MYOCARDIAL BLOOD FLOW AND OXYGEN CONSUMPTION DURING HALOTHANE–NITROUS OXIDE ANAESTHESIA FOR CORONARY REVASCULARIZATION

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SUMMARY

The effects of halothane on myocardial blood flow and myocardial oxygen balance were studied in seven male patients with stable angina and normal left ventricular function. Patients were receiving maintenance doses of β-receptor antagonists and underwent coronary artery bypass surgery. Anaesthesia consisted of halothane and 50% nitrous oxide in oxygen. Halothane decreased myocardial blood flow and myocardial oxygen consumption by 29% and 32%, respectively, after induction of anaesthesia, and during sternotomy. Myocardial lactate production was not observed at any time. Cardiac index, stroke volume index, mean arterial pressure and mean diastolic arterial pressure were decreased significantly after induction of anaesthesia and during sternotomy. Heart rate remained unchanged. The global myocardial oxygen supply and demand relationship was maintained. The results suggest that halothane is a safe anaesthetic for coronary revascularization in patients with unimpaired left ventricular function.

Anaesthesia for coronary artery surgery requires the maintenance of the physiological balance between myocardial oxygen supply and demand. Anaesthetic techniques based on opioids as primary agents, produce minimal cardiac depression, but do not reliably block undesirable cardiovascular responses to noxious stimuli in patients with coronary artery disease (Lowenstein, 1971; Waller et al., 1981) and, even in large doses, may fail to protect the myocardium from ischaemia (Hilfiker et al., 1982; Sonntag et al., 1982). The use of halothane in patients with myocardial ischaemia is controversial (Merin, 1981), since it is well established from a variety of investigations in animals (Prys-Roberts et al., 1972; Smith et al., 1974; Merin, Verdouw and de Jong, 1982) and man (Eger et al., 1970; Prys-Roberts et al., 1974; Sonntag et al., 1978; Sonntag et al., 1979) that this agent produces a dose-related depression of myocardial function. This is accompanied by decreases in myocardial oxygen consumption and coronary blood flow and a decrease in coronary perfusion pressure because of diastolic hypotension.

This study was designed to investigate the effects of nitrous oxide supplemented with halothane on myocardial blood flow, myocardial oxygen consumption and myocardial oxygen balance in patients undergoing coronary artery revascularization.

PATIENTS AND METHODS

Seven male patients undergoing two-vessel (two patients) or three-vessel (five patients) coronary artery bypass surgery (age range 38–54 yr and weight range 67–88 kg) were studied. The study was approved by the Human Subjects Review Committee of the German Research Foundation, SFB 89-Cardiology. Each patient gave informed consent at the time of the preoperative visit. Five of the patients gave a history of one myocardial infarction. No patient had a history of congestive heart failure or valvular heart disease, and none demonstrated evidence of pathological left ventricular wall motion. In all patients the ejection fraction was greater than 55% and the pre-angiogram left ventricular end-diastolic pressure was less than 15 mm Hg. Six patients were receiving the beta-receptor antagonist pindolol (15 mg per day) and one patient a calcium antagonist (verapamil). All medication, with the exception of the pindolol and verapamil, had been discontinued 48 h before operation. The last dose of pindolol or verapamil was administered at 10:00 p.m. on the night before surgery.

All patients were premedicated with promethazine 50 mg, and piritramide 15 mg, i.m., 60 min before operation.

Upon arrival of the patient in the induction room, ECG leads were attached and the following catheters...
were placed, under local anaesthesia: a Goodale–Lubin catheter (7F, USCI) into the coronary sinus via the right internal jugular vein (Seldinger technique, image intensification fluoroscopy) for measurement of coronary blood flow and withdrawal of blood samples; a Goodale–Lubin catheter (7F, USCI) into the left radial artery (arterial cut-down) for monitoring of arterial pressure and blood sampling; a pulmonary artery catheter (Edwards quadruple thermodilution model no. 93 A131–7F) inserted via a left or right antecubital vein for measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure, and cardiac output; and a polyethylene catheter into the superior vena cava for infusion of drugs. The position of all catheters was confirmed by image intensification fluoroscopy.

Body temperature was monitored with the thermistor of the pulmonary artery catheter. ECG and all pressures were monitored continuously and recorded on a 10-channel chart recorder (Hellige, Freiburg W-Germany).

After a rest period of 20 min, anaesthesia was induced with 50% nitrous oxide in oxygen, to which halothane was added to a maximum inspired concentration of 1.5%. Inspired and end-tidal concentrations of halothane were monitored continuously by mass spectrometry (Perkin Elmer 1100). Orotracheal intubation was facilitated with pancuronium 0.1 mg kg⁻¹. Following tracheal intubation, controlled ventilation with 50% nitrous oxide in oxygen was instituted using a constant volume ventilator (Engström ER 300). \( \text{Paco}_2 \) was maintained within the normal range and this was confirmed by serial blood-gas analyses. Anaesthesia was maintained by adjusting the inspired concentration of halothane according to the arterial pressure, the pulmonary capillary wedge pressure and the degree of surgical stimulation. Neuromuscular blockade was maintained with increments of pancuronium 2 mg.

Measurements were performed and blood samples taken with the patients awake (I), 15 min after the induction of anaesthesia and before any surgical stimulation (II) and during sternotomy (III). No drug was administered for 15 min before and during the period of data collection.

Measurements included: myocardial blood flow (MBF), using the argon wash-in technique (coefficient of variation ± 5.1%) as described by Tauchert, Kochsiek and Heiss (1970) with sampling from the coronary sinus and the radial artery after inhalation of a standard concentration of argon; cardiac output (CO) by thermodilution (cardiac output computer: Fischer BN 7206); mean arterial pressure (MAP); mean diastolic arterial pressure (MDAP; integrated from the pressure recording); mean pulmonary arterial pressure (MPAP); pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) (Statham P 23 Db). Immediately before and after each measurement of myocardial blood flow, samples were drawn from the coronary sinus and the radial artery. Samples were analysed for concentration of haemoglobin, oxygen saturation (CO-Oximeter 282, Instrumentation Lab.), \( \text{Paco}_2 \) and \( \text{PaO}_2 \) (standard electrodes, Radiometer Copenhagen), lactate (enzymatically, as described by Bergmeyer, 1971) (coefficient of variation ± 3.9%); CPK-MB isoenzyme (enzymatically), myoglobin (radioimmunossay, as described by Kaiser and others (1979)) and electrolyte concentrations (flame photometer, 543 IL).

Derived variables were calculated as follows. Coronary vascular resistance (CVR) as

\[
\text{CVR} = \frac{\text{MDAP} - \text{PCWP}}{\text{MBF}}
\]

where MDAP = mean diastolic arterial pressure. Cardiac index (CI) was calculated by dividing cardiac output by the body surface area, and stroke volume index (SVI) by dividing cardiac index by heart rate. Heart rate (HR) was obtained from the ECG. Myocardial oxygen uptake (\( m \text{VO}_2 \)) was calculated by multiplication of arterial—coronary sinus blood oxygen content difference by myocardial blood flow. Blood oxygen contents were calculated from measurements of haemoglobin concentration, oxygen saturation and oxygen partial pressure. Lactate uptake and production, respectively, were calculated by multiplication of arterial—coronary sinus blood difference of lactate by myocardial blood flow.

Statistical analysis was performed using a test combined with a rejective multiple test procedure as described by Holm (1979).

RESULTS

End-tidal halothane concentrations averaged 0.5% after induction of anaesthesia and 0.9% during sternotomy. No patient required vasodilator therapy at any time and none demonstrated ECG evidence of myocardial ischaemia during the study.

Figure 1 illustrates the individual values of certain
HALOTHANE AND MYOCARDIAL OXYGEN BALANCE

Fig. 1. Myocardial variables during halothane–nitrous oxide anaesthesia in seven patients. MBF = myocardial blood flow; mVO₂ = myocardial oxygen consumption; CVR = coronary vascular resistance; ind. = induction; Stern = sternotomy.

TABLE I. Myocardial and haemodynamic variables, haemoglobin content, PO₂, PCO₂, and pH during halothane–nitrous oxide anaesthesia. Mean values ± SEM. n = 7. *P < 0.05; **P < 0.01; ***P < 0.001 v. awake. MBF = myocardial blood flow; mVO₂ = myocardial oxygen consumption; CVR = coronary vascular resistance; HR = heart rate; Psys = systolic pressure; MAP = mean arterial pressure; MDAP = mean diastolic arterial pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; cor. sin. = coronary sinus. I = awake; II = after induction; III = during sternotomy.

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<th>I</th>
<th>II</th>
<th>III</th>
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<tr>
<td>MBF (ml min⁻¹/100 g)</td>
<td>111.14 ± 10.1</td>
<td>79 ± 3.6*</td>
<td>71 ± 7.3***</td>
</tr>
<tr>
<td>mVO₂ (ml O₂ min⁻¹/100 g)</td>
<td>13.68 ± 0.97</td>
<td>9.37 ± 0.41**</td>
<td>9.30 ± 0.82**</td>
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<tr>
<td>CVR (mm Hg/(ml min⁻¹/100 g))</td>
<td>0.74 ± 0.06</td>
<td>0.82 ± 0.04</td>
<td>1.00 ± 0.09</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>69 ± 4</td>
<td>72 ± 4</td>
<td>69 ± 4</td>
</tr>
<tr>
<td>Psys (mm Hg)</td>
<td>142 ± 7</td>
<td>108 ± 3***</td>
<td>111 ± 6**</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>103 ± 4</td>
<td>82 ± 2**</td>
<td>86 ± 6**</td>
</tr>
<tr>
<td>MDAP (mm Hg)</td>
<td>91 ± 3</td>
<td>74 ± 3***</td>
<td>78 ± 5*</td>
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<tr>
<td>PCWP (mm Hg)</td>
<td>10.3 ± 0.9</td>
<td>9.7 ± 1.1</td>
<td>9.3 ± 1.3</td>
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<tr>
<td>RAP (mm Hg)</td>
<td>5.6 ± 0.6</td>
<td>5.6 ± 0.5</td>
<td>5.9 ± 0.9</td>
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<tr>
<td>CI (litre min⁻¹ m⁻²)</td>
<td>3.48 ± 0.19</td>
<td>2.74 ± 0.14**</td>
<td>2.35 ± 0.16***</td>
</tr>
<tr>
<td>SVI (ml m⁻²)</td>
<td>51 ± 2</td>
<td>38 ± 1.5**</td>
<td>34 ± 1.8***</td>
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<tr>
<td>SVR (mm Hg/(ml min⁻¹ kg⁻¹))</td>
<td>1.14 ± 0.05</td>
<td>1.18 ± 0.08</td>
<td>1.41 ± 0.11*</td>
</tr>
<tr>
<td>Haemoglobin (g dl⁻¹)</td>
<td>15.0 ± 0.5</td>
<td>14.3 ± 0.5</td>
<td>14.4 ± 0.5</td>
</tr>
<tr>
<td>Po₂ cor. sin. (kPa)</td>
<td>2.75 ± 0.1</td>
<td>2.87 ± 0.1</td>
<td>2.54 ± 0.1</td>
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<tr>
<td>PaCO₂ (kPa)</td>
<td>11.6 ± 0.9</td>
<td>15.02 ± 1.4</td>
<td>16.89 ± 1.2</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>5.75 ± 0.1</td>
<td>4.92 ± 0.1</td>
<td>4.79 ± 0.1</td>
</tr>
<tr>
<td>pH (unit)</td>
<td>7.35</td>
<td>7.42</td>
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myocardial variables; mean values ± SEM are presented in table I. Halothane produced a significant decrease in myocardial blood flow and myocardial oxygen uptake of 29% and 32%, respectively, after induction of anaesthesia. These remained almost unchanged during sternotomy, while coronary vascular resistance increased significantly. Myocardial lactate production was not observed at any time. CK-MB and myoglobin were not released into the coronary sinus blood.

Heart rate did not change significantly after the induction of anaesthesia or during sternotomy, while mean arterial pressure and mean diastolic arterial pressure decreased significantly. Pulmonary capillary wedge pressures remained unchanged during the entire observation period. Cardiac index and stroke volume index decreased significantly after the induction of anaesthesia and were further reduced following sternotomy. Systemic vascular resistance increased during sternotomy. During the entire study period haemoglobin concentration, P\textsubscript{a}O\textsubscript{2}, P\textsubscript{a}CO\textsubscript{2}, acid–base measurements, electrolytes and body temperature remained within their physiological ranges.

**DISCUSSION**

In this study halothane–nitrous oxide anaesthesia was associated with a significant decrease in the oxygen consumption of the left ventricle, together with a corresponding decrease in coronary blood flow, both changes being the result of a decreased haemodynamic load on the myocardium and a decrease in contractility. Coronary vascular resistance increased by 11% because of the decrease in the metabolic demand of the myocardium.

Although halothane decreased coronary perfusion pressure by 20%, myocardial lactate production, which is the most commonly accepted metabolic index of global myocardial ischaemia, could not be demonstrated during the study. Also, there was no myocardial release of CK-MB and myoglobin, both indications of myocardial muscle cell damage. In addition, there was no clinical or ECG evidence of myocardial ischaemia during the observation period.

These data suggest that metabolic control of coronary blood flow and myocardial oxygen consumption was present during halothane anaesthesia. Apparently, the myocardial oxygen supply-and-demand relationship was maintained. These results are similar to those obtained in a previous study on human volunteers without cardiac disease (Sonntag et al., 1979) and in the intact heart in a variety of experimental animal preparations (Weaver, Bailey and Preston, 1970; Smith et al., 1974; Verrier et al., 1980).

There are few clinical investigations concerning the effects of anaesthetics on coronary blood flow and myocardial oxygen consumption in patients with myocardial ischaemia, and laboratory studies have been hampered by the lack of an animal model of chronic arteriosclerosis. Rather, the choice of anaesthetics for patients with myocardial ischaemia is based mainly on theoretical grounds by relating the pharmacological effects obtained in normal hearts to the pathophysiology of coronary artery disease or by extrapolating laboratory findings to clinical practice. Data concerning the effects of halothane on the ischaemic myocardium are inconsistent and controversy exists as to whether anaesthesia with myocardial depressants is beneficial for the ischaemic heart (Merin, 1981). While several authors have demonstrated favorable effects of halothane on myocardial ischaemia in experimental work (Bland and Lowenstein, 1976; Davis et al., 1979; Smith, Rogers and Thorburn, 1980; Verrier et al., 1980) and in clinical investigations (Kistner et al., 1979; Roizen, Hamilton and Sohn, 1981; Gerson, Hickey and Bainton, 1982) others have presented evidence of worsening myocardial ischaemia in animal studies (Lowenstein et al., 1981; Francis et al., 1982; Merin, Verdouw and de Jong, 1982).

It has been emphasized by Bland and Lowenstein (1976) that the circulatory actions of anaesthetics must be evaluated in terms of their effects on the determinants of myocardial oxygen supply and demand, particularly when coronary blood flow is limited. Anaesthetics are likely to produce ischaemia in the heart with coronary artery ateriosclerosis only when the balance between myocardial oxygen supply and demand is adversely affected. In our study halothane produced a net decrease in oxygen demand by a decrease in systolic wall tension and myocardial contractility accompanied by a decrease in coronary blood flow of approximately the same degree. However, coronary perfusion pressure, a major determinant of myocardial oxygen supply, was decreased also.

The production of a decrease in coronary perfusion pressure by inhalation anaesthetics is one of the main objections to the use of these agents in patients with coronary artery stenosis (Merin, 1981). According to Merin, myocardial oxygen consumption should be kept as close to the unanaesthetized
angina-free value as possible while maintaining coronary perfusion pressure. There is general agreement that anaesthetics which decrease coronary perfusion pressure may result in marked decreases of coronary blood flow and severe impairment of myocardial oxygen supply. However, adequate coronary perfusion pressure during clinical anaesthesia in patients with coronary artery disease has not been well defined at present. Also, Lowenstein and colleagues (1982) have emphasized that more investigation is necessary to establish the major differences between the pressure–flow relationships of normal coronary vascular units and those supplied by a stenotic artery to clarify the question of which anaesthetic regimen is least likely to result in an imbalance of myocardial oxygen supply and demand.

In our study the halothane-induced decrease in mean diastolic arterial pressure did not result in global myocardial ischaemia or a disturbance of global performance, supporting the opinion of Francis and co-workers (1982) that diastolic arterial pressure can only be a crude indicator of the adequacy of coronary blood flow during anaesthesia in patients with coronary artery disease. However, maintenance of global coronary blood flow and the net global lactate extraction of the myocardium in our patients does not preclude the presence of heterogeneity of blood flow and myocardial metabolism together with regional myocardial ischaemia. More sensitive indices of regional myocardial metabolism are required to answer this question.

Our data demonstrate that halothane–nitrous oxide anaesthesia administered to patients with coronary artery disease and receiving β-receptor antagonists, does not result in a global imbalance of myocardial oxygen demand and supply when inspired halothane concentrations are carefully adjusted to the requirements of anaesthetic and surgical procedures. Halothane seems to prevent disturbances in myocardial oxygen balance in these patients mainly by attenuating or preventing tachycardia, hypertension and sympathetic hyperactivity caused by noxious stimuli during anaesthesia and surgery. Interaction between halothane and the β-receptor antagonist pindolol might have contributed in part to the maintenance of a stable heart rate, even though pindolol, which has a plasma half-time of 3h, had been withdrawn 10h before the operation. Residual β-blockade cannot be excluded, since there is no evidence of a correlation between plasma concentration and therapeutic effect of β-receptor antagonists (Frishman, 1981).

Thus, our data support the widespread clinical experience that halothane is a well tolerated anaesthetic agent in patients with myocardial ischaemia and good left ventricular function. However, these conclusions are applicable only to patients not in cardiac failure.

ACKNOWLEDGEMENTS

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