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Effect of artificial respiratory volume on the cardiovascular responses to an α_1- and an α_2-adrenoceptor agonist in the air-ventilated pithed rat

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1 The effect of varying artificial respiratory volume (at a fixed rate of 54 min^{-1}) on cardiac output, its distribution and tissue blood flows were determined with tracer microspheres in control pithed rats or during pressor responses to either the α_1-adrenoceptor agonist phenylephrine or the α_2-agonist xylazine. Phenylephrine was investigated in the presence of propranolol (3 mg kg^{-1}). The rats were pithed under halothane anaesthesia.

2 A respiratory volume of 15 ml kg^{-1} produced modest hypercapnia ($Paco_2$ = 47 mmHg), hypoxia (Pao_2 = 60 mmHg) and acidosis (pH = 7.35) relative to control animals respired at 20 ml kg^{-1} ($Paco_2$ = 32 mmHg; Pao_2 = 77 mmHg; pH = 7.47). In rats respired at 15 ml kg^{-1}, total peripheral resistance was lower, and cardiac output greater (due to increased stroke volume), than in the controls. Lowering respiratory volume reduced distribution of cardiac output to the kidneys, increased it to the large intestine and also increased blood flow through the gastrointestinal tract, skin and spleen. A respiratory volume of 30 ml kg^{-1} gave mild hypocapnia ($Paco_2$ = 19 mmHg), hyperoxia (Pao_2 = 101 mmHg) and alkalosis (pH = 7.59) compared to 20 ml kg^{-1} but had no effect on cardiac output distribution or organ blood flow although heart rate was 29% greater at 30 ml kg^{-1}.

3 Xylazine (500 μg bolus followed by 100 $\mu g\,min^{-1}$ infusion) at all three respiratory volumes gave well-sustained mean pressor responses of 62–64 mmHg by increasing both total peripheral resistance and cardiac output (resulting from increased stroke volume). It increased the proportion of cardiac output passing to the liver, reduced that going to the spleen and gastrointestinal tract and increased cardiac, renal and hepatosplanchnic blood flows.

4 The secondary, relatively sustained, pressor effect of phenylephrine (5 μg bolus followed by 0.4 $\mu g\,min^{-1}$ infusion, i.v.) varied at the 3 respiratory volumes with mean values from 32 to 53 mmHg. This response was due to both increased total peripheral resistance and cardiac output (resulting from greater stroke volumes and/or heart rates). Phenylephrine increased the proportion of cardiac output passing to the gastrointestinal tract, heart, kidneys and hepatosplanchnic bed and increased cardiac, hepatosplanchnic, renal and gastrointestinal blood flows.

5 Respiratory volume had no effect on the cardiovascular effects of xylazine. However, respiratory volume modified the effects of phenylephrine on heart rate and changed the relative contributions of stroke volume and heart rate to the increased cardiac output. It also influenced the effects of phenylephrine on cardiac output distribution to the liver, epididimides and hepatosplanchnic bed and on blood flow through skeletal muscle and the large intestine.

6 Changes in respiratory volume of air ventilated pithed rats thus influence cardiac output, its distribution and regional blood flows. Such changes can also differently influence the responses of various vascular beds to phenylephrine whilst having no effect on their responses to xylazine.

Introduction

The pithed rat preparation demonstrates the existence of postjunctional α_1- and α_2-adrenoceptors in the vasculature, both of which may contribute to systemic pressor responses (Drew & Whiting, 1979; Docherty *et al.*, 1979; Docherty & McGrath, 1980). In peripheral vessels, local acidosis or alkalosis can

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also influence vascular tone. Acidosis, severe alkalosis or increased $PaCO_2$ all cause dilatation of arterioles, while mild alkalosis causes arteriolar constriction (Guyton, 1981).

In the pithed rat, studies have shown that variation of blood gases and blood pH by means of altering artificial ventilation volume or the inspired gas differentially alters α_1- and α_2-adrenoceptor-mediated pressor responses (McGrath *et al.*, 1982; Korstanje *et al.*, 1985). Grant *et al.* (1985) showed that the peak pressor responses to the α_1-adrenoceptor agonist phenylephrine and the α_2-adrenoceptor agonist xylazine were potentiated by alkalosis and acidosis respectively. They also found that hypoxia combined with hypercapnia selectively depressed the pressor responses to phenylephrine although these responses were enhanced as PaO_2 increased. This suggested that differences in blood gases and pH may affect the relative contributions of α_1- and α_2-adrenoceptors to vascular tone.

It has recently been demonstrated that α-adrenoceptor-mediated increases in cardiac output contribute to the pressor responses elicited by α_1- and α_2-adrenoceptor agonists in the pithed rat (Kalkman *et al.*, 1984; Hiley & Thomas, 1987). Also, selective α-adrenoceptor agonists differentially affect the regional distribution of cardiac output and organ blood flow (Hicks & Waldron, 1983; Waldron & Hicks, 1985; Hiley & Thomas, 1987). The aim of this study was to investigate the effect of moderate changes in artificial respiratory volume on cardiac output, its distribution and organ blood flows. The changes in respiratory volume were performed in air-breathing rats to obtain a range of blood gases and pH which may occur physiologically or experimentally. Phenylephrine and xylazine (an α_1- and an α_2-adrenoceptor selective agonist respectively) were used to evaluate the effect of the blood gas and pH changes on the cardiovascular responses to selective α-adrenoceptor activation.

Methods

Determination of cardiac output and its distribution

Male Wistar rats weighing 250–300 g (Bantin & Kingman Ltd, Hull) were pithed under halothane anaesthesia by passing a 16 gauge steel needle through the orbit, through the foramen magnum and down into the spinal canal. Immediately after pithing, the rats were respired with air through a tracheal cannula by means of a respiratory pump (BioScience, Sheerness, U.K.) operating at 54 cycles min^{-1} with a volume of either 15, 20 (taken to be the control) or 30 ml kg^{-1}.

The right femoral artery was cannulated and connected to a Bell & Howell type 4-422-0001 transducer to measure systemic arterial blood pressure which was recorded on a Grass 7D polygraph. The left femoral artery was also cannulated and connected to a Braun Perfusor IV pump (Melsungen, F.R.G.) for the withdrawal of blood. With the aid of pressure monitoring, a cannula was passed down the right common carotid artery into the left ventricle. Drugs were administered through a cannula placed in the left external jugular vein and, when a sustained pressor response had been obtained (see below under *Drugs*), 60000–80000 ^{113}Sn labelled microspheres ($15 \pm 3\,\mu m$; NEN, Boston, MA), suspended by ultrasonication in saline containing 0.01% Tween 80, were injected into the ventricle over 20 s. Blood was withdrawn from the left femoral artery at a rate of 0.5 ml min^{-1} during and for 70 s after the microsphere injection. The circulation was stopped with an air embolism and the organs dissected out, weighed and placed in scintillation vials for counting in a Packard Autogamma 500 γ-counter. The number of counts in the blood sample was also determined in order that cardiac output and tissue blood flow could be determined as described by McDevitt & Nies (1976): cardiac output (ml min^{-1}) is given by ([counts injected × blood withdrawal rate]/[counts in blood sample]); fraction of cardiac output to an organ by ([counts in organ]/[counts injected]); and organ blood flow (ml min^{-1} g^{-1} tissue) by ([cardiac output × fraction of cardiac output to organ]/[organ weight]).

Determination of arterial blood gases and pH

These were analysed in all animals by removing 125 μl of blood from the right femoral artery prior to agonist or saline administration. This was analysed with a Corning 166 micro blood gas analyser. It has previously been shown that, at a respiratory volume of 20 ml kg^{-1}, blood gases and pH do not change in the period between sampling and the end of the experiment after the microsphere injection (Hiley & Thomas, 1987); it is presumably because of the short time (about 3 min) between agonist administration and the stopping of the circulation that the blood gases are not changed by the pressor effects. The values obtained at the three respiratory volumes for blood gases and pH were as follows: 15 ml kg^{-1}, pH = 7.35 ± 0.01, $PaCO_2$ = 47.1 ± 0.1, PaO_2 = 60.0 ± 1.1; 20 ml kg^{-1}, pH = 7.47 ± 0.01, $PaCO_2$ = 31.7 ± 0.6, PaO_2 = 76.8 ± 1.6; 30 ml kg^{-1}, pH = 7.59 ± 0.01, $PaCO_2$ = 19.1 ± 0.5, PaO_2 = 101.0 ± 1.9. For all these three parameters, values of 15 ml kg^{-1} and 30 ml kg^{-1} were significantly different from those at 20 ml kg^{-} ($P < 0.001$; $n = 32$ for each respiratory

level). Within these overall means, there were no significant differences between any of the 4 groups (2 control and 2 agonist) at any one respiratory volume.

Drugs

All drugs were administered i.v. in 0.9% saline. The two agonists were given in the form of a bolus injection of 0.5 ml followed by an infusion of $0.1\,ml\,min^{-1}$; the phenylephrine (Sigma, Poole, Dorset) dose was a $5\,\mu g$ bolus followed by $0.4\,\mu g\,min^{-1}$ infusion and xylazine (Bayer U.K., Newbury, Berkshire) was given as a 0.5 mg bolus followed by a $100\,\mu g\,min^{-1}$ infusion.

For xylazine, there was a monophasic response and the microsphere injection was given as soon as the blood pressure ceased to rise. The response to phenylephrine was biphasic, as observed by other workers (e.g. Grant *et al.*, 1985), and the microsphere injection was made as soon as the second phase had ceased to rise. For both agonists this was less than 90 s from the start of the bolus injection.

Control animals received a bolus injection followed by an infusion of 0.9% saline. Animals which were given phenylephrine received propranolol (ICI Pharmaceuticals, Macclesfield, Cheshire), at a dose of $3\,mg\,kg^{-1}$ i.v., 10 min before starting the administration of phenylephrine; these animals were compared with control groups similarly pretreated with propranolol.

Statistical comparison

All results are given as the mean ± s.e. mean. The statistical significance of interactions between respiratory volume and drug effect was assessed by two-way, random block, analysis of variance. The statistically significant differences between groups were assessed by analysis of variance followed by the least significant difference procedure (Snedecor & Cochran, 1980).

Results

The effect of respiratory volume on cardiovascular responses

Table 1 shows that reducing respiratory volume from $20\,ml\,kg^{-1}$ to $15\,ml\,kg^{-1}$ resulted in a 27% lower total peripheral resistance. Despite this, mean arterial pressure was the same in the two groups because of a 42% greater cardiac output in the animals respired at $15\,ml\,kg^{-1}$. As heart rate was not affected, the increased cardiac output was accounted for by a 36% increase in stroke volume. It is noteworthy that these statistically significant effects on cardiac index and total peripheral resistance were not seen when comparison is made of the two groups pretreated with propranolol and respired at either 15 or $20\,ml\,kg^{-1}$. Also, the stroke volume was only 22% greater in the $15\,ml\,kg^{-1}$ group given propranolol relative to that determined in the $20\,ml\,kg^{-1}$ group given propranolol. Increasing respiratory volume from $20\,ml\,kg^{-1}$ to $30\,ml\,kg^{-1}$ produced a significant increase in the heart rate of 29%. Heart rate was not significantly different in the groups given propranolol and respired at either 20 or $30\,ml\,kg^{-1}$.

The percentage of cardiac output passing to the kidneys was reduced by 21% as a result of lowering respiratory volume to $15\,ml\,kg^{-1}$ from $20\,ml\,kg^{-1}$ (Table 2). Although there was no increase in the percentage of cardiac output passing to the gastrointestinal tract considered as a whole (that is, the sum of the distributions to the stomach, the small and large intestines and the pancreas/mesentery), more detailed analysis revealed a 38% increase in the proportion of cardiac output passing to the large intestine (from 4.1 ± 0.3% to 5.6 ± 0.4%; $P < 0.01$). These effects of changing respiratory volume were not present in the animals given propranolol. Increasing respiratory volume from $20\,ml\,kg^{-1}$ to $30\,ml\,kg^{-1}$ had no statistically significant effects on cardiac output distribution.

When the respiratory volume was decreased from $20\,ml\,kg^{-1}$ to $15\,ml\,kg^{-1}$, a 42% increase in blood flow in the gastrointestinal tract was produced (Table 3), largely due to an increased flow (88%) through the large intestine (from $0.6 \pm 0.1\,ml\,min^{-1}\,g^{-1}$ to $1.1 \pm 0.1\,ml\,min^{-1}\,g^{-1}$; $P < 0.001$), which was the product of both the increased cardiac output and an increase in the proportion of the cardiac output it received. There were also increases in blood flow in the skin (71%) and the spleen (62%). Since only a proportion of these latter changes can be accounted for by the 42% increase in cardiac output, there is evidence of vasodilatation within these vascular beds resulting from the decreased respiratory volume. However, there was only a 43% increase in blood flow through the total hepatosplanchnic bed, almost identical to the increase in cardiac index, which indicates that the overall resistance to flow through this bed was unchanged.

Despite the lower proportion of cardiac output passing to the kidneys in the animals respired at $15\,ml\,kg^{-1}$, renal blood flow was maintained by the greater cardiac output. All the effects of reducing respiratory volume on organ blood flows were absent when comparison was made between the groups

Table 1 Effects of xylazine and phenylephrine on blood pressure, cardiac index and heart rate in pithed rats at three artificial respiratory volumes

Group & Resp. vol. (ml kg^{-1})	*Diastolic pressure* (mmHg)	*Mean arterial pressure* (mmHg)	*Heart rate* (beats min^{-1})	*Cardiac index* (ml min^{-1} 100 g^{-1} b wt)	*Stroke volume* (ml)	*TPR* (mmHg, ml^{-1} min. 100 g body wt)
Saline (15)	37 ± 9	46 ± 1	318 ± 13			
	−2 ± 1	−2 ± 1	−3 ± 3	14.3 ± 0.9††	0.131 ± 0.011††	3.2 ± 0.2†
Saline (20)	36 ± 3	45 ± 3	292 ± 12			
	−1 ± 1	−1 ± 2	−3 ± 2	10.1 ± 0.8	0.096 ± 0.004	4.4 ± 0.2
Saline (30)	34 ± 1	40 ± 1	376 ± 7†††			
	−3 ± 1	−3 ± 1	−4 ± 3	9.5 ± 0.7	0.075 ± 0.006	4.2 ± 0.4
Xylazine (15)	37 ± 1	45 ± 1	336 ± 10			
	51 ± 6***	62 ± 7***	−12 ± 4	18.0 ± 0.7**	0.159 ± 0.006*	6.0 ± 0.5***
Xylazine (20)	35 ± 2	45 ± 2	330 ± 15			
	52 ± 6***	63 ± 6***	12 ± 7	17.3 ± 1.2***	0.145 ± 0.012***	6.5 ± 0.7***
Xylazine (30)	33 ± 3	41 ± 2	364 ± 17			
	54 ± 5***	64 ± 5***	2 ± 8	15.4 ± 0.9***	0.122 ± 0.006***	6.8 ± 0.3***
Propranolol	43 ± 1	51 ± 1	326 ± 8			
and saline (15)	−2 ± 1	−1 ± 1	−8 ± 8	14.7 ± 0.7	0.149 ± 0.009†	3.2 ± 0.2
Propranolol	38 ± 2	49 ± 2	331 ± 19			
and saline (20)	−1 ± 1	0 ± 1	2 ± 4	13.9 ± 0.7	0.122 ± 0.008	3.6 ± 0.1
Propranolol	38 ± 1	44 ± 1	364 ± 20			
and saline (30)	−4 ± 1	−3 ± 1	−33 ± 8†††	10.5 ± 1.0††	0.092 ± 0.006††	4.0 ± 0.2
Propranolol	41 ± 2	50 ± 2	308 ± 13			
and PE (15)	24 ± 6***	32 ± 6***	17 ± 3**	18.4 ± 1.1**	0.159 ± 0.011	4.5 ± 0.3**
Propranolol	38 ± 2	49 ± 2	322 ± 11			
and PE (20)	42 ± 7***	53 ± 6***	10 ± 8	18.7 ± 1.3***	0.161 ± 0.013**	5.5 ± 0.4***
Propranolol	31 ± 2	42 ± 2	313 ± 10***			
and PE (30)	33 ± 6***	43 ± 6***	21 ± 6***	16.8 ± 1.0***	0.142 ± 0.010***	4.5 ± 0.3

For all groups, $n = 8$.

Where two values are given in a column, the upper values are those immediately before administration of the agonist or saline. The lower value is the change between the basal value and that at the midpoint of the microsphere injection. Cardiac index is the absolute value determined by the tracer microsphere method. TPR is the total peripheral resistance calculated from cardiac index and mean arterial pressure during the microsphere injection assuming central venous pressure to be zero. PE = phenylephrine. Resp. vol. = artificial respiratory volume (54 cycles min^{-1}).

Significant differences between the xylazine or phenylephrine experimental groups and the saline or propranolol/saline controls, respectively, were determined by analysis of variance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Statistical comparison of the respiratory volume groups 15 ml kg^{-1} and 30 ml kg^{-1} with the 20 ml kg^{-1} within both the saline and propranolol/saline treatments were made by analysis of variance: † $P < 0.05$; †† $P < 0.01$; ††† $P < 0.001$.

respired at 15 or 20 ml kg^{-1} and given propranolol. Increasing respiratory volume from 20 ml kg^{-1} to 30 ml kg^{-1} had no effect on cardiac output distribution or organ blood flow.

The effect of respiratory volume on cardiovascular responses induced by phenylephrine and xylazine

Xylazine increased mean arterial pressure, cardiac index, stroke volume, and total peripheral resistance at all three respiratory volumes (Table 1). The increases in cardiac output were due to increases in stroke volume as heart rates were not affected. There was no significant interaction between respiratory volume and these effects of xylazine.

Table 1 also shows that phenylephrine significantly increased diastolic and mean arterial pressure and cardiac index at all three respiratory volumes. The response to phenylephrine was fairly well sustained for the duration of the microsphere injection and never declined by more than 5 mmHg during this period; the values given in the table are those obtained at the midpoint of the microsphere injection. It can also be seen from Table 1 that at a respiratory volume of 15 ml kg^{-1}, the increase in cardiac output (24%) was due to an increase in heart rate, stroke volume remaining unchanged. In con-

Table 2 Percentage of the cardiac output distributed to the various organs after administration of xylazine or phenylaphrine at three respiratory volumes

Group & Resp. vol (ml kg^{-1})	*Heart*	*Lungs*	*Kidneys*	*Testes*	*Epididimides*
Saline (15)	4.7 ± 0.7	3.9 ± 0.5	13.5 ± 0.6††	1.8 ± 0.1	0.27 ± 0.04
Saline (20)	3.9 ± 0.2	3.3 ± 0.6	17.0 ± 1.3	1.8 ± 0.1	0.27 ± 0.02
Saline (30)	5.6 ± 0.3	1.7 ± 0.2	15.7 ± 1.3	1.3 ± 0.1	0.27 ± 0.01
Xylazine (15)	8.2 ± 0.3**	7.3 ± 1.1**	15.4 ± 1.1	1.4 ± 0.1*	0.43 ± 0.06***
Xylazine (20)	8.5 ± 0.5***	6.3 ± 1.1**	16.1 ± 1.1	1.2 ± 0.1**	0.31 ± 0.04
Xylazine (30)	9.8 ± 1.0***	4.9 ± 0.7**	16.5 ± 1.1	1.1 ± 0.1	0.33 ± 0.03
Propranolol and saline (15)	3.7 ± 3.0	2.9 ± 0.4	11.5 ± 1.0	1.6 ± 0.1	0.27 ± 0.02
Propranolol and saline (20)	4.7 ± 0.5	2.2 ± 0.3	12.3 ± 0.6	1.4 ± 0.1	0.25 ± 0.02
Propranolol and saline (30)	4.7 ± 0.5	1.1 ± 0.2	14.0 ± 0.6	1.0 ± 0.1††	0.28 ± 0.02
Propranolol and PE (15)	7.5 ± 0.6**	3.3 ± 0.3	16.8 ± 0.9***	1.7 ± 0.2	0.28 ± 0.02
Propranolol and PE (20)	7.0 ± 0.8	5.6 ± 1.1**	16.9 ± 0.8**	1.4 ± 0.1	0.23 ± 0.02
Propranolol and PE (30)	9.3 ± 1.9***	4.0 ± 1.1**	17.0 ± 0.8*	1.1 ± 0.1	0.19 ± 0.02*

	Liver	*Spleen*	*G.I.T.*	*Total hepatosplanchnic*
Saline (15)	3.8 ± 0.4	1.55 ± 0.10	25.4 ± 1.0	30.7 ± 1.0
Saline (20)	4.1 ± 0.5	1.40 ± 0.13	24.8 ± 1.1	30.2 ± 1.2
Saline (30)	3.4 ± 0.3	1.40 ± 0.15	23.2 ± 1.7	28.0 ± 1.9
Xylazine (15)	9.0 ± 1.3***	0.92 ± 0.07***	22.5 ± 1.2	32.4 ± 1.0
Xylazine (20)	10.8 ± 0.6***	0.83 ± 0.06***	19.1 ± 0.6***	30.7 ± 0.8
Xylazine (30)	10.6 ± 1.0***	0.74 ± 0.05***	17.3 ± 0.8***	28.6 ± 1.5
Propranolol and saline (15)	3.6 ± 0.4	1.13 ± 0.09	20.9 ± 1.3	25.6 ± 1.3
Propranolol and saline (20)	3.7 ± 0.3	1.32 ± 0.14	21.6 ± 0.8	26.7 ± 0.7
Propranolol and saline (30)	3.5 ± 0.4	0.95 ± 0.03††	21.7 ± 0.6	26.2 ± 0.8
Propranolol and PE (15)	6.6 ± 0.6**	1.27 ± 0.09	27.8 ± 0.9***	35.7 ± 0.6***
Propranolol and PE (20)	9.8 ± 0.7***	1.12 ± 0.14	20.3 ± 1.2	31.2 ± 1.8**
Propranolol and PE (30)	6.7 ± 0.5***	0.90 ± 0.13	22.5 ± 1.3	30.0 ± 1.4*

For all groups, $n = 8$.
Significant differences between the xylazine or phenylephrine experimental groups and the saline or propranolol/saline controls, respectively, were determined by one-way analysis of variance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. PE = phenylephrine. Resp. vol. = artificial respiratory volume (54 cycles min^{-1}).
Statistical comparisons of the respiratory volume groups 15 ml kg^{-1} and 30 ml kg^{-1} with the 20 ml kg^{-1} group within both the saline and propranolol/saline treatments were made by analysis of variance: †† $P < 0.01$.

trast, at 20 ml kg^{-1} an increase in stroke volume (32%) alone was responsible for the increase (35%) in cardiac output whereas, at 30 ml kg^{-1}, increases in both heart rate (7%) and stroke volume (54%) contributed to the increased cardiac output (60%). It can also be seen from Table 1 that phenylephrine increased total peripheral resistance at 15 and 20 ml kg^{-1}. The effect of phenylephrine on heart rate was significantly modified by the changes in respiratory volume ($P < 0.01$).

Xylazine significantly increased the percentage of cardiac output distributed to the heart, lungs and liver, and reduced that to the spleen at all three respiratory volumes (Table 2). Further, at some of the

respiratory volumes, it reduced the fraction of the cardiac output passing to the gastrointestinal tract and testes but increased that fraction going to the epididimides as detailed in Table 2. Despite the variations in significance, there was no statistically significant effect of respiratory volume on these changes. It is interesting to note that the percentage of cardiac output received by the hepatosplanchnic bed as a whole was unaffected by xylazine at any of the respiratory volumes since the decreases in the proportion of cardiac output received by the gastrointestinal tract were almost exactly balanced by the increases in the fraction of cardiac output flowing through the hepatic artery.

It can also be seen from Table 2 that phenylephrine increased the percentage of cardiac output passing to the liver, kidneys and hepatosplanchnic bed at all three respiratory volumes. In some conditions it also increased the proportion of cardiac output flowing to the gastrointestinal tract, heart and lungs but decreased that going to the epididimides. There was a statistically significant interaction between respiratory volume and the effect of phenylephrine on cardiac output distribution to the liver ($P < 0.01$; peak effect at $20\,ml\,kg^{-1}$), epididimides ($P < 0.05$; a decrease only at $30\,ml\,kg^{-1}$), hepatosplanchnic bed ($P < 0.05$; decreasing effect as respiratory volume increased) and the gastrointestinal tract ($P < 0.01$; an increase only at the lowest respiratory volume).

At all three respiratory volume levels xylazine significantly increased blood flow in the heart, lungs, liver, kidneys, epididimides and hepatosplanchnic bed (Table 3). At some of the respiratory volumes employed, it reduced blood flow in the spleen but increased blood flow to skeletal muscle as detailed in Table 3. While the increased flows through the renal, hepatosplanchnic and skeletal muscle vascular beds were due to the increase in cardiac output, the increases in flow through the heart, lungs and liver were due to increases in both cardiac output and the percentage of cardiac output that they received. The combined effect of increased cardiac output and its percentage distribution increased blood flow in the epididimides at the lowest respiratory volume, whereas only an increase in absolute cardiac output was responsible for the increase in blood flow through this tissue at the higher respiratory volumes. While splenic blood flow decreased at a respiratory volume of $15\,ml\,kg^{-1}$ because of a decrease in the proportion of cardiac output flowing to it, at the higher respiratory levels its blood flow was maintained by the increased cardiac output. There were no significant interactions between the effects of respiratory volume and any of the effects of xylazine on regional blood flows.

Phenylephrine increased blood flows in the heart, liver, kidneys, gastrointestinal tract and hepatosplanchnic bed at all three respiratory volumes and caused increases in blood flow through the lungs, skin and testes at some of the respiratory volumes used as detailed in Table 3. Blood flow in skeletal muscle was both decreased (at the respiratory level of $15\,ml\,kg^{-1}$) and increased (at $30\,ml\,kg^{-1}$) by phenylephrine and, in this tissue, there was a statistically significant interaction between respiratory volume and these effects of the α_1-adrenoceptor agonist ($P < 0.05$). Although there was no such interaction with the gastrointestinal tract as a whole, more detailed analysis showed a significant interaction with the effect of phenylephrine on the large intestine ($P < 0.01$). The flow values ($ml\,min^{-1}\,g^{-1}$) for the large intestine at the three respiratory volume levels were (saline/phenylephrine and propranolol/phenylephrine groups respectively): $15\,ml\,kg^{-1}$, 1.32 ± 0.12 and 0.76 ± 0.12; $20\,ml\,kg^{-1}$, 1.13 ± 0.13 and 0.75 ± 0.06; $30\,ml\,kg^{-1}$, 0.90 ± 0.07 and 0.65 ± 0.10. While the increase in blood flow through the skin and gastrointestinal tract can largely be attributed to the increase in cardiac output, the increased blood flows in the lung, hepatosplanchnic, cardiac, hepatic and renal vascular beds were the product of both an increase in cardiac output and a change in its distribution in their favour.

Discussion

The effects of varying respiratory volume on the cardiovascular system

In the pithed rat, an increase in cardiac stroke volume could be caused by an increase in cardiac contractility (due to blood gas and pH changes or receptor-mediated events), an increase in venous return (by venous constriction and/or arteriolar dilatation), a decrease in intrathoracic pressure or by a combination of these effects. The results show that with the respiratory volume of $15\,ml\,kg^{-1}$ there was a greater stroke volume than at $20\,ml\,kg^{-1}$. The direct effect of hypercapnia on the myocardium is to depress contractility (Price & Helrich, 1955) and hypoxia has been variously reported to decrease contractility or to have no effect in addition to that of hypercapnia (Sonnenblick & Kirk, 1972; Beierholm *et al.*, 1975). Thus, this increase in stroke volume is not the result of direct stimulant actions of hypoxia or hypercapnia on the heart muscle but it is possible that decreasing respiratory volume at a constant rate would reduce intrathoracic pressure and hence increase stroke volume. However, this change in stroke volume was less marked in the animals which had been pretreated with propranolol

Table 3 Organ blood flow (ml min^{-1} g^{-1} organ wt) after administration of either xylazine or phenylephrine at three artificial respiratory volumes

Group & Resp. vol. (ml kg^{-1})	*Heart*	*Lungs*	*Kidneys*	*Testes*	*Epididimides*
Saline (15)	1.78 ± 0.26	1.25 ± 0.19	2.41 ± 0.15	0.25 ± 0.02	0.14 ± 0.01
Saline (20)	1.05 ± 0.07	0.77 ± 0.16	2.06 ± 0.21	0.19 ± 0.03	0.11 ± 0.02
Saline (30)	1.41 ± 0.11	0.39 ± 0.08	1.84 ± 0.11	0.13 ± 0.01	0.08 ± 0.00
Xylazine (15)	3.89 ± 0.23**	3.19 ± 0.51***	3.23 ± 0.31**	0.27 ± 0.02	0.26 ± 0.03***
Xylazine (20)	3.68 ± 0.39***	2.28 ± 0.46**	3.01 ± 0.23***	0.21 ± 0.01	0.18 ± 0.01**
Xylazine (30)	4.12 ± 0.82***	1.65 ± 0.29**	2.86 ± 0.15***	0.17 ± 0.02	0.14 ± 0.02**
Propranolol and saline (15)	1.54 ± 0.15	0.99 ± 0.14	2.27 ± 0.17	0.26 ± 0.02	0.16 ± 0.02
Propranolol and saline (20)	1.74 ± 0.18	0.65 ± 0.10	2.18 ± 0.17	0.23 ± 0.02	0.12 ± 0.11
Propranolol and saline (30)	1.27 ± 0.12	0.27 ± 0.06	1.91 ± 0.18	0.12 ± 0.02††	0.09 ± 0.01
Propranolol and PE (15)	3.59 ± 0.36**	1.33 ± 0.17	3.46 ± 0.17***	0.32 ± 0.04	0.16 ± 0.02
Propranolol and PE (20)	3.54 ± 0.60**	2.60 ± 0.69***	3.73 ± 0.23***	0.27 ± 0.03	0.16 ± 0.01
Propranolol and PE (30)	4.50 ± 1.18***	1.43 ± 0.48**	3.52 ± 0.21***	0.23 ± 0.04**	0.12 ± 0.01

	Muscle	*Skin*	*Liver*	*Spleen*	*G.I.T.*	*Hepatosplanchnic*
Saline (15)	0.085 ± 0.007	0.099 ± 0.010†	0.12 ± 0.01	0.89 ± 0.08††	0.81 ± 0.04†	4.33 ± 0.17††
Saline (20)	0.089 ± 0.010	0.058 ± 0.005	0.09 ± 0.01	0.55 ± 0.11	0.57 ± 0.04	3.03 ± 0.22
Saline (30)	0.115 ± 0.009	0.050 ± 0.008	0.07 ± 0.01	0.51 ± 0.04	0.48 ± 0.04	2.58 ± 0.12
Xylazine (15)	0.111 ± 0.008	0.075 ± 0.005	0.40 ± 0.06***	0.66 ± 0.05*	0.92 ± 0.10	5.87 ± 0.37***
Xylazine (20)	0.135 ± 0.015**	0.069 ± 0.006	0.44 ± 0.03***	0.55 ± 0.06	0.69 ± 0.06	5.26 ± 0.26***
Xylazine (30)	0.113 ± 0.009	0.066 ± 0.006	0.40 ± 0.04***	0.45 ± 0.05	0.57 ± 0.03	4.42 ± 0.34***
Propranolol and saline (15)	0.139 ± 0.018	0.093 ± 0.010	0.13 ± 0.01	0.73 ± 0.09	0.73 ± 0.08	4.12 ± 0.41
Propranolol and saline (20)	0.138 ± 0.011	0.068 ± 0.008	0.12 ± 0.01	0.76 ± 0.10	0.67 ± 0.04	3.72 ± 0.24
Propranolol and saline (30)	0.114 ± 0.005	0.041 ± 0.004	0.09 ± 0.01	0.39 ± 0.04†	0.58 ± 0.05	2.79 ± 0.28†
Propranolol and PE (15)	0.096 ± 0.005*	0.115 ± 0.009	0.27 ± 0.03***	0.83 ± 0.11	1.11 ± 0.09**	6.53 ± 0.38***
Propranolol and PE (20)	0.163 ± 0.026	0.153 ± 0.039***	0.42 ± 0.03***	0.76 ± 0.09	1.00 ± 0.18**	5.70 ± 0.19***
Propranolol and PE (30)	0.164 ± 0.022**	0.091 ± 0.012**	0.25 ± 0.02***	0.59 ± 0.11	0.84 ± 0.06*	4.98 ± 0.21***

PE = phenylephrine. Resp. vol. = artificial respiratory volume (54 cycles min^{-1}). Hepatosplanchnic refers to flow (ml min^{-1}) per 100 g body weight through the hepatosplanchnic bed. For all groups, $n = 8$.
Significant differences between the appropriate experimental groups and the saline or propranolol/saline controls were determined by analysis of variance: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
Statistical comparisons of the respiratory volume groups 15 ml kg^{-1} and 30 ml kg^{-1} with the 20 ml kg^{-1} group within both saline and propranolol/saline treatments were made by analysis of variance: † $P < 0.05$; †† $P < 0.01$.

(15 ml kg^{-1} 22% greater than control) than in the untreated animals (34% greater at the lower respiratory volume) and, since propranolol would not be expected to have any influence on mechanically mediated changes in intrathoracic pressure, this suggests that an increase in venous return contributed to the observed increase in cardiac output. It is interesting to note that all the other cardiovascular effects on the reduction in respiratory volume were abolished by propranolol which indicates that β-adrenoceptor-mediated mechanisms are involved in these responses.

In the absence of a functional sympathetic nervous system, as is the case in the pithed rat, other mechanisms must be brought into play to modify cardiovascular performance in order to compensate for

changes in physiological state. In this respect, there is evidence for a direct effect of hypoxia on adrenal catecholamine release (especially when the sympathetic nervous system is compromised) in the foetal calf (Comline & Silver, 1966), the dog (Nahas *et al.*, 1954; Hammill *et al.*, 1979), the piglet (Lee *et al.*, 1980) and the rat (Johnson *et al.*, 1983). In addition, hypercapnia and acidosis also stimulate adrenal catecholamine release and when they occur together stimulation of the gland is even greater, whether or not there is accompanying hypoxia (Morris & Millar, 1962; Nahas *et al.*, 1967). In the present study, reducing respiratory volume induced moderate respiratory acidosis, hypercapnia and hypoxia. It is possible that in the absence of an active sympathetic nervous system, this may be sufficient to induce adrenal catecholamine release. The catecholamine involved is most probably adrenaline, as this is the major catecholamine secreted in the pithed rat (Yamaguchi & Kopin, 1979), and the vascular effects of adrenal gland stimulation in the pithed rat are similar to those evoked by exogenous adrenaline (Flavahan *et al.*, 1985).

It is interesting to note that infusions of adrenaline, noradrenaline or isoprenaline decrease vascular capacitance and increase venous return in the rat, dog and cat, an effect which is attenuated by propranolol and attributed to β-adrenoceptor stimulation (see Hainsworth, 1986 for review). Although part of the response to isoprenaline in the anaesthetized dog was probably mediated by reflexes since it could be reduced or abolished by baroreceptor denervation (Müller-Ruchholtz *et al.*, 1977), β-adrenoceptor-mediated reductions in systemic capacitance after isoprenaline administration have been reported in anaesthetized, ganglion blocked dogs (Rutlen *et al.*, 1981). It was found that the capacitance response was due to changes in the splanchnic circulation which were associated with a reduction in hepatic post-sinusoidal resistance (Rutlen *et al.*, 1981). It is therefore possible that the effect of increasing cardiac stroke volume might be the result of the action of catecholamines of adrenal origin increasing venous return.

Another possibility is that changes in activity in the renin-angiotensin system are involved in bringing about the increase in stroke volume occurring during hypoxia and hypercapnia. There is considerable activity of this system in the pithed rat (de Jonge *et al.*, 1982; Vollmer *et al.*, 1984) and this helps to maintain blood pressure, apparently by actions on cardiac output rather than total peripheral resistance (Kaufman & Vollmer, 1985). The efficacy of propranolol in blocking this response might be due to the ability of β-adrenoceptor blocking agents to decrease renin release; this has been shown in anaesthetized rats (Oates *et al.*, 1978) and they are also known to block catecholamine stimulated release of renin from slices of rat kidney (Weinberger *et al.*, 1975). Recently we have found that the increase in cardiac output at low respiratory volume is abolished by administration of the angiotensin converting enzyme inhibitor, enalapril (MacLean & Hiley, unpublished).

Whatever the mechanism by which cardiac output is increased following the reduction in respiratory volume, the overall changes in the circulation would be insufficient to maintain the O_2 supply to such vital organs as the heart, liver, lungs and kidney in the face of a reduction in Pao_2. This indicates that haemodynamic compensation for impaired oxygen supply is severely compromised in the pithed rat.

Increasing respiratory volume from $20\,ml\,kg^{-1}$ to $30\,ml\,kg^{-1}$ increased heart rate by 29% but cardiac output was unchanged due to a reduction in stroke volume. Local alterations in cardiac metabolism caused by disturbances in blood gas and acid/base balance could contribute to an increase in sino-atrial node activity (see Bing, 1965 for review) and it is possible that this, in the absence of any other effect on the cardiovascular system, could account for the increase in heart rate observed in the rats ventilated at the higher rate.

The effects of respiratory volume on the cardiovascular responses induced by phenylephrine and xylazine

The effects of phenylephrine and xylazine (at the control respiratory volume of $20\,ml\,kg^{-1}$) on cardiac output, regional distribution of cardiac output and regional blood flow were essentially the same as previously reported and discussed (Hiley & Thomas, 1987). One notable feature is, however, that phenylephrine increased heart rate at respiratory volumes of 15 and $30\,ml\,kg^{-1}$. This is not likely to be due to β-adrenoceptor stimulation because of the presence of propranolol at a dose sufficient to abolish the heart rate response to 50 ng isoprenaline (C.R. Hiley, unpublished observations) and it has previously been shown that this heart rate response to phenylephrine is removed by the administration of prazosin (Hiley & Thomas, 1987). Also α_1-adrenoceptors mediating tachycardia have been reported by Flavahan & McGrath (1981) and McGrath *et al.* (1982). The present results also confirm that increases in both cardiac output and total peripheral resistance contribute to the pressor effects of selective α-adrenoceptor agonists.

There was no modification of the cardiovascular effects of xylazine by variations in respiratory volume and hence blood gases and pH. In contrast there was such an interaction with the effects of phenylephrine on heart rate, cardiac output distribution to the liver, epididimides, hepatosplanchnic bed

and gastrointestinal tract, and also on blood flow through the large intestine and skeletal muscle. Alteration of respiratory volume had varying influences on these effects of phenylephrine. Thus, the increased percentage of cardiac output passing to the liver was more pronounced at the respiratory volume of 20 ml kg^{-1} (165% as compared with 84% and 89% for 15 and 30 ml kg^{-1} respectively), whilst that to the hepatosplanchnic bed as a whole was greatest at the lowest respiratory volume (39% as compared with 17% and 155% for 20 and 30 ml kg^{-1} respectively). Further, a significant decrease (32%) in the proportion of cardiac output passing to the epididimides was evident only at the respiratory volume of 30 ml kg^{-1}, whilst an increase in cardiac output distribution to the gastrointestinal tract was only seen at 15 ml kg^{-1} (33%). The effect of phenylephrine on blood flow through the large intestine was greatest at the lowest respiratory volume (a 74% decrease as compared with 51% and 38% for respiratory volumes of 20 and 30 ml kg^{-1} respectively). There was a bimodal influence of respiratory volume on the effect of phenylephrine on skeletal muscle blood flow which was decreased by 31% at 15 ml kg^{-1} and increased by 44% at 30 ml kg^{-1}.

Our results show that there was no effect of moderate changes in blood gases and pH, induced by the changes in respiratory volume, on the net pressor effect of phenylephrine. This is in contrast to studies in which a greater range of blood gas and pH values have been investigated (McGrath *et al.*, 1982; Grant *et al.*, 1985; Korstanje *et al.*, 1985). Nevertheless, the present work does show that even these relatively small blood gas and pH changes differentially affect the responses of individual vascular beds to phenylephrine. In addition, it should be noted that the relative activity of the two agonists varies at different levels of artificial respiration. For example, if the changes in the proportion of cardiac output passing to, and blood flowing through the lungs are analysed, at a respiratory volume of 15 ml kg^{-1} there was no apparent effect of phenylephrine, while there were increases with xylazine. At the higher respiratory volumes, however, phenylephrine caused profound increases in both the percentage of cardiac output passing to the lungs and in their blood flow. It must be remembered that the microspheres trapped in the lungs include not only those reaching the lungs through the bronchial circulation but also those which are trapped in this organ after passing through arteriovenous anastomoses. Thus these effects could be due to action of the α-agonists on either part of the circulation.

In considering these differences between xylazine and phenylephrine, it must be borne in mind that propranolol was present in those animals given the α_1-adrenoceptor agonist but not in those given xylazine. Although all the phenylephrine groups were compared with appropriate saline control animals which had also been given propranolol, it is possible that differences in basal physiological state due to β-adrenoceptor blockade could be in part responsible for the different responses to the α-adrenoceptor agonists. Despite this possibility, it was considered desirable to include propranolol in order to allow for possible changes in the balance of the α_1- and β-adrenoceptor agonist activities of phenylephrine that might result from alterations in blood gas and pH.

In conclusion, this study shows that even moderate changes in blood gases and pH can influence cardiac output, its distribution and, hence, regional blood flow. They also affect the way in which different vascular beds respond to phenylephrine and xylazine. This study confirms that, when the pithed rat preparation is being used to study α-adrenoceptor responses, respiratory parameters should be scrutinized before cardiovascular responses to α-agonists are interpreted and compared.

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