ACUTE EFFECT OF FENTANYL ON HAEMODYNAMICS AND MYOCARDIAL CARBOHYDRATE UTILIZATION AND PHOSPHATE RELEASE DURING ISCHAEMIA

G. J. VAN DER VUSSE, H. VAN BELLE, W. VAN GERVEN, R. KRUGER AND R. S. RENEMAN

SUMMARY

The effect of fentanyl 25 µg/kg body weight i.v. on left ventricular haemodynamics, myocardial carbohydrate utilization and phosphate release during ischaemia in dogs was investigated. A reproducible degree of ischaemia could be obtained by partial occlusion (stenosis) of the interventricular artery, using an inflatable cuff. Inducing stenosis twice made it possible to use the animal as its own control. Arterio-local venous differences of glucose increased during ischaemia and lactate and inorganic phosphate were released from the ischaemic myocardium. Fentanyl administered before the second stenosis reduced heart rate and, to a lesser extent, mean aortic pressure and left ventricular dP/dt max. The release of lactate and inorganic phosphate was diminished during the period of ischaemia. These findings suggest that fentanyl prevents excessive breakdown of energy-rich phosphates and high anaerobic production rate of lactate by decreasing the energy demand of the ischaemic myocardium.

Ischaemic heart disease is commonly caused by an obstruction of one or more coronary arteries. Tissue hypoxia leads to anaerobic lactate formation and, in severe ischaemia, aerobic energy production is almost completely replaced by anaerobic energy supply. Breakdown of creatine phosphate and ATP results in a shortage of energy-rich phosphates for adequate muscle contraction (Opie, 1976). Cellular accumulation of carbon dioxide, lactate and inorganic phosphate occurs and produces acidosis which may contribute to cellular damage.

To diminish the chance of myocardial acidosis occurring during anaesthesia in patients with coronary artery disease, the drugs used should preferably decrease the oxygen demand of the ischaemic myocardium. Fentanyl has been reported to decrease the oxygen demand of the left ventricle (Freye, 1974; Kettler and Sonntag, 1974; Patschke, Gethmann et al., 1976; Patschke, Hesse et al., 1976) and to suppress the responses to stress (Florence, 1978; Hall, 1978).

The present investigation was designed to study in detail the effects of fentanyl on myocardial ischaemia. The influence of this drug on myocardial carbohydrate metabolism and inorganic phosphate release was investigated in dogs with a standardized stenosis of a coronary artery. A preliminary abstract of this study has been published elsewhere (Reneman et al., 1977).

MATERIALS AND METHODS

Experiments were performed on mongrel dogs of either sex and unknown age (weight 22–30 kg). The animals were premedicated with Hypnorm (1 ml/kg body weight i.m.) as described by Marsboom and others (1964). Anaesthesia was induced with sodium pentobarbitone (10 mg/kg body weight i.v.) and, after tracheal intubation, was maintained with nitrous oxide in oxygen. Pulmonary ventilation was kept constant, during the experiments, with a positive-pressure respirator (Bird). The e.c.g. was derived from limb leads. The chest was incised through the left fifth intercostal space and the pericardium opened over the antero-lateral aspect of the heart. Ascending aortic pressure was measured via the femoral artery with a polyethylene catheter connected to a pressure transducer (Telco). The pressure in the interventricular artery distal to the site of stenosis was measured through a small side branch (van der Meer and Reneman, 1972) with a polyethylene catheter (P.E. 50, Clay Adams) connected to a pressure transducer (Telco). The length and diameter of the catheters for aortic and coronary artery pressure measurements were such that no difference in delay could be detected between the measuring systems. Left ventricular pressure was measured through the...
left brachial artery with a catheter-tip micro manometer (Millar) and its maximal first derivative $dP/dt$ max was determined with an analog differentiator (Schaper, Lewi and Jageneau, 1965). The frequency response of the differentiator was 100 Hz (3 dB). The haemodynamic variables were recorded continuously using a multichannel Schwarzer recorder. Heparin 5000 i.u. was administered i.v. to keep patent the catheters used for pressure measurement.

An inflatable cuff was placed on the interventricular artery just distal to the diagonal branch. The cuff was connected through silastic tubing to a micrometer. The system was filled with distilled water so that the cuff could be inflated carefully until the desired degree of stenosis—mean coronary artery pressure of approximately 15–30 mm Hg—was reached. This range of pressures was selected since preliminary experiments had shown that lactate production occurred consistently at this degree of stenosis.

Arterial blood was sampled through the catheter used for aortic pressure measurement. Local venous blood samples were obtained through a polyethylene catheter (P.E. 60, Clay Adams) inserted into the interventricular vein by the Seldinger technique. The tip of the catheter was placed halfway between the site of stenosis and the apex, being approximately the site of maximum ischaemia (Jageneau et al., 1975). All blood samples were immediately deproteinized with cold perchloric acid and analysed using automated techniques for lactate (Apstein, Puchner and Brachfeld, 1970), inorganic phosphate (van Belle, 1970) and glucose.

After a recorded control period, the cuff was inflated to the desired degree of stenosis and was kept inflated for a period of 15 min. Then the cuff was deflated for approximately 30 min. After this period of stabilization, a second stenosis similar to the first was applied. In both procedures, arterial and venous blood samples were taken 10 min before, just before and usually 5, 10 and 15 min after the stenosis was induced. Haemodynamic variables were calculated at these times ($-10, 0, 5, 10, 15, 35, 45, 50, 55$ and $60$ min).

The animals were allocated to four groups. In group I control experiments were performed without constant heart rate ($n = 10$). In group II fentanyl 25 $\mu$g/kg body weight (Janssen, Niemegeers and Dony, 1963) was injected i.v. approximately 5 min before induction of the second stenosis ($n = 10$). In group III bipolar stimulation electrodes were sutured to the right ventricle. In these experiments ($n = 10$), heart rate was kept constant at 140 beat min$^{-1}$ with a programmable stimulator (Geivers et al., 1973). In group IV heart rate was kept constant as in group III and fentanyl 25 $\mu$g kg$^{-1}$ was injected i.v. 5 min before the second stenosis ($n = 6$).

**Data analysis**

Applying the same degree of stenosis twice makes it possible to use each animal as its own control. To study the effect of stenosis, the values of haemodynamic and biochemical measurements during each stenosis ($5, 10$ and $15$ min and $50, 55, 60$ min) were compared with those just before induction of the stenosis ($0$ and $45$ min). By comparing the values of the determined variables during the first ($5, 10$ and $15$ min) and the second stenosis ($50, 55$ and $60$ min), information can be obtained on the reproducibility of the changes induced by a stenosis of comparable severity (groups I and III) and on the effect of fentanyl during ischaemia (groups II and IV). The effect of fentanyl on the haemodynamic and biochemical variables in the non-ischaemic heart was investigated by comparing the values of these variables 10 min (time $35$ min) and just before (time $45$ min) induction of the second stenosis, in groups I–IV. Differences between the values of the various variables were evaluated for statistical significance by Wilcoxon's matched-pairs signed-ranks test (two-tailed probability). $P < 0.05$ was considered to be a significant difference.

**RESULTS**

**Group I. Control experiments without constant heart rate**

Mean coronary artery pressure decreased significantly from 69 mm Hg ($0$ min) to $24-27$ mm Hg (median values $5, 10$ and $15$ min) during the first stenosis and from $72$ mm Hg ($45$ min) to $24-25$ mm Hg ($50, 55$ and $60$ min) during the second stenosis (fig. 1). No significant differences could be detected between the mean coronary artery pressure values during the first and second stenosis. Systolic, diastolic and mean aortic pressure changed only slightly after induction of both the first and the second stenosis. Left ventricular $dP/dt$ max decreased slightly during the first stenosis, but remained constant thereafter. Heart rate did not change significantly during the experiment (fig. 1).

No significant differences could be detected between the arterio–local venous differences of glucose, lactate and inorganic phosphate during the control periods, before the two periods of stenosis (fig. 2). Arterio–local venous differences of glucose increased during the first stenosis from $0.8$ to $1.6–2.0$ mmol
HEART RATE (beat min⁻¹)

SYSTOLIC AORTIC PRESSURE (kPa)

DIASTOLIC AORTIC PRESSURE (kPa)

MEAN AORTIC PRESSURE (kPa)

LEFT VENTRICULAR dP/dt max (kPa s⁻¹)

MEAN CORONARY ARTERY PRESSURE (kPa)

GROUP II. Fentanyl without constant heart rate

Mean coronary artery pressure decreased significantly from 77 mm Hg (0 min) to 22–25.5 mm Hg during the first period of stenosis (P < 0.05). After administration of fentanyl 25 μg kg⁻¹ i.v. 5 min before the onset of the second stenosis, mean coronary pressure decreased significantly from 69 to 58 mm Hg (P < 0.05). Subsequent induction of stenosis decreased this pressure to 24–25.5 mm Hg (P < 0.05). These values were not significantly different from the corresponding values during the first period of stenosis (fig. 1).

Fentanyl caused a decrease in heart rate (P < 0.05). During the second stenosis heart rate increased gradually (P < 0.05) 10 and 15 min after induction of the stenosis, but remained less than during the first stenosis (P < 0.05). Left ventricular dP/dt max, diastolic and mean aortic pressure decreased slightly, but significantly, after the administration of fentanyl. During the second period of stenosis the values of these haemodynamic variables were significantly smaller than their corresponding values during the first stenosis. There were no significant changes in aortic systolic pressure.

Fentanyl 25 μg kg⁻¹ i.v. did not influence the arterio–local venous differences of glucose and}

(P < 0.05) and during the second stenosis from 1.2 to 1.9–2.4 mmol (P < 0.05) (fig. 2). Lactate uptake changed to lactate release after induction of the stenosis. Arterio–local venous differences changed significantly from +0.20 to (-1.45)–(-1.25) mmol during the first and from +0.18 to (-1.65)–(-1.35) mmol during the second stenosis. Induction of coronary artery stenosis caused a net release of inorganic phosphate from the ischaemic area. Arterio–local venous differences varied during the first stenosis from −0.53 to −0.43 mmol and during the second between −0.25 and −0.32 mmol. The control values of the biochemical variables just before the first and the second stenosis were not significantly different (0 v. 45 min). Apart from significantly greater phosphate values 5 min after the onset of the first stenosis, as compared with the corresponding values during the second stenosis (50 min), no significant differences could be detected between the biochemical variables during the first and second stenosis (fig. 2).
inorganic phosphate during the prestenosis control period, but it caused a slight decrease in arterio-local venous difference of lactate \((P<0.05)\) (fig. 2). No significant differences could be detected between the arterio-local venous differences of lactate and inorganic phosphate during the control periods, before the two periods of stenosis (0 and 45 min, respectively). Arterio-local venous differences of glucose showed a small, but significant increase during the control period before the second stenotic period. After induction of the second stenosis arterio-local venous differences of inorganic phosphate and lactate were significantly \((P<0.05)\) less negative than the corresponding values during the first period of stenosis (fig. 2). No consistent difference was found between the values of arterio-local venous difference of glucose during both periods of stenosis.

**Group III. Control experiments with constant heart rate**

Mean coronary artery pressure decreased significantly during the first and second periods of stenosis and varied in these periods between 21–22 mm Hg and 21–22.5 mm Hg respectively (fig. 3). No significant differences could be detected between the mean coronary artery pressure values during the first and second stenosis. Apart from a small but significant decrease in left ventricular \(dP/dt\) max 5 min after induction of the first stenosis no significant changes in this variable were found. Systolic aortic pressure decreased from 100 to 89 mm Hg during the first period of stenosis, but remained constant thereafter. Induction of stenosis had no significant effect on mean and diastolic aortic pressure, with one exception. Diastolic aortic pressure was reduced slightly 10 min
FENTANYL AND ISCHAEMIC MYOCARDIAL METABOLISM

SYSTOLIC AORTIC PRESSURE (kPa)

DIASTOLIC AORTIC PRESSURE (kPa)

MEAN AORTIC PRESSURE (kPa)

LEFT VENTRICULAR dP/dt max (kPa s⁻¹)

MEAN CORONARY ARTERY PRESSURE (kPa)

FIG. 3. Effect of fentanyl on left ventricular dP/dt max, and aortic and coronary artery pressure, before and during coronary artery stenosis. Heart rate was kept constant at 140 beat min⁻¹. Fentanyl 25 μg kg⁻¹ i.v. was administered between 35 and 45 min (black arrow). Open circles represent control experiments (n = 10), closed circles fentanyl experiments (n = 6). The median values and the 95% limits of the various variables are shown. Significantly different from (time): + = 0 min; O = 35 min; ▲ = 5 min; ▼ = 10 min; ■ = 15 min; X = 45 min.

after induction of the second stenosis. The control values of the biochemical variables just before the first and second stenosis were not significantly different (0 v. 45 min) (fig. 4). The changes in arterio-local venous differences of lactate and inorganic phosphate were similar after induction of the first and the second stenosis. Arterio-local venous differences of glucose increased from 0.5 to 1.1–2.1 mmol during the first stenosis and from 0.4 to 1.5–2.7 mmol during the second stenosis (fig. 4). The value, measured 10 min after the onset of the second stenosis, was significantly greater than the corresponding values in the first period.

Group IV. Fentanyl with constant heart rate (140 beat min⁻¹)

In the experiments in which heart rate was kept constant, fentanyl caused a significant decrease (P < 0.05) in systolic, diastolic and mean aortic pressure and mean coronary artery pressure (fig. 3). Coronary artery pressure decreased from 80 to 72 mm Hg. Mean coronary artery pressures, measured during the first and second stenosis, were not significantly different and varied between 17–19.5 mm Hg and 16.5–19.5 mm Hg respectively. During the second stenosis systolic, diastolic and mean aortic pressure were significantly smaller (P < 0.05) than during the first stenosis (fig. 3). Although no significant difference was found between the values of left ventricular dP/dt max 10 min and just before induction of the second stenosis, the latter value was smaller (P < 0.05) than its corresponding value before the first stenosis. Yet left ventricular dP/dt max was significantly smaller during the second than during the first stenosis (P < 0.05). Administration of fentanyl had no effect on arterio-local venous differences of glucose, lactate and inorganic phosphate during the control period before the second stenosis. The control values of the biochemical variables just before the first and the second stenosis were not significantly different (fig. 4). Arterio-local venous differences of glucose and inorganic phosphate during the second stenosis did not differ significantly from those during the first stenosis. Arterio-local venous differences of lactate were less negative during the second period of stenosis compared with the values during the first period. Only 10 min after induction of the stenosis, the arterio-local venous differences of lactate were significantly less negative during the second than during the first stenosis (P < 0.05) (fig. 4).
DISCUSSION

The present study indicates that fentanyl 25 \( \mu g \) kg\(^{-1}\) reduced heart rate, left ventricular \( dP/dt_{\text{max}} \) and aortic pressure. Since the release of inorganic phosphate and lactate from ischaemic heart tissue was reduced, fentanyl may prevent excessive breakdown of energy-rich phosphates and high rate of anaerobic production of lactate by decreasing the energy demand of the partially ischaemic myocardium. Results from experiments in which the heart rate was kept constant suggest that the negative chronotropic effect of fentanyl may be the most important factor in the beneficial effect of this drug on the ischaemic myocardium.

The reproducibility of the degree of ischaemia was indicated by the non-significant differences between the arterio-local venous differences of glucose, lactate and inorganic phosphate during the first and second stenosis at a comparable degree of coronary artery narrowing (there was no significant difference in mean coronary artery pressure during the first and second stenosis). This reproducible degree of ischaemia was achieved with and without a constant heart rate. Arterial and local venous concentrations of glucose and lactate were determined, to obtain information on aerobic and anaerobic carbohydrate metabolism in the left ventricular wall. Inorganic phosphate was measured since the increase of the concentration of this compound in local venous blood gives an indication of the degree of breakdown of energy-rich phosphates in the ischaemic heart tissue (Owen et al., 1970).

Stenosis was maintained for not longer than 15 min. Longer periods of ischaemia result in irreversible damage to the affected myocardium (unpublished observations) and the advantage of using the animal as its own control is lost. A period of stabilization between the periods of stenosis of longer than 30 min...
might improve the model. In the control experiments the arterio-local venous differences of inorganic phosphate were smaller during the second stenosis and this indicates that a period of 30 min is too brief for full restoration of the energy-rich phosphates.

An additional advantage of the present model is that, by partial occlusion of a major coronary artery, blood is obtained from a large, still perfused ischaemic area so that collateral circulation is not necessary for collecting local venous blood as in models in which ischaemia is induced by total occlusion of a small side branch of the interventricular artery (Owen et al., 1970; Opie et al., 1972). Moreover, partial occlusion (stenosis) of a coronary artery does not affect blood flow to the collateral areas (Jagleau et al., 1975).

Mean coronary artery pressure, as measured distal to the stenosis in a small side branch of the interventricular artery, rather than the reduction of mean blood flow in this artery, was used to estimate the degree of coronary artery narrowing. Under these conditions, the determination of pressure is easier and more accurate (Van der Meer and Reneman, 1972). Moreover, coronary artery pressure provides an indication of the contribution of collateral blood flow to the ischaemic area.

In the fentanyl experiments without constant heart rate (group II) the significantly reduced release of lactate and inorganic phosphate during the second stenosis indicates that, in the presence of fentanyl 25 µg kg⁻¹ i.v., a comparable degree of coronary artery stenosis resulted in a decrease in anaerobic energy production and in a less pronounced breakdown of energy-rich phosphates. These changes were not seen in the control experiments (group I). It is likely that the diminished energy demand resulted from the decrease in heart rate, left ventricular dP/dt max and mean aortic pressure seen after the administration of fentanyl. The latter finding is in agreement with the results obtained by Gardocki and Yelnosky (1964), Freye (1974), Eisele and others (1975), Liu and others (1976), Patschke, Gethmam and others (1976) and Patschke, Hesse and others (1976) who showed that fentanyl decreased the energy demand of the left ventricle in hearts with an unimpeded coronary circulation. The gradual increase in heart rate during the second stenosis probably resulted from the decreasing activity of fentanyl during the experimental period. This increase in heart rate, however, was not reflected in the biochemical measurements.

To differentiate chronotropic and other effects of fentanyl on myocardial metabolism during ischaemia, heart rate was kept constant at 140 beat min⁻¹ in an additional series of experiments (group IV). After the administration of fentanyl, left ventricular dP/dt max and systolic, diastolic and mean aortic pressure were significantly decreased (the same order of magnitude as in the experiments without constant heart rate) during the second stenosis as compared with the first, but no difference in arterio-local venous differences of inorganic phosphate could be detected. The arterio-local venous differences of lactate were less negative during the second stenosis, but these changes were less pronounced than in the experiments without constant heart rate. Only the values measured 10 min after the onset of stenosis differed significantly from the corresponding values during the first stenosis. This change in arterio-local venous differences of lactate was not seen in the control experiments with a constant heart rate (group III).

From the experiments performed with and without constant heart rate it may be concluded that the negative chronotropic effect of fentanyl is the major cause of the decrease in energy demand of the ischaemic myocardium. At slower heart rates the ischaemic myocardium benefits not only from the decreased energy demand, but also from the prolonged diastolic perfusion time.

Although it is difficult to extrapolate to clinical practice, it is likely that the use of fentanyl may be beneficial during anaesthesia, especially when the myocardium has a compromised circulation as a result of coronary artery stenosis.

ACKNOWLEDGEMENTS

The authors are indebted to Mr Jean Dony for help in the statistical analysis of the data and to Mrs Els Geurts and Mariet de Groot for help in preparing the manuscript. This study was supported by a grant from IWONL.

REFERENCES


EFECTO AGUDO DEL FENTANILÓ EN HEMODINÁMICA Y UTILIZACIÓN DE CARBOHIDRATO MIOCARDIAL, Y LIBERACIÓN DE FOSFATO DURANTE ISQUEMIA

SUMARIO
Se averiguó el efecto de 25 μg/kg de peso corporal de fentanilo i.v. en la hemodinámica ventricular izquierda, la utilización del carbohidrato miocardial y la liberación de fosfato durante isquemia en perros. Al usar esposas inflables, se pudo lograr un grado reproducible de isquemia mediante la oclusión parcial (estenosis) de la arteria interventricular. Induciendo la estenosis dos veces, fue posible usar al animal como su propio control. Las diferencias de glucosa arterio-venosa local aumentaron durante la isquemia y el miocardio isquémico liberó fosfato inorgánico y lactato. La administración de fentanilo antes de la segunda estenosis redujo el ritmo cardíaco y, en menor grado, la presión aórtica media y el máximo dP/dt ventricular izquierdo. La liberación de lactato y de fosfato inorgánico disminuyó durante el periodo de isquemia. Estos resultados sugieren que el fentanilo impide la ruptura excesiva de los fosfatos ricos en energía y un ritmo elevado de producción anaeróbica de lactato, al reducir la demanda energética del miocardio isquémico.