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EFFECT OF CO_2 ON MYOCARDIAL CONTRACTILITY AND AORTIC INPUT IMPEDANCE DURING ANAESTHESIA

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SUMMARY

The haemodynamic responses to hypocapnia and hypercapnia have been studied in the dog during intermittent positive pressure ventilation under halothane anaesthesia (1% halothane in oxygen) and under nitrous oxide anaesthesia (30% oxygen in nitrous oxide). In the absence of significant variations of either myocardial contractility or left ventricular end-diastolic pressure, the changes of stroke volume and cardiac output (diminution because of hypocapnia, augmentation because of hypercapnia) were determined by alterations of systemic vascular resistance (augmentation because of hypocapnia, diminution because of hypercapnia).

The haemodynamic responses to changes in blood-carbon dioxide concentrations are of a complex nature and marked differences have been noted between the responses of conscious man and experimental animals, and those observed during various forms of anaesthesia. Variations of Pco_2 exert direct effects on the isolated myocardium or the isolated heart (Jerusalem and Starling, 1910; Nahas and Cavert, 1957; McElroy, Gerdes and Brown, 1958; Ng, Levy and Zieske, 1967; Pannier and Brutsaert, 1968) and on systemic vascular segments (Roddie, Shepherd and Whelan, 1957; Blair et al., 1960; Barcroft, 1963; Jung, Walsh and Hyman, 1971). Sympathetic nervous activity is also modified by changes in blood-carbon dioxide concentrations (Nahas and Ligou, 1959; Morris and Millar, 1962; Tenney and Lamb, 1965; Moster et al., 1969) and the overall circulatory response to either an increase or decrease in Pco_2 appears to be a balance between the direct effects of carbon dioxide-induced changes in blood pH, and the secondary effects of the same changes on the central and autonomic nervous systems. This is particularly relevant during anaesthesia, since the sympathoadrenal response to changes in Pco_2 may be enhanced or suppressed by different anaesthetic agents (Price et al., 1959; Price, 1966).

It is generally agreed that in conscious man and in conscious dogs, hypercapnia induces an increase in arterial pressure, heart rate, cardiac output and right atrial pressure, associated with a reduction of systemic vascular resistance (Dripps and Comroe, 1947; Fishman, Fritts and Cournand, 1960; Sechzer et al., 1960; Richardson, Wasserman and Patterson, 1961; Horwitz, Bishop and Stone, 1968) and an increased release of catecholamines and 17-OH corticosteroids (Sechzer et al., 1960; Morris and Millar, 1962); the implication is that the autonomic response to hypercapnia overrides any initial direct depressant effects of respiratory acidosis on the heart (Noble, Trenchard and Guz, 1967). In anaesthetized man and animals, a wide range of responses to hypercapnia has been observed depending on whether ventilation was spontaneous or controlled, on the choice of anaesthetic agent, and on the resultant modification of sympathoadrenal responses (Price et al., 1960; Auld et al., 1962; Manley, Nash and Woodbury, 1964; Carson et al., 1965; Prys-Roberts et al., 1967, 1968; Morgan et al., 1967; Cullen, Eger and Gregory, 1969; Cullen et al., 1971). While these studies have shown the general cardiovascular responses, they have given little indication on the effects of hypercapnia and hypocapnia on myocardial contractility, or to the behaviour of the left ventricle as a pump whose performance is modified by changes in the load imposed by the systemic vasculature (Wilcken et al., 1964).

In conscious man, hypocapnia has usually been studied in association with voluntary hyperventilation, whereas during anaesthesia hypocapnia is almost always the result of passive artificial hyperventilation. In the latter situation the cardiovascular responses to hypocapnia have been shown to be a reduction in cardiac output and stroke volume,

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negligible changes of arterial pressure and of heart rate, and increased systemic vascular resistance (Theye, Milde and Michenfelder, 1966; Prys-Roberts et al., 1967, 1968; Morgan et al., 1967). These effects of hypocapnia have been shown to be exaggerated in hypertensive patients during anaesthesia and artificial ventilation (Prys-Roberts et al., 1972a).

The present studies were performed in order to clarify the overall circulatory effects of hypercapnia and hypocapnia in dogs anaesthetized with either halothane, a potent suppressor of sympathoadrenal responses (Biscoe and Millar, 1966) or nitrous oxide. We have attempted to define the interaction of changes of Pco_2 and anaesthesia on the contractile state of the myocardium, on the distribution of energy during left ventricular ejection, and on the load to ventricular ejection expressed by the aortic input impedance. The modification of these relationships by beta-adrenergic receptor blockade has been described elsewhere (Foëx and Prys-Roberts, 1974).

METHODS

Fifteen mongrel dogs (mean weight 16.7 kg, SD 5.7 kg) were studied. Premedication consisted of morphine (0.8 mg/kg) and chlorpromazine (0.8 mg/kg). After induction of anaesthesia with thiopentone (5 mg/kg) and endotracheal intubation, anaesthesia was maintained with halothane 1% in a mixture of 30% oxygen in nitrous oxide, under constant volume IPPV using a Penlon-Oxford ventilator (Longworth Scientific Instruments Ltd, Abingdon) set to provide a nominal tidal volume of 40 ml/kg at a rate of 12/min. An infra-red carbon dioxide analyser (Hartmann and Braun URAS 4) sampled continuously from the airway and end-tidal Pco_2 was adjusted to the desired value by adding carbon dioxide to the inspired gas mixture. Oesophageal temperature was measured with a digital Thermistor thermometer (Digitec 501 NSR 1K) and maintained within the range 36.5–37.5°C by undertable heating. The electrocardiogram was recorded from standard limb leads.

Through a left lateral thoracotomy, a cuffed electromagnetic flow transducer (SEM 230 Series, SE Laboratories) was implanted around the ascending aorta and coupled to a sine-wave electromagnetic flowmeter (Type SEM 275, SE Laboratories). A short, stiff, wide-bore Teflon cannula was inserted into the left ventricular cavity through the apex, and connected to a Statham P23De pressure transducer. The amplitude/frequency response of this transducer/catheter system has been demonstrated to be flat (±5%) to 60 Hz with a negligible phase shift (Gersh, Hahn and Prys-Roberts, 1971). A 20-cm Teflon catheter was inserted through the left carotid artery and advanced until its tip lay within the ascending aorta at the level of the flow transducer. A similar catheter was inserted through the right ventricular infundibulum, and its tip advanced into the pulmonary artery. The wound was closed in such a way as to ensure minimal exposure of the intrathoracic organs during the experiments.

The flowmeter output signal ($\dot{Q}$) was integrated electronically to give beat-by-beat estimates of stroke volume (SV) and differentiated to give aortic blood acceleration ($\ddot{Q}$). The derived stroke volume was calibrated *in vivo* against simultaneous estimates of stroke volume obtained by the dye dilution technique using indocyanine green. The maximum rate of increase of left ventricular pressure (max LV dP/dt) was obtained by differentiating the left ventricular pressure signal. All these variables were recorded on an 8-channel ink-jet recorder (Elema-Schonander EM81). Max LV dP/dt was divided by the instantaneous developed pressure in the ventricle (IP) to give the index of myocardial contractility (max LV (dP/dt)/IP) which has been described by Veragut and Krayenbühl (1965) and reassessed in this department by Gersh (1970) and Prys-Roberts and colleagues (1972b).

Arterial and mixed venous blood samples were analysed at each stage of the experiment; Po_2, Pco_2 and pH were measured with conventional electrode systems using amplifiers as described by Hahn (1969, 1971). Corrections were applied for temperature and elapsed time according to Kelman and Nunn (1966) and a blood-gas difference of 1.04 was applied for Po_2.

Computations.

Systemic vascular resistance (SVR) was calculated as the ratio of mean systemic arterial pressure and cardiac output, neglecting mean right atrial pressure (McDonald, 1960; Gersh et al., 1972).

From the recorded traces, ordinates of aortic pressure and flow were manually digitized at 20-msec intervals throughout the cardiac cycle, taking the sharp increase in aortic pressure after valve opening as a reference point. The resulting values, together with the calibration constants, were transferred to punched cards and analysed on an ICL

Atlas computer (Atlas Computer Laboratory, Science Research Council, Chilton, Berks) programmed to calculate aortic input impedance spectra and the distribution of left ventricular work and power (Gersh et al., 1972). For this purpose, Fourier analysis of the aortic pressure and flow signals was carried out and the first 10 harmonics of pressure and flow were calculated. The modulus of impedance for each harmonic was calculated as the ratio of the modulus of pressure to that of flow and the phase angle was calculated as the difference of the phase angle of pressure and that of flow for each particular harmonic. The modulus of impedance at zero frequency was calculated as the ratio of mean pressure to mean flow whereas characteristic impedance was calculated as the mean of the impedance moduli between the first and the tenth harmonic (Gersh et al., 1972). Instantaneous left ventricular power was calculated as the product of instantaneous pressure and flow at each 20-msec interval and expressed in $erg.sec^{-1}$. Pressure-flow work was obtained by integrating the values of power over the period of systole and expressed in erg. Kinetic work was derived from the instantaneous velocity of blood and from the mean mass of blood ejected ($\frac{1}{2}$ mv^2). Total work was obtained by summing the values of pressure-flow work and kinetic work. Steady work was calculated as the product of mean aortic pressure and mean flow, while pulsatile work was obtained by subtracting the value of steady work from that of total work (Gersh et al., 1972).

Experimental protocol.

Following the surgical preparation, anaesthesia was modified to conform with the appropriate experimental protocol. Eight animals were studied under halothane anaesthesia (1% halothane in oxygen) and seven animals were studied under nitrous oxide anaesthesia (70% nitrous oxide in oxygen) supplemented by not more than two doses of pentobarbitone 5–10 mg. The animals were allowed to achieve a steady cardiovascular state over a period of at least 1 hr, during which the acid-base state was checked by sampling arterial and mixed-venous blood. Carbon dioxide was added to the inspiratory gas mixture in order to maintain the arterial Pco_2 at 40 mm Hg and the arterial pH was adjusted to 7.40 by infusion of small volumes of sodium bicarbonate 4.2%.

After the steady state had been achieved at Pco_2 40 mm Hg, the haemodynamic variables were recorded and arterial and mixed venous blood samples were withdrawn. Hypocapnia was obtained by withdrawing carbon dioxide from the inspired gas mixture without altering the mechanical characteristics of artificial ventilation. Records of the haemodynamic variables were taken at frequent intervals and were found to be stable after 20 min of hypocapnia. Recordings and blood samples were thus taken systematically 20 min after the concentration of carbon dioxide in inspired gas had been modified. Reintroduction of carbon dioxide in the inspired gas enabled a second normocapnic phase to be achieved, for which recordings and blood samples were taken after 20 min. Hypercapnia was obtained by increasing carbon dioxide concentration in the inspired gas so as to produce an end-tidal carbon dioxide concentration of about 10%. The 20-min period was also found to be sufficient to achieve a steady haemodynamic state following establishment of hypercapnia. Another normocapnic phase was finally recorded 20 min after the carbon dioxide concentration in the inspired gas had been appropriately reduced. At each stage records were taken while respiration was stopped (airway pressure 0 cm H_2O lung volume at functional residual capacity).

RESULTS

Effects of hypocapnia and hypercapnia on systemic haemodynamics during halothane anaesthesia.

The values of haemodynamic variables observed during hypocapnia and hypercapnia, together with the blood-gas data appropriate to each stage of the study are shown in tables I and II.

Hypocapnia. The induction of hypocapnia was associated with insignificant changes of systemic arterial pressure or of left ventricular end-diastolic pressure (l.v.e.d.p.). There was a significant reduction of stroke volume (18%), but since heart rate increased by an average of 9%, there was a consistent but insignificant decrease of cardiac output (9%). The contractile state of the myocardium was unaltered, since there were insignificant changes of max LV (dP/dt)/IP or of aortic blood acceleration. Systemic vascular resistance and aortic input impedance at zero frequency increased during hypocapnia, but the changes did not reach statistical significance. Neither the impedance moduli, nor the phase angles of the frequency-dependent components of the impedance spectrum were modified during hypocapnia (fig. 1).

The distribution of energy during left ventricu-

TABLE I. *Changes in arterial and mixed venous blood-gas values.*

A. During halothane anaesthesia in eight dogs				
	Control (normocapnia)	Hypocapnia	Control (normocapnia)	Hypercapnia
Pa_{O_2} (mm Hg)	441±34	459±37	449±29	408±33*
Pa_{CO_2} (mm Hg)	41.3±1.3	16.8±1.3†	41.1±0.7	74.1±1.2†
pHa (units)	7.383±0.023	7.673±0.040	7.349±0.020	7.139±0.013 †
B. During nitrous oxide/oxygen anaesthesia in seven dogs				
	Control (normocapnia)	Hypocapnia	Control (normocapnia)	Hypercapnia
Pa_{O_2} (mm Hg)	144±5	128±10*	143±5	143±4
Pa_{CO_2} (mm Hg)	38.9±1.0	16.2±0.6†	40.9±1.7	73.2±1.9†
pHa (units)	7.370±0.015	7.584±0.014†	7.332±0.017	7.161±0.010†

Mean values±1 SEM with significance for two-tailed Student's *t* tests: *P<0.05; †P<0.005.

TABLE II. *Haemodynamic responses to changes of Pa_{CO_2} values during halothane anaesthesia.*

	Control (normocapnia)	Hypocapnia	Control (normocapnia)	Hypercapnia
Heart rate (beats/min)	122±8	133±8*	116±8	132±8*
Aortic pressure: systolic	83±4	81±6	83±5	85±4
(mm Hg) diastolic	59±4	59±5	58±5	56±3
mean	67±4	67±5	66±5	65±3
L.v.e.d.p. (mm Hg)	3.3±0.7	3.2±0.7	3.9±0.7	4.5±1.0
Stroke volume (ml)	10.7±1.5	8.8±1.1†	10.4±1.8	11.7±2.7
Normalized cardiac output (ml/min/kg)	79.3±4.8	72.1±5.3	72.0±5.7	95.2±13.1*
Systemic vascular resistance (dyn.sec.cm^{-5})	4,570±1,484	4,990±541	5,090±742	4,080±679†
Max LV (dP/dt) (mm Hg.sec^{-1})	1,600±173	1,725±181*	1,550±177	1,750±286
Max LV(dP/dt)/IP (sec^{-1})	34.5±3.0	35.0±2.5	32.7±2.5	36.9±4.4
Peak aortic blood acceleration (ml.sec^{-2})	3,510±587	3,780±704	3,320±576	3,760±802
Peak aortic blood flow (ml.sec^{-1})	118±19	105±19	115±18	123±23

Mean values±1 SEM of eight experiments. Significances for two-tailed paired Student's *t* tests: *P<0.05; †P<0.005.

lar ejection (table III) was modified significantly during hypocapnia, in that total left ventricular work was reduced by 19%, although most (90%) of this reduction was a result of the reduction of steady work. The changes in kinetic work, while statistically significant, represented only a small fraction of the changes in pressure-flow work.

Hypercapnia. Systemic arterial pressure did not increase during hypercapnia, but cardiac output was significantly increased (29%) as a result of increased heart rate and stroke volume. The contractile state of the myocardium was not modified by hypercapnia, and although a minor increase in l.v.e.d.p. occurred, this was not statistically significant. Systemic vascular resistance was significantly reduced during hypercapnia, as was aortic input impedance at zero frequency. The frequency-dependent components of the impedance spectra were not modified by hypercapnia (fig. 2). Changes in the distribution of energy during left ventricular ejection were consistently opposite to those observed in response to hypocapnia, but did not reach statistical significance when compared with the eucapnic phase.

With the exception of the changes in heart rate, the haemodynamic responses to hypercapnia were in the opposite direction to those during hypocapnia. When the values during hypocapnia were compared with those during hypercapnia, there were significant reductions in cardiac output and stroke volume, and significant increases of systemic vascular resistance, without modification of the contractile state of the myocardium.

Effects of hypercapnia and hypocapnia on systemic haemodynamics during nitrous oxide anaesthesia.

The control values (eucapnia) of many haemo-

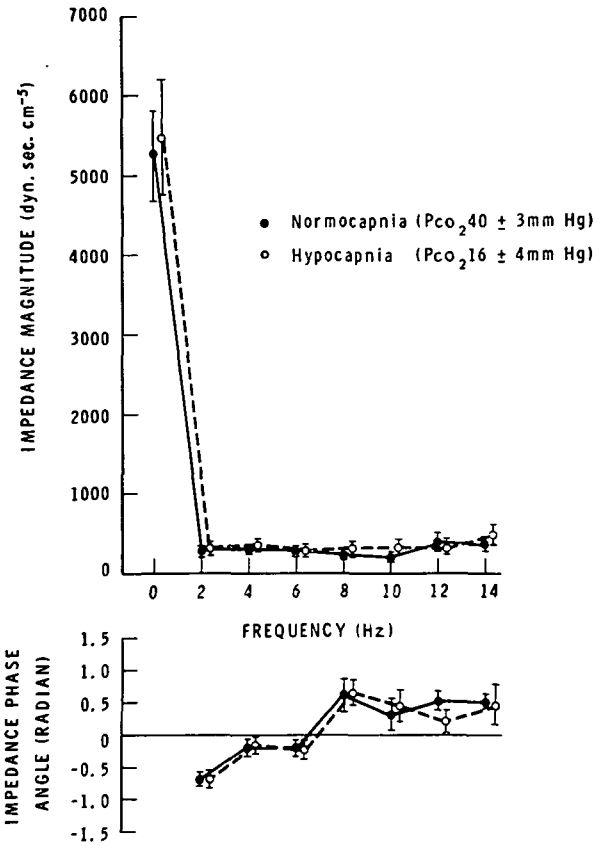

FIG. 1. Aortic input impedance spectra obtained during normocapnia (●——●) and hypocapnia (○- - - -○) under halothane anaesthesia. The values given are the mean of values (±1 SEM) obtained in six dogs and calculated for classes of 2-Hz bandwidth.

dynamic variables were higher during nitrous oxide anaesthesia than the values observed in the similar phase during halothane anaesthesia. The higher arterial pressures were the result of the increased cardiac output, since systemic vascular resistance was similar in both groups of dogs. The increased cardiac output was related to both increased heart rate and stroke volume and to an enhanced myocardial contractile state.

The haemodynamic responses to both hypocapnia and hypercapnia were small and inconsistent, and no clear-cut pattern of response could be identified (table IV). The only significant changes were the increase in cardiac output and the decrease in systemic vascular resistance during hypercapnia, both responses being similar in direction and magnitude to those observed during halothane anaesthesia.

DISCUSSION

The main purpose of these studies was to use an experimental animal model to allow invasive methods to be used to provide an explanation of the circulatory responses to changes in Pco_2 observed under two anaesthetic agents commonly used in man. We were especially interested in defining the mechanism whereby cardiac output and stroke volume decrease during hypocapnic hyperventilation in anaesthetized man (Theye, Milde and Michenfelder, 1966; Prys-Roberts et al., 1967, 1968). Furthermore, we were interested in the relationship between the circulatory response to hypercapnia and changes in left ventricular filling, since, in man, hypercapnia is associated with increased right atrial filling pressures (Prys-Roberts et al., 1967, 1968).

In order to place the present studies in the correct perspective in relation to the data available from human studies (Cullen and Eger, 1974) and

TABLE III. *Distribution of energy of left ventricular contraction.*

	Control (normocapnia)	Hypocapnia	Control (normocapnia)	Hypercapnia
Peak power (erg.sec^{-1}. 10^3)	9,961±2,904	8,112±2,461	8,586±2,437	9,123±2,528
Pressure flow work (erg. 10^3)	927±346	752±310*	803±323	827±208
Kinetic work (erg. 10^3)	23.2±16.0	14.2±9.4*	15.7±9.2	17.4±9.7
Total work (erg. 10^3)	950±360	766±317*	819±332	844±215
Steady work (erg. 10^3)	886±326	720±299*	766±301	772±174
Pulsatile work (erg. 10^3)	64.0±39.7	46.5±26.3	53.0±34.4	71.6±48.1
Kinetic work (%) / Total work	2.2±1.0	1.7±0.8*	1.8±0.6	2.0±0.8
Pulsatile work (%) / Total work	6.2±2.4	6.0±2.2	5.5±3.4	7.8±4.2
Kinetic work (%) / Pulsatile work	40.8±10.1	32.1±10.8	35.8±8.0	28.5±12.1

Mean values ±1 SEM of six experiments. Significance for paired two-tailed Student's *t* tests: *P < 0.05.

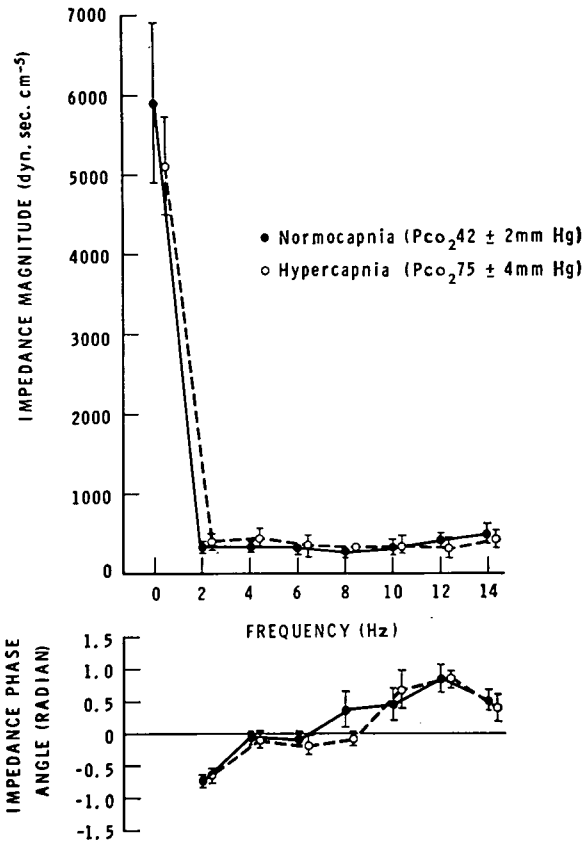

FIG. 2. Aortic input impedance spectra obtained during normocapnia (●——●) and hypercapnia (○- - -○) under halothane anaesthesia. The values given are the mean values (±1 SEM) obtained in six dogs and calculated for classes of 2-Hz bandwidth.

from previous studies in animals, it is important to consider the basic cardiovascular state of the animals in the eucapnic (control) stages of this study. These animals showed a marked degree of circulatory depression characteristic of animals studied immediately after completion of a major surgical procedure; their cardiovascular state was comparable to that of animals studied by Gersh (1970) and Prys-Roberts and colleagues (1972a,b). The indices of myocardial contractile state (max LV dP/dt, and max LV (dP/dt)/IP) indicate a marked impairment during anaesthesia with 1% halothane, associated with a low cardiac output and a high systemic vascular resistance. By contrast, our more recent studies of animals, in which the flow and pressure transducers had been implanted some days previously (Roberts et al., 1974), showed that for a comparable anaesthetic state the impairment of myocardial contractility was similar, but in the absence of acute surgical intervention the overall cardiac performance (cardiac output higher, systemic vascular resistance lower) was much better. The present studies are more akin to the situation of a human patient during major surgery, those in intact animals being more akin to most of the studies of effects of changes in Pco_2 in anaesthetized humans, most of which were performed either before the onset of surgery or in volunteer subjects.

Circulatory response to hypocapnia.

It has been established, both in man (Prys-Roberts et al., 1967) and in the dog (Morgan et al., 1967), that the circulatory response to passive

TABLE IV. *Haemodynamic responses to changes in Pa_{CO_2} during nitrous oxide anaesthesia.*

	Control (normocapnia)	Hypocapnia	Control (normocapnia)	Hypercapnia
Heart rate (beat/min)	156±8	151±9	140±12	145±10
Aortic pressure: systolic	114±4	114±3	116±7	114±5
(mm Hg) diastolic	85±3	85±4	83±6	74±5
mean	94±3	94±3	94±6	87±5
L.v.e.d.p. (mm Hg)	3.7±0.8	3.7±0.9	3.2±0.9	4.8±1.3
Stroke volume (ml)	12.5±1.6	13.1±1.7	13.6±2.3	15.5±3.4
Normalized cardiac output (ml/min/kg)	112.7±11.6	113.6±12.2	106.5±12.8	122.1±14.8†
Systemic vascular resistance (dyn.sec.cm^{-5})	4,490±724	4,360±624	4,870±887	4,000±732*
Max LV (dP/dt) (mm Hg. sec^{-1})	2,520±286	2,750±297	2,595±339	2,755±286
Max LV (dP/dt)/IP (sec^{-1})	44.9±4.6	42.4±3.9	43.8±3.9	44.8±4.3
Peak aortic blood acceleration (ml.sec^{-2})	5,580±778	5,790±870	5,640±1,014	6,110±1,067
Peak aortic blood flow (ml.sec^{-1})	165±23	164±24	161±27	183±32*

Mean values ±1 SEM of seven experiments. Significance for two-tailed paired Student's *t* tests: *P < 0.05; †P < 0.01.

hyperventilation is caused by changes in Pco_2 rather than by the mechanical effects of an increased airway pressure. In man, the response to hypocapnia during either nitrous oxide/relaxant or halothane anaesthesia is characterized by a decrease of cardiac output and stroke volume without change of mean arterial pressure or of heart rate. This implies that the ratio of mean arterial pressure to mean flow (systemic vascular resistance) has increased. These aspects of the response to hypocapnia were observed in the present studies, the exception being the consistent increase in heart rate observed in the dogs, which minimized the reduction of cardiac output.

In previous studies, the relationship between the impairment of myocardial contractility by anaesthetic agents and the impairment of the performance of the left ventricle as a pump (reduced stroke volume and cardiac output) has been shown to be influenced by the changes of the opposition offered to blood flow by the systemic vasculature (Prys-Roberts et al., 1972b; Gersh et al., 1972). The explanation for the reduction of cardiac output during hypocapnia might also lie in the interaction of the effects of a low Pco_2 on the contractile state of the myocardium and on the systemic vascular beds. In the present studies we found no evidence of an impaired myocardial contractility during hypocapnia. The insignificant increases in the average values of max LV (dP/dt)/IP and of aortic blood acceleration would be consistent with the enhancement of the contractile state observed in isolated papillary muscles subjected to low Pco_2 and high pH (Pannier and Brutsaert, 1968).

In the absence of any significant increase in l.v.e.d.p., the decrease in stroke volume can be accounted for by the increase in systemic vascular resistance. An acute increase in systemic vascular resistance may increase arterial pressure, but cause a marked reduction in stroke volume in animals whose hearts are paced at a constant rate (Prys-Roberts et al., 1972b). Such an effect has been observed in animals (Sonnenblick and Downing, 1963; Bugge-Asperheim and Kiil, 1973), normal patients, patients with depressed left ventricular function (Ross and Braunwald, 1964) and in patients recovering from open intracardiac operations (Kouchoukos, Sheppard and Kirklin, 1972).

It is probable, therefore, that the reduction in stroke volume during hypocapnia results from the inability of the ventricular muscle, pharmacologically depressed by halothane or other anaesthetic agents, to maintain its ejection characteristics in the face of a moderate increase in systemic vascular resistance. This concept is supported by observations that the response of hypertensive patients to hypocapnia is characterized by a much greater increase in SVR and a correspondingly greater reduction in stroke volume and cardiac output (Prys-Roberts et al., 1972b).

The circulatory response to hypercapnia during anaesthesia.

The increase in cardiac output and stroke volume and the decrease in systemic vascular resistance during hypercapnia were similar to those observed in man during both nitrous oxide/relaxant or halothane anaesthesia (Prys-Roberts et al., 1967, 1968). While there was a modest increase in l.v.e.d.p. in response to hypercapnia, the changes were not statistically significant, and thus it is unlikely that the increase in cardiac output resulted from increased ventricular diastolic filling. The modest increase in heart rate and the lack of a significant change in myocardial contractile state do not point to major activation of the sympathetic nervous system during hypercapnia. From our knowledge of the direct effect of hypercapnic acidosis on the isolated myocardium (Pannier and Brutsaert, 1968), we could predict that the effects observed in the present study represent a balance between direct depression of myocardial contractility by acidosis and its secondary enhancement by some sympathetic nervous activation. That some activation of the sympathetic nervous system was present is confirmed by the suppression of these haemodynamic responses after a beta-adrenergic receptor blocker had been administered to these animals (Foëx and Prys-Roberts, 1974). In the absence of significant variation in myocardial contractility and of filling pressure, the increase in stroke volume and cardiac output can only be the result of a reduction in systemic vascular resistance.

Aortic input impedance and systemic vascular resistance.

The load opposing left ventricular ejection can be best represented by the aortic input impedance, that is the ratio of oscillatory pressure to oscillatory flow at the input to the systemic vasculature (McDonald, 1960; O'Rourke and Taylor, 1967; Gessner, 1973; Gersh et al., 1972). In normal man and animals, the impedance to the pulsatile components of blood flow represents less than 10% of

the total impedance; the predominant component of the impedance spectrum is represented by the resistance to steady flow through the terminal systemic arterioles. Thus, systemic vascular resistance represents at least 90% of the total load against which the left ventricle ejects and for most purposes can be considered as an adequate representation of the load. Our measurements of the distribution of the energy of blood flow in the aorta support these previous statements since, in the eucapnic control phase, the ratio of pulsatile to total work was only 6% and was not significantly modified by either hypocapnia or hypercapnia. This indicates that there was little change in the pulsatility of blood flow during either intervention and that changes in Pco_2 have little influence on the distribution of left ventricular work. This highlights the difference between the changes in response to hypercapnia observed during anaesthesia and those observed during hypercapnia associated with ventilation failure in the conscious patient, in whom a "hyperdynamic" circulatory state is a well-described phenomenon.

The findings of the present study indicate that hypocapnia causes little change in the myocardial contractile state, or in ventricular diastolic filling, and that the changes in stroke volume and cardiac output observed in both man and dog represent the failure of the left ventricle to maintain its ejection against a modest increase in load.

During hypercapnia, the overall circulatory response is the result of a reduced load to left ventricular ejection and also of the balance between direct and indirect effects of hypercapnic acidosis on the myocardium; thus it is influenced by the degree of suppression of sympathetic responses associated with the anaesthetic agent being administered.

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REFERENCES

Auld, P. A. M., Davenport, H. T., Sekelj, P., Jegier, W., Beaudry, P., and McGregor, M. (1962). The effect of increased Pco_2 on cardiac output during respiratory control in the anaesthetized child. *Can. Med. Assoc. J.*, **86**, 212.

Barcroft, H. (1963). Peripheral circulation in man: introduction. *Br. Med. Bull.*, **19**, 97.

Biscoe, T. J., and Millar, R. A. (1966). The effect of cyclopropane, halothane and ether on sympathetic ganglionic transmission. *Br. J. Anaesth.*, **38**, 3.

Blair, D. A., Glover, W. E., McArdle, L., and Roddie, I. C. (1960). The mechanism of the peripheral vasodilatation following carbon dioxide inhalation in man. *Clin. Sci.*, **19**, 407.

Bugge-Asperheim, B., and Kiil, F. (1973). Preload, contractility and afterload as determinants of stroke volume during elevation of aortic blood pressure in dogs. *Cardiovasc. Res.*, **7**, 528.

Carson, S. A., Chorley, G. E., Hamilton, F. N., Lee, D. C., and Morris, L. E. (1965). Variation in cardiac output with acid-base changes in the anaesthetized dog. *J. Appl. Physiol.*, **20**, 948.

Cullen, B. F., Eger, E. I. (II), Smith, N. T., Sawyer, D. C., and Gregory, G. A. (1971). The circulatory response to hypercapnia during fluroxene anesthesia in man. *Anesthesiology*, **34**, 415.

Cullen, D. J., and Eger, E. I. (II) (1974). Cardiovascular effects of carbon dioxide in man. *Anesthesiology*, **41**, 345.

—— —— Gregory, G. A. (1969). The cardiovascular effects of carbon dioxide in man, conscious and during cyclopropane anesthesia. *Anesthesiology*, **31**, 407.

Dripps, R. D., and Comroe, J. H., jr. (1947). The respiratory and circulatory response of normal man to inhalation of 7.6 and 10.4 per cent CO_2 with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of CO_2 and maximal voluntary hyperventilation. *Am. J. Physiol.*, **149**, 43.

Fishman, A. P., Fritts, H. W., jr., and Cournand, A. (1960). Effects of breathing carbon dioxide upon the pulmonary circulation. *Circulation*, **22**, 220.

Foëx, P., and Prys-Roberts, C. (1974). Interactions of beta-receptor blockade and Pco_2 levels in the anaesthetized dog. *Br. J. Anaesth.*, **46**, 397.

Gersh, B. J. (1970). Ventricular function and haemodynamics in the dog during anaesthesia. D.Phil. Thesis, Oxford.

—— Hahn, C. E. W., and Prys-Roberts, C. (1971). Physical criteria for measurement of left ventricular pressure and its first derivative. *Cardiovasc. Res.*, **5**, 32.

—— Prys-Roberts, C., Reuben, S. R., and Schultz, D. L. (1972). The effects of halothane on the interactions between myocardial contractility, aortic impedance and left ventricular performance. II: Aortic impedance, and the distribution of energy during ventricular ejection. *Br. J. Anaesth.*, **44**, 767.

Gessner, U. (1973). Vascular input impedance; in *Cardiovascular Fluid Dynamics* (ed. Bergel, D. H.), p. 315. London and New York: Academic Press.

Hahn, C. E. W. (1969). The measurement of oxygen micro-cathode currents by means of a field effect transistor operational amplifier system with digital display. *J. Sci. Instrum.*, **2**, 48.

—— (1971). The p-n-p transistor used exponentially to linearize the voltage output of the Pco_2 physiological electrode. *Rev. Sci. Instrum.*, **42**, 1164.

Horwitz, L. D., Bishop, V. S., and Stone, H. L. (1968). Effects of hypercapnia on the cardiovascular system of conscious dogs. *J. Appl. Physiol.*, **25**, 346.

Jerusalem, E., and Starling, E. H. (1910). On the significance of carbon dioxide for the heart beat. *J. Physiol. (Lond.)*, **40**, 279.

Jung, R. C., Walsh, J. A., and Hyman, C. (1971). Response of human forearm muscle blood vessels to hyperventilation. *Cardiovasc. Res.*, **5**, 347.

Kelman, G. R., and Nunn, J. F. (1966). Nomograms for correction of blood Po_2, Pco_2, pH and base excess for time and temperature. *J. Appl. Physiol.*, **21**, 1484.

Kouchoukos, N. T., Sheppard, L. C., and Kirklin, J. W. (1972). Effect of alterations in arterial pressure on cardiac performance early after open intracardiac operations. *J. Thorac. Cardiovasc. Surg.*, **64**, 563.
McDonald, D. (1960). Blood flow in arteries; in *Physiological Society Monographs*. London: Edward Arnold Publishers.
McElroy, W. T., Gerdes, A. J., and Brown, E. B., jr. (1958). Effects of CO_2, bicarbonate and pH on the performance of isolated perfused guinea pig hearts. *Am. J. Physiol.*, **195**, 412.
Manley, E. S., jr., Nash, C. B., and Woodbury, R. A. (1964). Cardiovascular responses to severe hypercapnia of short duration. *Am. J. Physiol.*, **207**, 634.
Morgan, B. C., Crawford, E. W., Hornbein, T. E., Martin, W. E., and Guntheroth, W. G. (1967). Hemodynamic effects of changes in arterial carbon dioxide tension during intermittent positive pressure ventilation. *Anesthesiology*, **28**, 866.
Morris, M. E., and Millar, R. A. (1962). Blood pH/plasma catecholamine relationships: respiratory acidosis. *Br. J. Anaesth.*, **34**, 672.
Moster, W. G., Reier, C. E., Gardier, R. W., and Hamelberg, W. (1969). Cardiac output and postganglionic sympathetic activity during acute respiratory alkalosis. *Anesthesiology*, **31**, 28.
Nahas, G. G., and Cavert, H. M. (1957). Cardiac depressant effect of CO_2 and its reversal. *Am. J. Physiol.*, **190**, 483.
—— Ligou, J. C. (1959). Effects of acute arterial blood pH changes on catecholamine plasma levels and circulatory adaptations. *Surg. Forum*, **10**, 111.
Ng, M. L., Levy, M. N., and Zieske, H. A. (1967). Effects of changes of pH and carbon dioxide tension on left ventricular performance. *Am. J. Physiol.*, **213**, 115.
Noble, M. I. M., Trenchard, D., and Guz, A. (1967). Effect of changes in Pa_{co_2} and Pa_{o_2} on cardiac performance in conscious dogs. *J. Appl. Physiol.*, **22**, 147.
O'Rourke, M. F., and Taylor, M. G. (1967). Input impedance of the systemic circulation. *Circulation Res.*, **20**, 365.
Pannier, J. L., and Brutsaert, D. L. (1968). Contractility of isolated cat papillary muscle and acid-base changes. *Arch. Int. Pharmocodyn. Ther.*, **172**, 244.
Price, H. L. (1966). The significance of catecholamine release during anaesthesia. *Br. J. Anaesth.*, **38**, 705.
—— Linde, H. W., Jones, R. E., Black, G. W., and Price, M. L. (1959). Sympatho-adrenal responses to general anesthesia in man and their relation to hemodynamics. *Anesthesiology*, **20**, 563.
—— Lurie, A. A., Black, G. W., Jechzer, P. H., Linde, H. W., and Price, M. L. (1960). Modification by general anesthetics (cyclopropane and halothane) of circulatory and sympathoadrenal responses to respiratory acidosis. *Ann. Surg.*, **152**, 1071.
Prys-Roberts, C., Foëx, P., Greene, L. T., and Waterhouse, T. D. (1972a). Studies of anaesthesia in relation to hypertension. IV: The effects of artificial ventilation on the circulation and pulmonary gas exchange. *Br. J. Anaesth.*, **44**, 335.
—— Gersh. B. J., Baker, A. B., and Reuben, S. R. (1972b). The effects of halothane on the interactions between myocardial contractility, aortic impedance and left ventricular performance. I: Theoretical considerations and results. *Br. J. Anaesth.*, **44**, 634.
—— Kelman, G. R., Greenbaum, R., Kain, M. L., and Bay, J. (1968). Haemodynamics and alveolar arterial Po_2 differences at varying Pa_{co_2} in anaesthetized man. *J. Appl. Physiol.*, **25**, 80.
—— —— —— Robinson, R. H. (1967). Circulatory influences of artificial ventilation during nitrous oxide anaesthesia in man. II: Results; the relative influence of mean intrathoracic pressure and arterial carbon dioxide tension. *Br. J. Anaesth.*, **39**, 533.
Richardson, D. W., Wasserman, A. J., and Patterson, J. L., jr. (1961). General and regional circulatory responses to change in blood pH and carbon dioxide tension. *J. Clin. Invest.*, **40**, 31.
Roberts, J. G., Foëx, P., Clarke, T. N. S., Prys-Roberts, C., and Bennett, M. J. (1974). Cardiovascular interactions of halothane, high dose propranolol and hypoxaemia in the dog. *Br. J. Anaesth.*, **46**, 321.
Roddie, I. C., Shepherd, J. T., and Whelan, R. F. (1957). Humoral vasodilatation in the forearm during voluntary hyperventilation. *J. Physiol. (Lond.)*, **137**, 80.
Ross, J., jr., and Braunwald, E. (1964). The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. *Circulation*, **23**, 739.
Sechzer, P. H., Egbert, L. D., Linde, H. W., Cooper, D. Y., Dripps, R. D., and Price, H. L. (1960). Effect of carbon dioxide inhalation on arterial pressure, ECG, and plasma catecholamines and 17-OH corticosteroids in normal man. *J. Appl. Physiol.*, **15**, 454.
Sonnenblick, E. H., and Downing, S. E. (1963). Afterload as a primary determinant of ventricular performance. *Am. J. Physiol.*, **204**, 604.
Tenney, S. M., and Lamb, T. W. (1965). Physiological consequences of hypoventilation and hyperventilation; in *Handbook of Physiology*, Section 3: Respiration, Volume 2, p. 979. Washington D.C.: American Physiological Society.
Theye, R. A., Milde, J. H., and Michenfelder, J. D. (1966). Effect of hypocapnia on cardiac output during anesthesia. *Anesthesiology*, **27**, 778.
Veragut, U. P., and Krayenbühl, H. P. (1965). Estimation and quantification of myocardial contractility in the closed-chest dog. *Cardiology*, **47**, 96.
Wilcken, D. E. L., Charlier, A. A., Hoffman, J. I. E., and Guz, A. (1964). Effects of alterations in aortic impedance on the performance of the ventricles. *Circulation Res.*, **14**, 283.

EFFET DU CO_2 SUR LA CONTRACTILITE DU MYOCARDE ET SUR L'IMPEDANCE AORTIQUE PENDANT L'ANESTHESIE

RESUME

Les réponses hémodynamiques à l'hypocapnie et à l'hypercapnie ont été étudiées sur des chiens sous ventilation sous pression positive intermittente, sous anesthésie à l'halothane (1% d'halothane dans l'oxygène) et sous anesthésie au protoxyde d'azote (30% d'oxygène dans le protoxyde d'azote. En l'absence de variations importantes soit dans la contractilité du myocarde, soit dans la pression télé-diastolique ventriculaire gauche, les variations du volume d'éjection systolique et du débit cardiaque (diminution à cause de l'hypocapnie, augmentation en raison de l'hypercapnie) ont été déterminées par les modifications de la résistance vasculaire systémique (augmentation à cause de l'hypocapnie, diminution en raison de l'hypercapnie).

WIRKUNG VON CO_2 AUF MYOKARDIALE KONTRAKTILITÄT UND AUF AORTA-AUFNAHMEIMPEDANZ BEI NARKOSE

ZUSAMMENFASSUNG

Die hämodynamischen Reaktionen auf Hypo- und Hyperkapnie wurden an Hunden während gelegentlicher positiver Druckbelüftung bei Halothannarkose (1% Halothan in Sauerstoff) und bei Stickstoffoxydnarkose (30% Sauerstoff in Stickstoffoxyd) studiert. In Abwesenheit wesentlicher Variationen der myokardialen Kontraktilität oder des enddiastolischen Drucks im linken Ventrikel, waren die Veränderungen des Pulsvolumens und der Herzleistung (Verringerung wegen Hypokapnie, Erhöhung wegen Hyperkapnie) bestimmt durch Änderungen

des systemischen Gefäßwiderstandes (Erhöhung wegen Hypokapnie, Verringerung wegen Hyperkapnie).

EFECTO DEL CO_2 SOBRE LA CONTRACTIBILIDAD MIOCARDIACA Y LA IMPEDANCIA DE ADMISION AORTICA DURANTE ANESTESIA

SUMARIO

Las respuestas hemodinámicas a la hipocapnia y a la hipercapnia se han estudiado en el perro durante ventilación impelente intermitente bajo anestesia con halotano (1% halotano en oxígeno) y bajo anestesia con óxido nitroso (30% oxígeno en óxido nitroso). En la ausencia de variaciones significativas tanto de la contractibilidad miocardiaca como de la presión enddiastólica ventricular izquierda, los cambios del volumen de carrera y salida cardiaca (disminución a causa de hipocapnia, aumento a causa de hipercapnia) se determinaron por alteraciones de la resistencia vascular sistemática (aumento a causa de hipocapnia, disminución a causa de hipercapnia).