blood lactate and pyruvate.

"Washout" acidosis following resection of aortic aneurysm: Clinical metabolic study of reactive hyperemia and effect of dextran on excess lactate and pH.

Hemodynamic alterations associated with epidural anaesthesia.
Surgery 62, 79.

Haemodynamic changes due to clamping of the abdominal aorta.

Cardiovascular effects of epidural analgesia.

Otton, P.E., Wilson, E.J. (1966):
The cardiovascular effects of upper thoracic epidural analgesia.

Parmley, W.W., Tyberg, J.V. (1976):
determinants of myocardial oxygen demand.
In Yu, P.N., Goodwin, J.F. (eds):
Progress in Cardiology, Philadelphia, Lea & Febiger.

Perry, M.O. (1968):
The haemodynamics of temporary abdominal aortic occlusion.

Hemodynamic effects of catecholamines on the coronary circulation in the unanesthetized dog (abstr.).
Pottecher, T., Meloche, R. (1977):
The use of aminophyllin for correction of haemodynamic repercussions of clamping of the aorta.

Randall, W.C., McNally, H., Cowan, J., Caliguiri, L., Rohse, W.G. (1957):
Functional analysis of the cardioaugmentor and cardioaccelerator pathways in the dog.
Am. J. Physiol. 191, 213.

Hemodynamic effects of dopamine in septic shock.
Intens. Care Med. 3, 47.

The role of prostaglandin E in the hemodynamic response to aortic clamping and declamping.
Surgery 80, 137.

Rosenthal, T.B. (1948):
The effect of temperature on the pH of blood with plasma in vitro.

Rutherford, R.B. (1977):
In discussion with Bush, H.L.
Arch. Surg. 112, 1306.

Metabolic and hemodynamic effects and some pharmacokinetics of a new selective β3-adrenoceptor agonist, prenalterol, in man.

Hemodynamic effects and some pharmacokinetics of a new selective beta3-adrenoceptor agonist, prenalterol and its interaction with metoprolol in man.

Vasodilator material in ischemic tissue.

Oxyhaemoglobin dissociation curve correction for temperature and pH variation in human blood.
J. Appl. Physiol. 12, 485.

Shal'kov, Iu.L., Levendiuk, A.M., Beresnev, A.V. (1975):
Angiographic aspects of mesenteric blood flow in peritonitis.


