THE EFFECTS OF HALOTHANE ON THE INTERACTIONS BETWEEN MYOCARDIAL CONTRACTILITY, AORTIC IMPEDANCE, AND LEFT VENTRICULAR PERFORMANCE

I: THEORETICAL CONSIDERATIONS AND RESULTS*

C. PRYS-ROBERTS, B. J. GERSH, A. B. BAKER, AND S. R. REUBEN

SUMMARY

The effects of halothane (1.0–1.5%) on myocardial contractility, systemic vascular resistance (representing the majority of impedance to oscillatory flow), and left ventricular performance, and the interactions of these functions have been studied in open-chested dogs, artificially ventilated and maintained in a state of basal narcosis with chloralose and urethane. Halothane reversibly depressed myocardial contractility as estimated by three indices: maximum left ventricular (dP/dt)/IP, maximum left ventricular (dP/dt)/PCIP, and maximum aortic acceleration, but produced no significant changes of left ventricular end-diastolic pressure or of systemic vascular resistance. Stroke volume fell in proportion to the depression of myocardial contractility at constant heart rates maintained by atrial pacing, though the reduction of stroke volume was greatest when systemic vascular resistance increased slightly. The concept is proposed that, irrespective of minor changes in the peripheral venous bed during halothane anaesthesia, depression of myocardial contractility impairs ventricular emptying rather than ventricular filling. This concept is based on the observation that since peak aortic flow and acceleration are decreased during halothane anaesthesia, the force acting on blood and the momentum imparted to it during the early phase of ventricular ejection are reduced. Experimental evidence supported this hypothesis: thus, when the contractility of the myocardium was depressed by halothane anaesthesia, independent changes of systemic vascular resistance significantly modified the stroke output of the heart. It is concluded that the major cause of arterial hypotension during halothane anaesthesia is a fall in cardiac output, and that the predominant mechanism causing this fall is the depression of myocardial contractility.

Halothane has justifiably achieved wide popularity in clinical use, and yet, despite the wide range of both clinical and experimental studies of its actions, there is still uncertainty about its effects on the cardiovascular system. While most observers are agreed that halothane causes a dose-dependent arterial hypotension in most species, not all are agreed as to whether in man this is predominantly the result of reduced cardiac output (Severinghaus and Cullen, 1958; Deutsch and colleagues, 1962; Shionoziaki, Mazuzan and Abajian, 1968; Prys-Roberts and colleagues, 1968; Eger and colleagues, 1970) or the result of reduced systemic vascular resistance (Wyant and colleagues, 1958; Payne, Gardiner and Verner, 1959; Virtue and colleagues, 1962), or a combination of both. In searching for a predominant cardiovascular action of halothane in animals, Price and Price (1956) concluded that there was no single or predominant cause for the circulatory depression produced by halothane. Further studies have conclusively demonstrated that in concentrations which are associated with surgical anaesthesia, halothane decreases the myocardial contractile force in both man.

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(Bloodwell and colleagues, 1961; Mahaffey and colleagues, 1961), and in animals (Morrow and colleagues, 1961; Price and Price, 1966; Li, Gamble and Etsten, 1968). However, the force developed by contracting ventricular muscle is not a simple function, but is dependent on the resting or pre-contraction fibre length (the Frank-Starling relationship), and an inherent state of activity of the contractile elements of the muscle whose mechanical state is variously described either in terms of “contractility” or “inotropism”. While the definition, application, and interpretation of these terms, when applied to either the isolated muscle or the intact myocardium, have caused considerable confusion, there is nevertheless indisputable evidence that halothane like most other anaesthetic agents, reduces the force of contraction in isolated cardiac muscle maintained at a constant resting fibre-length (Goldberg and Ullrick, 1967; Sugai, Shimosato and Etsten, 1968; Brown and Crout, 1970). Despite the evidence outlined above, Price (1967) stated: “Except during a near lethal overdose, the level of cardiac output during anesthesia is not determined by primary changes in contractile force, but depends mainly on venous return, output impedance, and autonomic nervous activity.” While intuitively we could not reconcile Price’s conclusion with existing concepts of ventricular ejection, we considered that experimental justification of either opinion was required.

This paper explores the relationships between myocardial contractility, assessed from a mechanical rather than biochemical point of view, and the hydraulic load presented to the left ventricle by the impedance of the systemic vascular bed, and the effect of this interaction on left ventricular performance during halothane anaesthesia. A hypothesis of haemodynamic effects of halothane is based on the above relationships, and supported by experimental evidence, both in this and subsequent papers.

THEORETICAL CONSIDERATIONS

Myocardial contractility.

Definition of the term myocardial contractility is essential to the thesis of this paper, yet we are conscious of the caveat of Blinks and Koch-Weser (1962) who stated in their review of the subject that many workers had thought of changes in contractility in terms of an index “appropriate to the conditions of their experiments rather than in terms of fundamental properties of the muscle itself”. Since a study of the biochemical nature of the excitation-contraction coupling of the myocardial sarcomere was outside the scope of the study, we sought to quantify in mechanical terms the contractile state of the left ventricular myocardium in the intact animal, in order that its relationship to the stroke volume might be defined in the context of the pharmacological effects of halothane. A definition of myocardial contractility must be based on the quantification of that inherent quality of cardiac muscle whereby the contractile elements of the muscle fibres can develop more or less tension from a given pre-contraction fibre length. This independence from length-dependent changes clearly differentiates contractility from the Frank-Starling mechanism, whereby the tension developed by the contractile elements can be modified by changes in resting fibre length. The quantification of contractility has largely been based on extrapolations to both isolated papillary muscles and the intact heart of concepts based on theoretical models (Siegel, 1969) of skeletal muscle activity after Hill (1938). While these conceptual models do not entirely correlate with the observed behaviour of cardiac muscle, they nevertheless form the basis for the derivation of a number of indices which satisfy both the theoretical requirements and the somewhat empirical but practical definitions of contractility. A number of these indices, directly or indirectly related to the force-velocity relation of contracting cardiac muscle, have been assessed as to their suitability for the experimental quantification of contractility. The theoretical and experimental validation of these indices, and the acceptance of two specific indices has been described in detail elsewhere (Gersh, 1970; Taylor, 1970; Gersh, Pryse-Roberts and Baker, in preparation). Suffice it to say that such an index should be highly sensitive to agents which alter the force-velocity relation of isolated cardiac muscle, and yet be independent and unaffected in the intact animal by changes in end-diastolic fibre length, and by alterations in the hydraulic load of the ejecting ventricle.

The maximum rate of change of left ventricular pressure during isometric contraction (max LV dP/dt) has been widely used as an index of changes in “inotropism”, but many authors have found this index to vary significantly with changes in end-diastolic pressure or volume (Reeves and colleagues, 1950; Wallace, Skinner and Mitchell, 1963; Schaper, Lewi and Jageneau, 1965; Taylor and colleagues, 1967). Our own studies (Gersh 1970) confirmed that max LV dP/dt was significantly altered by changes.
in left ventricular diastolic volume or pressure (LVEDP), and also by changes in aortic diastolic pressure where these were accompanied by changes in LVEDP (homeometric autoregulation: Sarnoff, et al., 1950). However, changes in aortic diastolic pressure at a constant heart rate and LVEDP were not associated with significant changes in max LV \( \frac{dP}{dt} \). Although max LV \( \frac{dP}{dt} \) was extremely sensitive to both positive and negative inotropic influences (sympathetic nerve stimulation, infusions of noradrenaline, isoprenaline, and calcium gluconate, ligation of a major coronary artery), the dependence on LVEDP mediated against its use as an index of contractility.

The index of contractility we have chosen and used in this series of studies is the rate of change of ventricular pressure normalized for changes in muscle length. This normalization is achieved by dividing max LV \( \frac{dP}{dt} \) by the instantaneous developed pressure (actual pressure—LVEDP) at the moment of max LV \( \frac{dP}{dt} \). The resulting index: max LV \( \frac{(dP/dt)}{IP} \) was first described by Veragut and Krayenbühl (1965), but although they stated that this index was independent of changes in LVEDP, their evidence was based on a small number of experiments. Our studies (Gersh, 1970) confirmed their statement, and we found that in 14 experiments in dogs whose heart rates were maintained constant by atrial pacing, changes in LVEDP from a mean value of 6.4 mm Hg to 14.8 mm Hg were associated with changes of less than 2% in \( (dP/dt)/IP \), whereas \( dP/dt \) simultaneously changed by an average of 28%. By contrast, inotropic influences caused marked changes in \( (dP/dt)/IP \). Maximal stimulation of the right and left sympathetic nerves to the heart (ansa subclaviae) in 9 dogs caused an average increase of more than 100% in \( (dP/dt)/IP \), and increases of similar magnitude were observed during infusions of noradrenaline, isoprenaline, or calcium gluconate in the same animals. Max LV \( (dP/dt)/IP \) was altered by only 5% in response to increasing heart rate by atrial pacing from 123 to 169 beats/min in 16 experiments. These experimental validations of max LV \( (dP/dt)/IP \) as an index of contractility were supported by theoretical justifications based on the equivalence of this index to the maximal velocity of shortening \( (V_{\text{max}}) \) of the isolated papillary muscle (Siegel, et al., 1964; Mason, 1969; Gersh, 1970; Taylor, 1970).

Another index, the maximum acceleration of blood in the aorta (Noble, 1965; Noble, Trenchard, and Guz, 1966a), was also used simultaneously in some of the studies presented in this paper, and although at the time, no comparable validation of this index was attempted, recent comparisons (Foex and Prys-Roberts, unpublished observations) show a strong and significant correlation between maximal aortic acceleration and max LV \( (dP/dt)/IP \) \((r=0.675; P<0.001)\). Because maximal aortic acceleration cannot occur before aortic valve opening (and therefore cannot be a direct measure of the velocity of shortening of the ventricular muscle, which occurs during the period of isometric contraction), we have regarded this index as a second order approximation. A third index: max \( (dP/dt)/PCIP \) (Mason, 1969) was used for a specific reason. PCIP stands for peak common isovolumic pressure; that is, if measurements are made under two different conditions, the appropriate value of \( dP/dt \) is divided by the highest ventricular pressure common to both conditions. This index, although sensitive to changes in end-diastolic fibre length, is useful for comparing situations in which max \( dP/dt \) occurs after aortic valve opening.

Other indices, which we rejected, have also been used to quantify contractility: \( (dP/dt)/IIT \) (Siegel and colleagues, 1963; Smith and Schwede, 1969), \( (dP/dt)/KP+c \) (Mason, Spann and Zelis, 1968; Shimosato, 1969). We found these indices to be either less sensitive or difficult to calculate with any degree of accuracy or consistency without on-line digital computation. Indices based on the time course of the phases of systole, while attractive as non-invasive indices applicable to the study of man, were rejected for the same reasons. We found that measurements of the pre-ejection period (PEP) and its derivatives (Weissler, Feeler, and Roehill, 1961) correlated poorly with simultaneous measurements of max LV \( (dP/dt)/IP \) in the anaesthetized dog, and have also been shown to be influenced by changes of aortic pressure, LVEDP, and conduction abnormalities (Weissler, Harris, and Schoenfeld, 1969).

**Theoretical considerations regarding the dynamics of left ventricular ejection.**

If we consider the left ventricle at the end of diastole, the volume of blood contained within its cavity determines the end-diastolic fibre length. The volume and pressure within the ventricle are related by its compliance, which reflects the elastic, viscous, and inertial properties of the ventricular wall (Noble, et al., 1969). Most of the published evidence suggests that the diastolic compliance of the left ven-
tricle is not altered by inotropic stimuli (Noble et al., 1969) nor by the administration of halothane (Hamilton, et al., 1966; Gersh, 1970). Thus the measurements of left ventricular end-diastolic pressure (LVEDP) within the range measured in the present study were proportional to changes in end-diastolic volume.

During isometric contraction the ventricle is a closed chamber, whose shape is best approximated by a prolate ellipsoid; that is, an ellipse rotated about its major axis (Wong and Rautaharju, 1968; Stockert, 1969; Hood, et al., 1969). Thus although the myocardial fibres are orientated in all directions, the circumferential fibres behave in such a way that the tension developed is maximal at the equator of the ellipsoid (Wong and Rautaharju, 1968) and the contractile power and energy are similarly disposed (Stockert, 1969). As the force developed by the contracting muscle increases, the pressure in the ventricle rises, and its rate of change (dP/dt) is directly proportional to the rate of change of force (dF/dt) and is closely related to the velocity of shortening of the contractile element of the muscle fibre (Mason, Spann and Zelis, 1968; Stockert, 1969; Gersh, 1970; Taylor, 1970). The energy developed by the contracting sarcomeres is stored during this period as potential energy in those elastic parts of the ventricular fibres which are functionally in series with the contractile elements. The process may be likened to a mass (equivalent to that of the volume of blood contained in the ventricle) held in contact with a spring which is tensed by a force equivalent to that generated by the contracting sarcomeres. The total force generated is dependent not only on the end-diastolic fibre length, and on the contractility of the muscle, but also on the time available, and alterations in the impedance to ejection will have a significant effect on the developed force, because the duration of isometric contraction will be greater (Goodyer, Goodkind and Landry, 1962).

When the pressure gradient across the aortic valve (PLV–Paorta) is greater than 0, then the valve opens and the ejection of blood commences. The pulsatile ejection of a non-Newtonian fluid into a vessel of complex geometry and elastic properties precludes the traditional application of the Poiseuille relationship between pressure and flow. This was emphasized by the work of Peterson (1954) and a series of studies by Spencer and his colleagues (1956; 1958; 1962). They demonstrated a positive pressure gradient between the left ventricle and the aorta during the first 35–45% of systole, and a negative pressure gradient during the remainder (fig. 1). During the first part of ejection there is a rapid rise in the acceleration and velocity of blood in the aorta, and in aortic pressure, but despite the large positive pressure gradient, little bulk flow occurs and only about 5–10% of the final stroke volume is ejected (fig. 1). This is characteristic of a system having inertia and is analogous with an electrical circuit having inductance (Noble, et al., 1967). If we accept that viscous losses are insignificant, then, according to Newton’s Second Law of Motion, in a purely inertial system, acceleration is dependent on the force acting on the mass of blood, and the product of this force and the time during which it acts is the impulse, or change in momentum. Thus the rate of change of momentum is equal to the force producing it.

![Fig. 1. Inter-relationships of pressure and flow during left ventricular ejection. Note the changing pressure relationships between left ventricular and aortic pressure throughout the ejection period, where the maximum positive pressure gradient is related to the maximum acceleration of blood in the aorta. Note also that during this period of positive pressure gradient, less than 15% of the stroke volume has been ejected, and that the bulk of flow occurs against the pressure gradient.](image)
The prime result of this early phase of ejection is that the ventricular impulse, which is dependent on the force of myocardial contraction, imparts momentum to the blood in the left ventricle and aorta, which thus acquires sufficient kinetic energy to overcome the inertia which provides the major contribution to the impedance to ejection during this phase (Wilcken, et al., 1964; Noble, Trenchard and Guz, 1966a; Noble, 1958).

The majority of the stroke volume is ejected during the later phase of ejection against the pressure gradient (fig. 1), while the blood is decelerating. At this time, the active state of the contracting myocardial sarcomere is declining in intensity, and shortening of the whole muscle is largely achieved by shortening of the series elastic elements (the spring) of the muscle as pressure and tension in the ventricular wall decrease. That active contraction of the contractile elements contributes little at this stage of ejection was demonstrated by Noble (1968), in that occlusion of the aorta during the later stages of ejection resulted in a fall in ventricular pressure as opposed to the rise which occurred in response to aortic occlusion during the inertial phase of ejection. Thus during the later part of ejection, the bulk of flow into the aorta is the result of the momentum and kinetic energy acquired during the earlier phase. The volume of blood which is ejected during any given beat, and its distribution within the arterial system, will be governed by the dissipation of this energy, largely in overcoming the viscous resistance to flow through the vascular bed. The total hydraulic impedance to flow is a complex function (McDonald, 1960) and is represented by the ratio of oscillatory pressure to oscillatory flow. The mean systemic vascular resistance (ratio of mean pressure to mean flow) is the dominant term of this impedance, but whereas the impedance to pulsatile flow is a significant fraction of the total impedance in the pulmonary artery (Bergel and Milnor, 1965), the role of pulsatility in the aorta is of much less significance (Gersh, Prys-Roberts, Reuben and Schultz, 1972). Thus the mean systemic vascular resistance, representing the hydraulic load against which the left ventricle ejects, is seen to be a major determinant of ventricular performance (Sonnenblick and Downing, 1963; Wilcken et al., 1964; Noble, Trenchard and Guz, 1966b; Stockert, 1969). Left ventricular performance is thus determined by the interaction between the contractile energy produced by the ventricular muscle, its transfer to the mass of blood, and the dissipation of the resulting kinetic energy in overcoming the hydraulic impedance of the systemic vascular bed. The purpose of this paper is to provide evidence that the predominant cardiovascular effect of halothane can be explained in terms of this hypothesis.

METHODS

Unpremedicated mongrel dogs weighing between 10 and 28 kg were induced with thiopentone sodium 10 mg/kg and subsequently maintained in a state of basal narcosis with chloralose 100 mg/kg and urethane 500 mg/kg. The trachea was intubated, and ventilation with oxygen enriched air (approximately 40% O<sub>2</sub>) was controlled by intermittent positive pressure ventilation by an East-Radcliffe ventilator using high tidal volumes (25 ml/kg). A mechanical dead-space of between 400 and 600 ml was interposed between the ventilator and the tracheal tube, and further small amounts of carbon dioxide were added to the inspired gas mixture in order to maintain arterial P<sub>co2</sub> at a constant level for each animal within the range 38–44 mm Hg. Samples of arterial blood were analysed for P<sub>ao2</sub>, P<sub>co2</sub>, pH, haematocrit, and haemoglobin concentration at regular intervals throughout the study, and small infusions of sodium bicarbonate were used to combat minor degrees of non-respiratory acidosis before commencement of the experimental protocol. Oesophageal temperature was measured with a thermistor in the region of the left atrium, and blood temperature was measured with a similar thermistor inserted through the external jugular vein into the superior vena cava. The animals' temperatures were maintained at 36°–37°C by a warming pad, and towels. Midline sternotomy was performed, and after opening the pericardium and dissecting the fatty tissues around the ascending aorta, an electromagnetic flow transducer (Statham M 4001) was implanted on this vessel. The transducer was selected so that its internal diameter was about 5% smaller than the external diameter of the aorta as measured with calipers, and each transducer was tested to ensure that axial rotation of the transducer around the aorta produced no significant change in zero baseline nor in the measured peak velocity. The transducer was energized, and its output current demodulated using a phase sensitive sine wave flowmeter. The amplitude/frequency response of this custom-built instrument was flat (±5%) to 40 Hz, and phase lag was negligible within this range (Reuben, 1970). The output of this instrument was fed into a level-shifting buffer amplifier (Type 141C, Analog Devices) so that the
zero velocity signal during late diastole could be set to read 0 volts on a Tektronix 549 storage oscilloscope. The buffered signal was then fed into a comparator/integrator circuit (Types 350 and 141C, Analog Devices) which integrated all positive voltages, thus representing the stroke volume for each beat (fig. 1). The mean difference between 20 stroke volumes determined in this way, and the same volumes determined by planimetry of the velocity signal, was less than 0.1 ml (SD 0.6 ml). The stroke volume obtained from the flowmeter was scaled to the mean stroke volume obtained by a number of dye dilution curves (indocyanine green) in each animal (fig. 2). The buffered flowmeter signal was also fed into a differentiating circuit (Gersh, Hahn and Prys-Roberts, 1971) to provide a continuous record of aortic acceleration.

A stiff, wide-bore teflon cannula, connected by a metal three-way stopcock to a Statham P23De strain gauge transducer, was inserted into the cavity of the left ventricle through a stab incision in the apex of the ventricle. The amplitude/frequency response of this system was tested before and after each experiment using a sine wave hydraulic pressure generator (Gersh, 1970), and found to be consistently flat (±5%) to better than 60 Hz. The details of the stringent dynamic characteristics required for recording of the left ventricular pressure and its first derivative (dP/dt) were described in detail by Gersh, Hahn, and Prys-Roberts (1971). Left ventricular pressure was amplified and subsequently electronically differentiated using a similar circuit to that used for aortic acceleration. A 14-cm teflon catheter (i.d. 1.2 mm) was retrogradely introduced into the ascending aorta through the left internal mammary artery, and its tip positioned at the same site as the flow transducer. Aortic pressure was measured with a Statham P23De transducer. A catheter of similar dimensions was inserted into the left atrium through its appendage, and atrial pressure recorded with an Elema-Schonander EMT 33 transducer. Ventricular and aortic pressure transducers were at the same level, and were calibrated against the same pressure reference, and the gain of their respective amplifiers matched on the recording paper. Left ventricular end-systolic and end-diastolic pressures were obtained by expanding the gain of the left ventricular pressure signal on a separate channel (fig. 1). All variables, together with the electrocardiogram and time signal, were recorded on an eight-channel ink-jet recorder (Elema-Schonander EM 81) and some were simultaneously recorded at much slower paper speeds on a Devices M4 recorder. Instantaneous heart rate was monitored and recorded from a Neilson cardiotachometer (Devices Instruments Ltd) triggered from the R-wave of the e.c.g.

In most of the animals studied, both vagus nerves were divided in the neck in order to interrupt the efferent pathway of reflexes involving the parasympathetic nervous systems. The sympathetic chains between T1 and T4 were dissected on both sides, and together with the stellate ganglia were divided from all nervous connections other than the ansae subclaviae and cardiac sympathetic nerves (Mizeres, 1958). These nerves were preserved for stimulation experiments described in a subsequent publication (Gersh, Prys-Roberts and Baker, 1972). Pacing electrodes were sutured to the right atrial appendage and connected to a square wave stimulator for control of heart rate.
Experimental protocol.

Following the surgical preparation, the animals were allowed to settle for a period of between 60 and 90 minutes, during which time the temperature, acid-base state, arterial oxygenation, and haemoglobin concentration were measured and stabilized, and approximately 250–300 ml of warmed lactated Ringer solution was infused to offset the minimal blood loss occasioned by surgery. Supplementary doses of chloralose/urethane were given during this period but never less than 30 minutes before the control measurements which were made when the animal was judged to be in a steady state. A complete set of records was obtained with the animal un-paced, and a further set during atrial pacing at a rate of about 140 per minute. Ventilation was stopped for a period of 15–20 seconds during recording. A sample of arterial blood was withdrawn for blood gas analysis and haematocrit.

Halothane was administered from a Dräger Halothane Vapor (Drägerwerk, Lübeck) with 40% oxygen in air as the carrier gas. The concentration of halothane in the inspired gas (1.0 or 1.5%) and the expired gas was measured with an ultraviolet analyser (Hook and Tucker Ltd) which had been accurately calibrated against a Rayleigh refractometer. Haemodynamic measurements at the controlled and uncontrolled heart rates were made at intervals up to 30 minutes after the commencement of halothane administration, at which time a complete set of recordings was taken, and samples of arterial blood withdrawn. After completion of measurements, halothane was discontinued and a second set of control measurements was obtained one hour after withdrawal. In three of the animals, halothane was not withdrawn, but ouabain was administered, and the effects on the depression of myocardial contractility by halothane were assessed (Gersh, 1970). In two animals, after reaching the second control set of measurements, the experiment was repeated using a higher concentration of halothane in the inspired gas mixture (1.8–2.0% halothane).

In some animals, the effects on stroke volume of deliberately increasing or decreasing the systemic vascular resistance and aortic impedance were studied before and during the administration of halothane. In one dog, trimetaphan (Arfonad) was infused in a dose of 10 mg intravenously. In two other dogs, the changes of SVR were produced by intra-aortic (descending) infusion of acetylcholine (10 μg) or phenylephrine (25–100 μg), both before and after the administration of halothane.

RESULTS

The effects of administration of halothane on 12 occasions in 10 dogs are summarized in table I. Heart rate was maintained constant in each animal by atrial pacing at a rate of about 140 per minute. In 10 experiments, a significant decrease of 12 beats/min (P<0.01) of the unpaced spontaneous heart rate occurred. Halothane significantly reduced systolic, mean and diastolic arterial pressures, and these changes reflected significant reductions of stroke volume, since there was no significant change in the mean value of SVR. All the measured indices (max LV dP/dt; max LV (dP/dt)/IP; max LV (dP/dt)/PCIP; and maximal aortic acceleration) indicated a significant reduction of myocardial contractility, the magnitude of which varied from 21% reduction of (dP/dt)/IP to between 33 and 44% of the others. While there was no significant change in LVEDP or mean left atrial pressure, early diastolic pressure (EDP) was significantly increased, as was the difference between early and end-diastolic pressures (LVEDP–EDP). Peak aortic velocity was significantly reduced. In 9 animals in whom measurements were made after withdrawal of halothane, with the exception of EDP, all variables returned to within 5% of control (table I).

While stroke volume and max LV (dP/dt)/IP decreased together in every animal, the changes of these variables correlated poorly. Although the mean values for SVR before and during halothane administration were similar, in individual animals SVR showed small but distinct changes in both directions. It was observed that in those animals in whom SVR increased in association with halothane anaesthesia, the reduction of stroke volume was markedly greater than in those animals in whom the SVR fell (fig. 3). There was a much stronger correlation between the change in stroke volume per unit change of contractility (dP/dt)/IP and the change of SVR (fig. 4). A strong correlation was observed between the changes in aortic acceleration and those of stroke volume (fig. 5).

The immediate effects of trimetaphan (table II) show that this agent markedly reduced SVR and LVEDP without changing max LV (dP/dt)/IP. This reduction of hydraulic load was associated with an 85% increase in stroke volume and a 28% increase in peak aortic velocity. Ninety seconds after the initial fall in blood pressure, the haemodynamic effects were completely different and probably attributable to the histamine-releasing effects of this agent in a sensitive species. It was noted that at the very low aortic diastolic pressures encountered...
**TABLE I. Summary of the haemodynamic effects of halothane (1%) in 12 experiments in 10 dogs. Heart rate maintained constant by arterial pacing. Mean values are shown with SD in brackets.**

<table>
<thead>
<tr>
<th></th>
<th>Control chloralose/urethane</th>
<th>During administration of halothane</th>
<th>After recovery from halothane (mean of 9 experiments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>139 (12)</td>
<td>139 (12)</td>
<td>139 (12)</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>126 (12)</td>
<td>89 (16)</td>
<td>128 (7)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>99 (11)</td>
<td>68 (12)</td>
<td>98 (5)</td>
</tr>
<tr>
<td>Mean</td>
<td>108 (11)</td>
<td>75 (14)</td>
<td>108 (5)</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6.1 (1.5)</td>
<td>6.4 (1.7)</td>
<td>n.s. 6.1 (1.2)</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>3.3 (1.9)</td>
<td>4.7 (2.0)</td>
<td>** 3.7 (1.3)</td>
</tr>
<tr>
<td>LVEDP-EDP (mm Hg)</td>
<td>2.8 (0.7)</td>
<td>1.7 (0.7)</td>
<td>*** 2.8 (0.9)</td>
</tr>
<tr>
<td>LV max (dP/dt) (mm Hg/sec(^{-1}))</td>
<td>2140 (370)</td>
<td>1190 (230)</td>
<td>*** 2080 (360)</td>
</tr>
<tr>
<td>LV max (dP/dt)/IP (sec(^{-1}))</td>
<td>42 (8)</td>
<td>33 (6)</td>
<td>*** 42 (7)</td>
</tr>
<tr>
<td>Peak aortic flow (ml sec(^{-1}))</td>
<td>150 (36)</td>
<td>110 (22)</td>
<td>*** 150 (27)</td>
</tr>
<tr>
<td>Max aortic acceleration (ml sec(^{-2}))</td>
<td>3987 (1624)</td>
<td>2516 (813)</td>
<td>** -</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>17 (4)</td>
<td>12 (2)</td>
<td>*** 17 (3)</td>
</tr>
<tr>
<td>Cardiac output (ml min(^{-1}))</td>
<td>2300 (520)</td>
<td>1630 (350)</td>
<td>*** -</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne sec cm(^{-5}))</td>
<td>3900 (800)</td>
<td>3700 (600)</td>
<td>n.s. 3700 (700)</td>
</tr>
</tbody>
</table>

LVEDP Left Ventricular End-Diastolic Pressure
EDP Left Ventricular Early Diastolic Pressure
Statistical Comparisons: Paired two-tailed t test.
- n.s. not significant
- \* P<0.05
- ** P<0.01
- *** P<0.001

**TABLE II. Haemodynamic changes produced by infusion of trimetaphan (10mg) in one dog maintained at a constant heart rate of 138 beat/min.**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>After 60 sec</th>
<th>After 3 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>111</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>Diastolic</td>
<td>90</td>
<td>29</td>
<td>524</td>
</tr>
<tr>
<td>Mean</td>
<td>97</td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6.3</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>7.0</td>
<td>5.0</td>
<td>4.6</td>
</tr>
<tr>
<td>LV max dP/dt (mm Hg/sec(^{-1}))</td>
<td>1500*</td>
<td>930*</td>
<td>810*</td>
</tr>
<tr>
<td>LV max (dP/dt)/IP (sec(^{-1}))</td>
<td>33</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>LV max (dP/dt)/PCIP (sec(^{-1}))</td>
<td>86</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Stroke volume ml</td>
<td>7</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Peak aortic flow (ml sec(^{-1}))</td>
<td>85</td>
<td>109</td>
<td>88</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne sec cm(^{-5}))</td>
<td>6890</td>
<td>1670</td>
<td>1630</td>
</tr>
</tbody>
</table>

*Max dP/dt occurred after aortic valve opening.

**FIG. 3. Relationship between the changes of stroke volume and those of systemic vascular resistance during halothane anaesthesia.**
during the administration of trimetaphan, max LV dP/dt occurs after aortic valve opening, and no longer has any validity as an index of contractility. The haemodynamic responses to intra-aortic infusion of acetylcholine, before and after the administration of halothane, are characterized in figures 6 and 7. During chloralose/urethane narcosis, intra-arterial infusion of acetylcholine consistently reduced aortic diastolic pressure without altering max LV dP/dt or max LV (dP/dt)/IP or maximal aortic acceleration. In two dogs, stroke volume increased by an average of 16% at a constant heart rate, in association with a mean reduction of SVR from 3190 to 1455 dyne sec cm\(^{-5}\). During administration of halothane, the baseline values of most variables were lower, and intra-arterial infusion of acetylcholine (10\(\mu\)g) consistently reduced aortic pressure without altering the indices of contractility. There was a greater increase in stroke volume (+27%) at a constant heart rate during halothane administration, though the average reduction of SVR was similar to that in the control state (2940 falling to 1451 dyne sec cm\(^{-5}\)).

The haemodynamic responses to intra-arterial infusion of phenylephrine are characterized in figures 8 and 9. During chloralose/urethane narcosis the immediate effects of phenylephrine (25\(\mu\)g) were to increase aortic diastolic pressure and to cause a 14% decrease in stroke volume despite a 2 mm Hg rise of LVEDP. No consistent changes of max LV dP/dt or max LV (dP/dt)/IP were observed. After this initial effect, a secondary response was observed, where the increased aortic pressures were associated with an increase in stroke volume at a constant heart rate secondary to a marked increase in LVEDP (+12 mm Hg), but without any change in contractility. Thus the undepressed myocardial muscle was able to increase its force of contraction in response to an increased load (heterometric autoregu-
EFFECTS OF HALOTHANE ON INTERACTIONS

CONTROL

ACETYLCHOLINE

FIG. 6. Haemodynamic response to acute reduction of aortic impedance by the intra-arterial infusion of acetylcholine during chloralose/urethane narcosis. Note that despite a large decrease in aortic pressure, max LV dP/dt occurred marginally before aortic valve opening (as evidenced by the onset of flow) but was also unchanged. Aortic acceleration was slightly decreased, but stroke volume increased by 16%.

Fig. 7. Haemodynamic response to reduction of aortic impedance due to intra-arterial infusion of acetylcholine during halothane anaesthesia. Compare the absolute values of each variable with those in figure 6 (same animal). Although the indices of myocardial contractility were depressed by halothane, no changes occurred in response to the decrease in aortic impedance and diastolic pressure, but stroke volume increased by 27%.

DISCUSSION

The experimental findings during steady-state halothane anaesthesia were compatible with the hypothesis that halothane depressed the contractility of the myocardium in intact animals, and that despite a marginal increase in end-diastolic fibre length, the total force of contraction was markedly reduced. If under these circumstances, SVR had also decreased, then the stroke volume and cardiac output could have been maintained at or slightly below the control level. However, under the conditions of the present studies, in which halothane was administered to an animal maintained at a constant temperature, a normal acid-base state, and during IPPV, no significant or consistent changes in SVR occurred, and the stroke volume fell. This reduction of stroke volume was, then, the result of the interaction between reduced blood momentum during ejection and the unaltered hydraulic load of the ventricle, the former...
CONTROL

10 sec. after infusion of phenylephrine

30 sec. after infusion

Fig. 8. Haemodynamic response to increased aortic impedance during phenylephrine infusion under chloralose/urethane narcosis. The centre panel shows the immediate response of the undepressed heart to an increased load. Contractility remained unaltered. LVEDP was marginally increased, but stroke volume decreased by 14%. The right hand panel shows the subsequent effect of the raised end-diastolic volume (LVEDP increased by 8 mm Hg), where stroke volume increased 15% over the control. Although LV (dP/dt)/IP and aortic acceleration had not altered.

Control during halothane anaesthesia

30 sec. after infusion of phenylephrine

Fig. 9. Haemodynamic response to increased aortic impedance due to phenylephrine infusion during halothane anaesthesia. Despite a marked increase in LVEDP (9 mm Hg), stroke volume fell by more than 50%, with no obvious changes in contractility.

The interaction of contractile energy, hydraulic impedance and the stroke volume.

From the classical work of McDonald (1960), Wilcken et al. (1954), Noble and colleagues (1966a; 1966b), Noble (1968), and Stockert (1969), we may surmise that the true hydraulic load against which the ventricle ejects is the impedance to oscillatory flow rather than the aortic diastolic pressure, since pressure in the vascular system is the result of blood flow and not vice versa. Since the mean SVR is the predominant term of impedance, it represents a more appropriate term than the aortic pressure alone being the direct result of reduced power and energy storage during the phase of isometric contraction. The subsequent experiments to increase or decrease the hydraulic impedance without changing the myocardial contractility, and the simultaneous effects on stroke volume strongly supported the hypothesis, especially since the response of the halothane depressed myocardium was so much more enhanced by a reduction of SVR than that of the undepressed heart. Similarly, the drastic effect on the ejection of the halothane-depressed ventricle, caused by the raised hydraulic impedance as a result of phenylephrine infusion, also supported the hypothesis. Can previous studies in both man and animals be correlated with this hypothesis, particularly with regard to the effects of halothane and other anaesthetic agents?
EFFECTS OF HALOTHANE ON INTERACTIONS

(Sonnenblick and Downing, 1953). The key to the relationships that we have discussed is the transformation of chemical into mechanical energy by the myocardial cell, its storage during isometric contraction, its transformation into kinetic energy during ejection, and finally the dissipation of this energy, to a small extent in overcoming the inertia of blood in the aorta, but predominantly in overcoming the viscous resistance to blood flow through the vascular bed. Based on current concepts of myocardial contractility derived from the force/velocity relation of isolated cardiac muscle, Stockert (1969) used a hybrid computer to derive a theoretical relationship for the interaction of contractile power and energy density, the hydraulic impedance of the systemic vascular bed, and the stroke volume, and compared the predictions obtained from the computer program with the results of an experimental investigation in the dog. The computer program allowed for the pre-load (LVEDP) and heart rate to be kept constant, the aortic input impedance to be variable but related to aortic size and the mean systemic vascular resistance, and the contractile power density to be the input function. Thus he was able to compare the effect on stroke volume, of altering the impedance at a constant level of contractility and vice versa. Not only did he obtain an excellent correlation between his theoretical solution and his experimental results, but also with the findings of the present study. The only important difference between his studies and ours was in the method by which myocardial contractility was reduced; he used myocardial ischaemia induced by a period of coronary occlusion, whereas we used the pharmacological effects of halothane. Our results concerning the effects of halothane on left ventricular energetics and aortic input impedance (Gersh, 1970) will be published separately (Gersh, Prys-Roberts, Reuben and Schultz, 1972).

Effects of halothane on myocardial contractility.

Most of the published evidence that halothane depresses the contractility of both the isolated muscle and the intact heart have already been cited, and the results of the present study serve to confirm both the direction and magnitude of these changes, and the results of more recent studies (Rusy, Moran and Fox, 1970; Gil-Rodriguez, Hill and Lundberg, 1971). We also confirm the finding that in alveolar concentrations above 0.6%, halothane does not cause a decrease in left ventricular end-diastolic pressure or volume. During anaesthesia with concentrations of halothane of the order of 0.5% or less, and during the first few minutes of the administration of higher concentrations (1.0–1.5%), LVEDP may fall transiently (Gander et al., 1965; Goldberg, 1965; Hamilton et al., 1966). Nevertheless the concept that the fall in cardiac output during halothane anaesthesia is caused by decreased cardiac filling does not merit serious consideration, and the evidence is scanty. Gander and colleagues (1965) found a 10% decrease in left ventricular end-diastolic volume during anaesthesia with 0.5% halothane in dogs, but this was accompanied with a marked and unexplained increase in heart rate (which would tend to decrease end-diastolic volume) compared with the control state, a most unusual response to halothane. Hamilton and his colleagues (1966) also found a 10% reduction of LVEDP and volume during anaesthesia with 0.6% halothane, but this was accompanied by a marked decrease in the ratio of the ejected stroke volume to the end-diastolic volume. Calculations from their data suggest that had this ratio been unchanged, the reduction of the end-diastolic volume would have reduced cardiac output by a mere 7% compared with the 41% reduction actually observed. Thus, while a reduction of end-diastolic volume may transiently contribute to the reduction of stroke volume and cardiac output (the Frank-Starling mechanism), there is little doubt that this effect is secondary to a redistribution of blood in the systemic capacitance vessels since the reduction of myocardial contractility occurs very rapidly. Our observations of the time course of the changes of dP/dt and of maximum aortic acceleration confirm those of Eisele and colleagues (1969). They noted a decrease in aortic acceleration within 8 seconds of administering either halothane, or nitrous oxide, and could not detect any difference between the responses of intact dogs, and those in which cardiac denervation had been performed. The halothane depressed ventricle is characterized by a failure to empty rather than a failure to fill.

Relevance to the clinical use of halothane.

Despite the difference in species and the complexity of the animal preparation, the observed changes in heart rate (unpaced), systemic arterial pressures, cardiac output and mean systemic vascular resistance agree in both direction and magnitude (making due allowance for differences in weight) with many studies of halothane anaesthesia in man (Severinghaus and Cullen, 1958; Kutoba and Vandam, 1962; Prys-Roberts et al., 1968; Shinozaki,
BRITISH JOURNAL OF ANAESTHESIA

Mazuzan and Abajian, 1968; Eger et al., 1970). There is little evidence that, in man, the arterial hypotension so characteristic of halothane anaesthesia results from a decrease of systemic vascular resistance, although the observation of cutaneous vasodilatation led many clinicians to imply the existence of widespread vasodilation and a fall of systemic vascular resistance. That a fall of SVR can occur during halothane anaesthesia with spontaneous ventilation is not in doubt (Payne, Gardiner and Verner, 1959; Virtue et al., 1962; Deutsch et al., 1962, Lundborg, Rahimtoola and Swan, 1967), but in these studies, moderate to severe hypercapnia almost certainly accounted for both the reduced SVR and the maintained or increased cardiac output (Prys-Roberts et al., 1968).

The most practical and clinically relevant aspect of these studies concerns the introduction of additional loads to a heart already depressed by halothane. This may occur during hyperoxia (Shinozaki, Mazuzan and Abajian, 1968), hypacapnia (Prys-Roberts et al., 1968) or hypovolaemia leading to an increase in SVR. It is particularly relevant to the hypertensive patient whose SVR is usually high, and in whom stimuli which cause arteriolar constriction during halothane anaesthesia may cause a severe hypotension and marked reduction of cardiac output, leading to myocardial ischaemia (Prys-Roberts and colleagues, 1971a, 1971b, 1972). Attempts to raise the arterial pressure during halothane anaesthesia by the use of pressor amines (Wyant et al., 1958; Mahaffey et al., 1961) or synthetic octapeptides (Valentin and Nielsen, 1969) may have drastic effects on the stroke volume and cardiac output as exemplified in figure 9.

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EFFECTS OF HALOTHANE ON INTERACTIONS


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Die Wirkungen von Halothan auf die Wechselwirkungen zwischen Kontraktilität des Myokards, dem Widerstand der Aorta und der Leistung des linken Ventrikels

I: Theoretische Überlegungen und Ergebnisse

Zusammenfassung

LOS EFECTOS DEL HALOTANO SOBRE LAS INTERACCIONES ENTRE CONTRACTILIDAD MIOCARDICA, IMPEDANCIA AORTICA Y RENDIMIENTO VENTRICULAR IZQUIERDO

RESUMEN
Los efectos del halotano (1,0–1,5%) sobre la contractilidad miocárdica, resistencia vascular sistémica (que representa la mayor parte de la impedancia al flujo) y el rendimiento ventricular izquierdo, y las interacciones de estas funciones han sido estudiados en perros con pecho abierto, ventilados artificialmente y mantenidos en un estado de narcosis basal con cloralosa y uretano. El halotano deprimió de forma reversible la contractilidad miocárdica valorada mediante tres índices: (dP/dt) ventricular izquierda máxima/IP, (dP/dt) ventricular izquierda máxima/PCIP, y aceleración aórtica máxima, pero no produjo cambios significativos de la presión diastólica final del ventrículo izquierdo o de la resistencia vascular sistémica. El volumen sistólico disminuyó proporcionalmente a la depresión de la contractilidad miocárdica con frecuencias cardíacas constantes mantenidas mediante marcapaso atrial, aunque la reducción del volumen sistólico fue mayor cuando la resistencia vascular sistémica aumentó ligeramente. Se postula que, independientemente de cambios menores en el venoso periférico durante la anestesia por halotano, la depresión de la contractilidad miocárdica deteriora el vaciamiento ventricular más bien que la repleción ventricular. Este concepto está basado en la observación de que como el flujo aórtico pico y aceleración son disminuidos durante la anestesia por halotano, queda reducida la fuerza que actúa sobre la sangre y el impetu que le es comunicado durante la primera fase de la expulsión ventricular. Datos experimentales han apoyado esta hipótesis y así cuando la contractilidad del miocardio era deprimida por la anestesia por halotano, cambios independientes de la resistencia vascular sistémica modificaron significativamente el gasto sistólico del corazón. Se concluye que la causa principal de la hipotensión arterial durante la anestesia por halotano es la disminución del gasto cardíaco y que el mecanismo principal que ocasiona esta disminución es la depresión de la contractilidad miocárdica.

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