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The Effects of Short Intravenous Infusions of Thiopentone on Myocardial Function, Blood Flow and Oxygen Consumption in Sheep

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SUMMARY

The cardiovascular effects of slow (over two minutes) intravenous infusions of thiopentone 750 mg in conscious instrumented sheep breathing 100% oxygen were examined for 30 minutes following the start of the infusion.

The maximum rate of rise of left ventricular pressure (an index of myocardial contractility) decreased significantly from 1 to 10 minutes, to a minimum of 45% of baseline. Heart rate increased by up to 33% above baseline from 0.5 min onwards. Both mean arterial pressure and cardiac output were decreased from between 1 and 7 min. Left ventricular minute work was transiently decreased, but left coronary blood flow and myocardial oxygen consumption showed little or no change from baseline.

We conclude that in vivo, thiopentone administered at a relatively slow rate caused large reductions in myocardial contractility, and therefore cardiac reserve, in the absence of significant changes in myocardial blood flow or oxygen consumption.

Key Words: ANAESTHETICS, INTRAVENOUS: thiopentone; HEART: mean arterial pressure, heart rate, cardiac output, myocardial contractility, left coronary blood flow, myocardial oxygen consumption

The haemodynamic effects of intravenous bolus doses of thiopentone have been widely studied[1]. Venodilation and the subsequent peripheral pooling of blood following thiopentone administration generally results in a 10 to 20% reduction of mean arterial pressure in patients with normal baroflexes[2]. However, there is conflicting evidence regarding the magnitude of its effects on myocardial contractility, coronary blood flow and myocardial oxygen consumption[3-6]. For example, a number of studies reported that thiopentone decreased myocardial contractility[7-9] to varying degrees in animals anaesthetized with other agents. However, Turner et al[3] reported that contractility remained unchanged after thiopentone administration to initially conscious dogs.

Some of the reported variability in the direct effects of thiopentone on the heart may be attributed in part to the variety of experimental preparations used[1]. Isolated heart preparations have the disadvantage of not having normal autonomic control, while whole animal preparations are often complicated by concurrent anaesthesia with another drug. Furthermore, the respiratory depression caused by thiopentone[10,11] can potentially cause hypoxia in spontaneously breathing individuals, which can also cause cardiovascular changes. The rate of administration of thiopentone is also important as it has been proposed that the reductions in mean arterial blood pressure caused by thiopentone are a balance between the rate of compensatory sympathetic increases in vascular tone and its rate of injection[1,4,12]. The combination of

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these factors can therefore contribute to the observed cardiovascular effects of thiopentone in a given experimental or clinical paradigm.

In a previous series of studies, we reported the myocardial pharmacokinetics of thiopentone and its relationship to the reductions in myocardial contractility caused by thiopentone[13] in a chronically instrumented sheep preparation[14]. The purpose of this paper is to report cardiovascular measurements made during these studies as they constitute a detailed study of the cardiac effects of thiopentone in a preparation which minimized many of these confounding factors discussed above. The initially conscious nature of this preparation obviated the need for concurrent anaesthesia, while the administration of 100% oxygen removed the potential cardiovascular effects of hypoxia (but not hypercarbia). Thiopentone was injected at a relatively slow rate (over two minutes) to reveal any intrinsic effects of thiopentone rather than the effect of rapid injection, which can produce high transient concentrations of some drugs in the myocardium[15] and does not allow time for sympathetically mediated increases in vascular tone.

MATERIALS AND METHODS

The study protocol was approved by the institutional Animal Ethics Review Committee. Adult merino ewes weighing approximately 50 kg were prepared as described below with chronic intravascular catheters and Doppler flow probes to allow drug administration, cardiovascular function monitoring and the measurement of blood flow. All animals had free access to food and water and were housed in metabolic crates throughout the study period.

Animal Preparation

The sheep were prepared in two stages as described previously[13] and in brief below. Two weeks before experimentation, sheep were anaesthetized with sodium thiopentone 20 mg/kg and 1.5% halothane in 40% oxygen; balance nitrogen. A left thoracotomy at the fourth intercostal space and a pericardiotomy were performed to expose the pulmonary artery and the left main coronary artery. Doppler flow probes (Titronics Medical Instruments, Iowa City, Iowa, U.S.A.) were secured around the left main coronary artery and pulmonary artery respectively as described previously[14]. One week later, the sheep were re-anaesthetized for catheterization of various blood vessels using a modification of the method reported previously[14]. The right carotid artery and jugular vein were exposed via a neck incision. Using a modified Seldinger technique, two 7Fr (polyethylene) and a 9Fr (William A. Cook, Sydney, N.S.W., Australia) catheters were placed in the ascending aorta, with their tips located approximately 2 cm above the aortic valves via the carotid artery. Through the jugular vein a 7F polyethylene catheter was placed in the inferior vena cava (IVC); a 7F catheter (Multi-purpose B1 catheter, Cordis Corporation, Miami, FL, U.S.A.) in the coronary sinus; a flow-directed thermodilution catheter (Swan-Ganz, Edwards Laboratories, Irvine, CA, U.S.A.) in the pulmonary artery. Following surgery, the sheep were housed in metabolic crates with free access to food and water and the catheters were continuously flushed with heparinized (5 IU/ml) 0.9% saline at a rate of 3 ml/h using a gas powered system[16]. Experiments were not started until one week later so that the sheep could recover fully from surgery.

Cardiovascular Function and Blood Flow Measurements

The Doppler frequency shifts from both Doppler flow probes were amplified using a four-channel Doppler Flowmeter (Bioengineering, The University of Iowa, 56 M.R.F. Iowa City, Iowa, U.S.A.) and recorded, together with the other haemodynamic variables, using an analog to digital card (Metrabyte DAS 16-G2) and a personal computer (486 based IBM compatible) at a sampling rate of 1 Hz (except LVP). Cardiac output was determined using the pulmonary artery Doppler flow probes, which were calibrated in vivo against a thermodilution method as described previously[14]. Myocardial blood flow was determined from the left coronary artery Doppler probes, which were calibrated in vitro at the termination of the studies using the beaker and stop-watch method[14].

Mean arterial blood pressure (MAP) was measured using a pressure transducer (Model 4-327-I, Bell and Howell Inc., Pasadena, CA, U.S.A.) connected via polyethylene pressure tubing (PT 36, Sorenson Research Co., Salt Lake City, UT, U.S.A.) to one of the 7F arterial catheters in the ascending aorta.

Immediately before an experiment, a 5F Millar Mikro-Tip pressure transducer catheter (Millar Instruments Inc., Houston, Texas, U.S.A.) was introduced, using sterile technique, into the left ventricle of the sheep via a Touhy-Borst adaptor (William A. Cook, Sydney, N.S.W.) and the 9F catheter previously placed in the aortic arch. The left ventricular pressure measured using the Millar catheter was recorded at a sampling frequency of 150 Hz using the data acquisition system described above. The maximum rate of

left ventricular pressure rise (LV dp/dt_{max}) was calculated numerically and was used as an index of myocardial contractility. Heart rate at a given time interval was obtained by multiplying the number of LV dp/dt peaks recorded over six seconds by 10. Stroke volume was calculated from cardiac output divided by heart rate, and an index of left ventricular minute work was calculated from the product of cardiac output and MAP.

Arterial and coronary sinus blood samples were taken at 0, 3, 10 and 20 minutes after the start of the dose for blood gas analysis (Ciba-Corning Diagnostics, Medfield, MA, U.S.A.) and oximetric analysis of haemoglobin concentration and saturation, and oxygen content (IL 482, Instrumentation Laboratories Company, Lexington, MA, U.S.A.) using absorption coefficients previously determined for sheep blood [17]. Myocardial oxygen consumption at each time was calculated from the product of the difference between the arterial and coronary sinus oxygen contents and myocardial blood flow.

Study Design

The sheep were administered 750 mg doses of thiopentone (Abbott Australasia, Kurnell, N.S.W., Australia) diluted with sterile water (20 ml) as a two-minute IV infusion into the right atrium. During the experiments, the sheep were breathing 8 l/min of oxygen via a facemask, and were supported in a comfortable sling inside their metabolic crates in order to minimize movement that would influence the haemodynamic measurements. After the placement and the calibration of the haemodynamic measurement devices, sheep were allowed to "settle down" approximately 30 minutes before baseline measurements of the haemodynamic variables were recorded. Following the start of the thiopentone infusion, the haemodynamic variables were continuously recorded for the next 30 minutes.

Data Handling and Statistical Analysis

Six studies were conducted using a total of five sheep. In one sheep the MAP measurements were unreliable because of partial occlusion of the measurement catheter, and in another sheep measurements of myocardial blood flow and cardiac output were not possible due to failure of the Doppler flow probes. Due to the unavailability of the necessary instruments, blood gas analysis was not possible in one sheep and measurement of oxygen content was not possible in two sheep. The total number of studies analysed for each variable therefore ranged between four and six, as indicated in the legends to the figures. All times are referenced to the time of the start of the infusion (t=0).

The haemodynamic variables were analysed as per cent change from baseline, as only the thiopentone-induced changes are of interest in this paper. There are a variety of methods that can be used for the statistical analysis of these types of data. We used a two-way ANOVA to determine if there was an overall statistically significant change in a variable throughout the 30 minute study period. The mean data were then plotted with their upper and lower 95% confidence limits to examine the time-course of any changes. In these plots, any mean that lies outside of the confidence intervals of the baseline or time zero data is statistically different from the baseline data ($P>0.95$).

RESULTS

Respiratory depression but not hypoxia was observed following thiopentone administration (Table 1). Arterial carbon dioxide tension (P_aCO_2) was significantly increased, and arterial pH was significantly decreased, at 3, 10 and 30 minutes. Arterial oxygen tension increased, and oxygen contents decreased throughout the study (Table 1) due to a reduction in the haemoglobin concentration, but the haemoglobin saturation was greater than 98% throughout the study.

TABLE 1

The effect of thiopentone on blood gases and oxygen contents. Data are expressed as mean and (SEM)

	Arterial				Coronary Sinus
Min	PO_2 (mmHg, n=5)	PCO_2 (mmHg, n=5)	pH (n=5)	O_2 Content (ml %, n=4)	O_2 Content (ml %, n=4)
0	277 (45)	39.58 (0.72)	7.48 (0.00)	12.4 (0.5)	3.7 (0.5)
3	368 (28)*	58.50 (2.30)*	7.35 (0.02)*	11.6 (0.6)	3.8 (0.6)
10	469 (41)*	49.52 (1.95)*	7.40 (0.02)*	11.1 (0.04)*	4.1 (0.05)
30	435 (40)*	47.90 (3.13)*	7.40 (0.02)*	11.2 (0.2)*	4.4 (0.4)

*Indicates a statistically significant difference from the time zero measurement.

Mean arterial pressure (MAP) was significantly decreased from baseline from 1 to 7 minutes (Figure 1), and the maximum rate of rise of left ventricular pressure (LV dp/dt_{max}) decreased significantly from 1 to 10 minutes. The maximum depression was to 1988 mmHg/sec (45% of baseline) which occurred at 2.5 minutes (Figure 1).

Cardiac output (CO) was significantly decreased from baseline from 1 to 7 minutes (Figure 2), while heart rate (HR) was significantly increased from 0.5 minutes onwards (Figure 2). The net result was that stroke volume was slightly decreased, but not to statistical significance (Figure 2).

Left ventricular minute work (LVMW) showed a significant decrease from 2 to 4.5 minutes (Figure 3) to a minimum of 51% of baseline. However, this calculated value was highly variable in the later part of the study, and its time-course after approximately 5 minutes cannot be stated with confidence. This transient reduction in work by the heart was not of sufficient duration to be reflected in statistically significant changes in mean left coronary blood flow (LCBF). However, myocardial oxygen consumption (MVO_2) was significantly below baseline at 30 minutes after the dose, which may reflect the sedated state of the animal following recovery from anaesthesia.

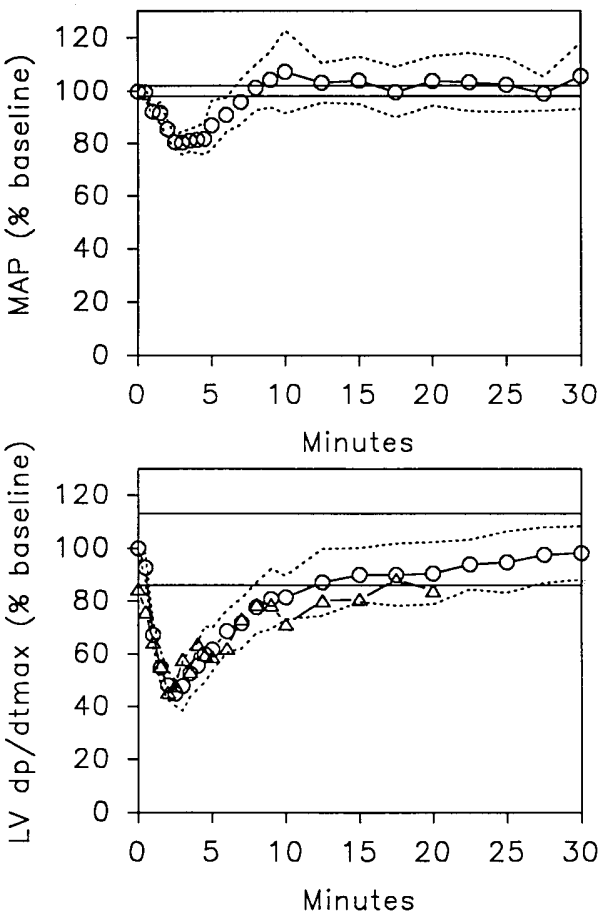

FIGURE 1: Upper panel—The time-course of mean arterial pressure (mean and upper and lower 95% confidence intervals). There was a statistically significant reduction ($P<0.05$, 2 way ANOVA, n=6) from 1 to 7 min. Lower panel—The time-course of the maximum rate of rise of left ventricular pressure (LV dP/dt_{max}, circles, mean and upper and lower 95% confidence intervals). There was a statistically significant reduction ($P<0.05$, 2 way ANOVA, n=6) from 1 to 10 min. The time-course of dP/dt at a developed pressure of 40 mmHg is shown by the triangles.

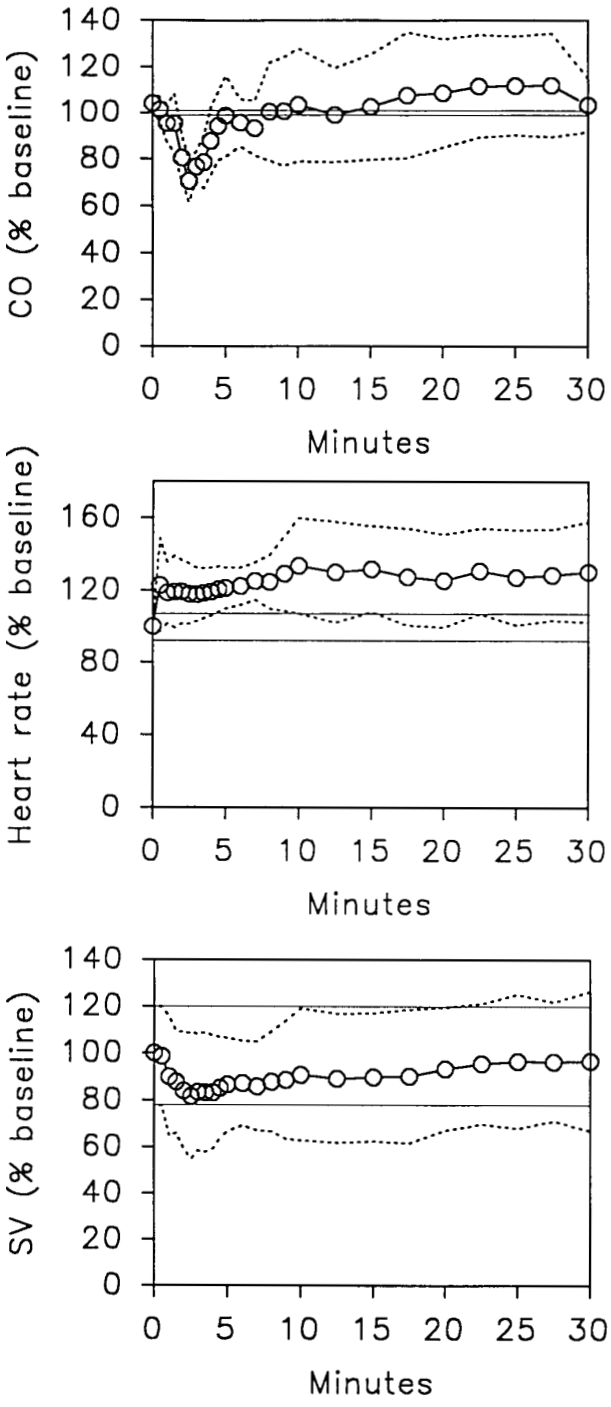

FIGURE 2: Upper panel—The time-course of cardiac output (mean and upper and lower 95% confidence intervals). There was a statistically significant reduction ($P<0.05$, 2 way ANOVA, n=5) from 1 to 7 min. Middle panel—The time-course of heart rate (mean and upper and lower 95% confidence intervals). There was a statistically significant increase ($P<0.05$, 2 way ANOVA, n=6) from 0.5 min onwards. Lower panel—The time-course of stroke volume (mean and upper and lower 96% confidence intervals). There was no statistically significant change ($P=0.15$, 2 way ANOVA, n=5). In each figure, the solid lines are the confidence limits of the baseline or time zero data.

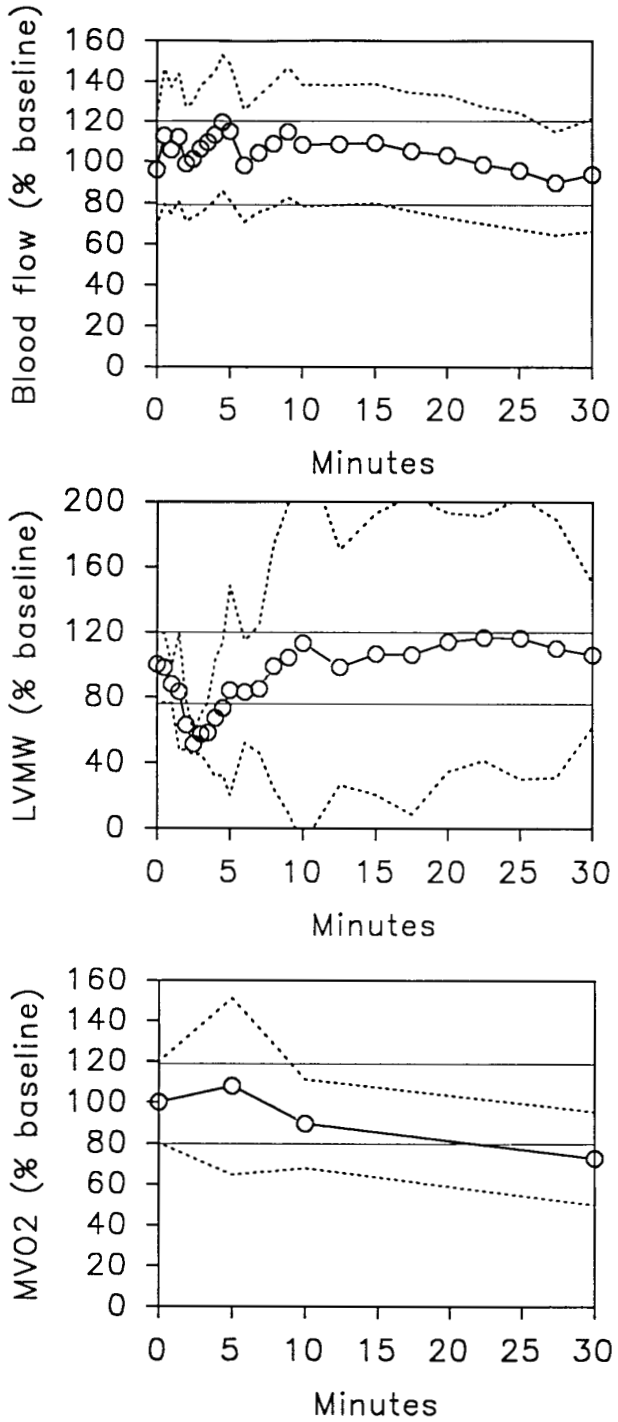

FIGURE 3: Upper panel—The time-course of left myocardial bloodflow (mean and upper and lower 95% confidence intervals). There was no statistically significant change (P=0.29, 2 way ANOVA, n=5). Middle panel—The time-course of the calculated left ventricular minute work (mean and upper and lower 95% confidence intervals). There was a statistically significant reduction (P<0.05, 2 way ANOVA, n=4) from 2 to 4.5 min. Lower panel: The time-course of the calculated myocardial oxygen consumption (mean and upper and lower 95% confidence intervals). There was a statistically significant decrease (P=0.02, 2 way ANOVA, n=4) at 30 min.

DISCUSSION

A dose of 750 mg of thiopentone over 2 minutes was used for studies of the cerebral pharmacokinetics and dynamics of thiopentone in a similar experimental preparation[18]. This dose produced loss of consciousness for approximately 20-25 minutes in these animals. This dose is also comparable to the dose of 1000 mg routinely used for the induction of anaesthesia in sheep in our institution.

As expected, a dose sufficient to cause anaesthesia also caused respiratory depression. Gaudy[11] reported barbiturates to be potent central respiratory depressants, with a biphasic response (tachypnoea during light anaesthesia and progressive bradypnoea as anaesthesia deepens). In this study, we wished to avoid the cardiovascular sequelae of hypoxia, which was achieved by letting the animals breathe 100% oxygen. However, some cardiovascular effects may be attributed to the hypercarbia and acidosis produced by this respiratory depression. These will be discussed subsequently, and their occurrence in vivo is clearly a function of whether or not respiration is supported mechanically.

In the present study, the negative inotropic effects of thiopentone lasted from 1 to 10 minutes. The maximum decrease of dP/dt_{max}, which occurred at 2.5 minutes, was to 45% of baseline. The reductions observed in initially conscious sheep were greater than those observed previously in anaesthetized animals. Chamberlain et al[8] reported only 15-17% reductions of contractility in dogs, but in these studies thiopentone was infused directly into only one of the left coronary arteries, which suggests that not all of the heart was exposed to thiopentone. In more convincing studies, McGrath[9] showed 40% reductions in contractility in autonomically blocked rabbits. Patschke et al[7] reported a 34% reduction following bolus administration of thiopentone to dogs. The present study showed greater reductions than either of these latter two studies, which may reflect species or dose differences, or may be a result of the concurrent anaesthesia used in these preparations already depressing the myocardium. Interestingly, Turner et al[3] reported that contractility remained unchanged after thiopentone administration to initially conscious dogs. However, their preparation was profoundly hypoxic, and we suggest that the negative inotropic effects of thiopentone were counter-balanced by the initial positive inotropic effects of hypoxia.

Early reports concluded that dP/dt_{max} is an unreliable indicator of myocardial contractility when there are concurrent changes in heart rate, preload or afterload[19] as observed in the present study. However,

more recent work based on measurements in conscious, closed-chest animals have shown that dP/dt_{max} is well suited to the study of acute changes in myocardial contractility, is not affected by changes in afterload and is only affected by relatively large changes in pre-load[20,21]. The effect of left ventricular end diastolic pressure (LVEDP) changes over the range 4 to 25 mmHg is removed by calculating the dP/dt at a developed LV pressure of 40 mmHg ([dP/dt]/DP 40)[21]. In the present study LVEDP ranged from 4 to 12 mmHg and dP/dt/DP 40 had a similar time-course to that of dp/dt_{max} after the administration (Figure 1). Finally, increasing heart rate exerts a positive inotropic effect, although this effect is less prominent in intact conscious animals[20]. In our study, HR was initially increased but was constant for the period in which myocardial contractility was decreased. The observed reductions in myocardial contractility are therefore not accounted for by the altered heart rate. It can be concluded that the observed decreases in LV dp/dt_{max} reflected true reductions in myocardial contractility following thiopentone.

It has also been speculated that the cardiovascular depression caused by thiopentone can be the result of a combination of centrally mediated vagal effects and direct depression of contractility by thiopentone in the heart[4-6,9]. However, in vitro isolated perfused heart preparations (with no vagal supply by definition) from a number of species have shown significant reductions in contractility with thiopentone[6,22,23]. We conclude that the large reductions in contractility observed in vivo in our studies are accurate measurements, and are probably a direct effect of thiopentone on the heart and are related to the concentrations of thiopentone in the myocardium[13].

The implications of reductions in myocardial contractility itself are essentially concerned with loss of cardiac reserve. We have observed large reductions in contractility following the administration of lignocaine and pethidine in this preparation with only minor changes in MAP and cardiac output[14,24] which is consistent with the output of the heart being maintained by raised central venous pressure in the presence of cardiac dilatation[25]. In our study, both CO and MAP were transiently decreased. This is consistent, qualitatively, with the venodilatation caused by thiopentone[1] but it is clear from the above discussion that this venodilatation also negates the normal compensatory mechanism of reduced myocardial contractility. The observed reductions in CO and MAP may therefore be due to both venodilatation and the reduction in myocardial contractility.

The most prolonged change following the administration of thiopentone was an increase in HR. Although the initial rise may be a baroflex response to the initial reduction in MAP[5], this was a transient effect and cannot explain the sustained increases in HR observed in the later stages of the study. These latter effects could be due to thiopentone enhancing sympathetic nerve stimulation[9], or most likely due to the slight cardio-stimulation caused by the hypercarbia and acidosis.

An analysis of myocardial blood flow and oxygen consumption (MVO_2) should consider the work done by the heart, as these will be related in the absence of a direct vasodilatory effect of thiopentone on the heart. The calculated work of the heart was highly variable from approximately five minutes onwards, but was significantly reduced from 2 to 4.5 minutes. However, this reduction in work was sufficiently transient not to be reflected in changes in myocardial blood flow and oxygen consumption. In contrast, there are reports of increased MVO_2 in anaesthetized dogs[7], but decreased MVO_2 in isolated rabbit hearts[6]. This reinforces the concept that the cardiovascular response of a particular experimental paradigm to thiopentone is highly dependent on the conditions of the study and its methodology.

In conclusion, these data support the concept of transient depression of the heart with substantial reductions of cardiac reserve following thiopentone. This would be of concern in cases where cardiac reserve is already compromised, and importantly, these effects are not ameliorated by a slower rate of administration of thiopentone.

REFERENCES

1. Conway CM, Ellis DB. The haemodynamic effects of short-acting barbiturates. A review. Br J Anaesth 1969; 41:534-542.
2. Reilly CS. Intravenous anaesthetic agents: Pharmacology. In: Nimmo WS, Rowbotham DJ, Smith G, eds. Anaesthesia. Blackwell Scientific Publications, Oxford, 1994; 87-105.
3. Turner DM, Ilkiw JE. Cardiovascular and respiratory effects of three rapidly acting barbiturates in dogs. Am J Vet Res 1990; 51:598-604.
4. Runciman WB, Mather LE, Selby DG. Cardiovascular effects of propofol and of thiopentone anaesthesia in the sheep. Br J Anaesth 1990; 65:353-359.
5. Aun CS, Sung RY, O'Meara ME, Short TG, Oh TE. Cardiovascular effects of i.v. induction in children: comparison between propofol and thiopentone. Br J Anaesth 1993; 70:647-653.
6. Mouren S, Baron JF, Albo C, Szekely B, Arthaud M, Vaiars P. Effects of propofol and thiopentone on coronary blood flow and myocardial performance in an isolated rabbit heart. Anesthesiology 1994; 80:634-641.
7. Patschke D, Bruckner JB, Gethman JW, Tarnow J, Weymar A. Comparison of the immediate effects of etomidate, propandid and thiopentone on haemodynamics, coronary bloodflow and

myocardial oxygen consumption. An experimental study. Acta Anaesth Belg 1975; 26:112-119.
8. Chamberlain JH, Seed RGFL, Chung DCW. Effect of thiopentone on myocardial function. Br J Anaesth 1977; 49:865-870.
9. McGrath JC, Mackenzie JE. The effects of intravenous anaesthetics on the cardiovascular system of the rabbit. Br J Pharmacol 1977; 61:199-212.
10. Carlon GC, Kahn RC, Goldiner PL, Howland WS, Turnbull A. Long-term infusion of sodium thiopental: hemodynamic and respiratory effects. Crit Care Med 1978; 6:311-316.
11. Gaudy JH, Dauthier C, Galliot M. Ventilatory effects produced by the IV administration of incremental doses of thiopentone in the dog. Br J Anaesth 1983; 55:977-984.
12. Seltzer JL, Gerwon JI, Allen FB. Comparison of the cardiovascular effects of bolus vs incremental administration of thiopentone. Br J Anaesth 1980; 52:527-529.
13. Upton RN, Huang YF, Grant C, Gray EC, Ludbrook GL. The myocardial pharmacokinetics of thiopental in sheep after short term administration—Relationship to thiopental induced reductions in myocardial contractility. J Pharm Sci 1996; 85:863-867.
14. Huang YF, Upton RN, Rutten AJ, Runciman WB. Intravenous bolus administration of subconvulsive doses of lignocaine to conscious sheep. Effect on circulatory function. Br J Anaesth 1992; 69:368-374.
15. Huang YF, Upton RN, Runciman WB. Intravenous bolus administration of subconvulsive doses of lignocaine to conscious sheep. Myocardial pharmacokinetics. Br J Anaesth 1993; 70:326-332.
16. Runciman WB, Ilsley AH, Mather LE, Carapetis RJ, Rao MM. A sheep preparation for studying interactions between blood flow and drug disposition I: Physiological profile. Br J Anaesth 1984; 56:1015-1028.
17. Langston PG, Jarvis DA, Lewis G, Osborne GA, Russell WJ. The determination of absorption coefficients for measurement of carboxyhaemoglobin, oxyhaemoglobin, reduced haemoglobin, and methaemoglobin in sheep using the IL 482 CO-Oximeter. J Anal Toxicol 1993; 17:278-283.
18. Upton RN, Ludbrook GL, Grant C, Gray EC. In vivo relationships between the cerebral pharmacokinetics and pharmacodynamics of thiopentone in sheep after short-term administration. J Pharmacokin Biopharm 1996; 24:1-18.
19. Mason DT. Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. Am J Cardiology 1969; 23:516-527.
20. Strobeck JE, Sonnenblick EH. Myocardial contractile properties and ventricular performance. In: Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE, eds. The Heart and Cardiovascular System, Raven Press, New York, 1986; 31-49.
21. Davidson DM, Covell JW, Malloch CI, Ross J. Factors influencing indices of left ventricle contractility in the conscious dog. Cardiovasc Res 1974; 8:299-312.
22. Davies AE, McCans JL. Effect of barbiturate anesthetics and ketamine on the force-frequency relation of cardiac muscle. Eur J Pharmacol 1979; 59:65-73.
23. Kavanagh BP, Ryan MP, Cunningham AJ. Myocardial contractility and ischaemia in the isolated perfused rat heart with propofol and thiopental. Can J Anaesth 1991; 38:634-639.
24. Huang YF, Upton RN, Mather LE. The hemodynamic effects of intravenous bolus doses of meperidine in conscious sheep. Anesth Analg 1994; 78:442-449.
25. Guyton AC, Hall JE. Circulatory Physiology IV. University Press, Baltimore, 1982.