Left ventricular contractility is reduced by hypercapnic acidosis and thoracolumbar epidural anesthesia in rabbits

[La contractilité ventriculaire est réduite par l'acidose respiratoire et l'anesthésie péridurale thoraco-lombaire chez les lapins]

Yuzo Mizukoshi MD,* Keizo Shibata MD,† Masahiro Yoshida MD*

Purpose: We have previously observed that sympathetic blockade by epidural anesthesia (EA) modifies the cardiovascular response to marked hypercapnic acidosis in dogs. Our objective was to determine whether the combination of marked hypercapnic acidosis and EA reduce left ventricular contractility.

Methods: We randomly assigned 22 Japanese white rabbits anesthetized with isoflurane (1.0%) to two groups according to the absence (control group, $n = 11$) or presence (EA group, $n = 11$) of thoracolumbar EA. After epidural injection ($0.5 \text{ mL} \cdot \text{kg}^{-1}$ of 0.9% saline in the control group or 1% mepivacaine in the EA group) and during subsequent hypercapnia (mean arterial CO_2 tension 85 mmHg), we measured left ventricular pressure, left ventricular volume by using conductance catheter and plasma catecholamine concentrations. Left ventricular contractility was assessed by the slope of the linear approximation of the left ventricular end-systolic pressure-volume relationship, [i.e., end-systolic elastance (Ees)].

Results: The combination of hypercapnic acidosis and thoracolumbar EA caused a 65% decrease in Ees ($P < 0.05$). Hypercapnic acidosis alone caused a 16% decrease ($P < 0.05$) and thoracolumbar EA alone caused a 49% decrease in Ees ($P < 0.05$). In the EA group, epidural injection caused an 85% decrease in the epinephrine concentration ($P < 0.05$) and a 39% decrease in the norepinephrine concentration ($P < 0.05$), even during hypercapnic acidosis. However, in the control group, hypercapnic acidosis caused no change in the circulating epinephrine concentration but a 74% increase in the circulating norepinephrine concentration ($P < 0.05$).

Conclusion: Combined hypercapnic acidosis and EA markedly reduce left ventricular contractility in an additive fashion in rabbits receiving general anesthesia.

Objectif: Nous avons déjà observé que le blocage sympathique relevant de l'anesthésie péridurale (AP) modifie la réponse cardiovasculaire à une acidose hypercapnique marquée chez les chiens. Notre objectif était de déterminer si la combinaison d'acidose hypercapnique marquée et l'AP réduisent la contractilité ventriculaire.

Méthode : Nous avons réparti au hasard 22 lapins blancs japonais anesthésiés avec de l'isoflurane (1,0 %) en deux groupes selon l'absence (groupe témoin, $n = 11$) ou la présence (groupe AP, $n = 11$) d'AP thoraco-lombaire. Après l'injection péridurale ($0,5 \text{ mL} \cdot \text{kg}^{-1}$ de solution salée à 0,9 % dans le groupe témoin ou de mépivacaïne à 1 % dans le groupe AP) et pendant l'hypercapnie subséquente (pression artérielle moyenne de CO_2 85 mmHg), nous avons mesuré la pression ventriculaire gauche, le volume ventriculaire gauche au moyen d'une cathéter à conductance et les concentrations plasmatiques de catécholamine. La contractilité ventriculaire a été évaluée par la pente de l'approximation linéaire de la relation pression-volume télosystolique ventriculaire gauche, [c.-à-d., l'élastance télosystolique (Ets)].

Résultats : La combinaison d'acidose hypercapnique et d'AP thoraco-lombaire a causé une baisse de 65 % de l'Ets ($P < 0,05$). L'acidose hypercapnique à elle seule a diminué l'Ets de 16 % ($P < 0,05$) et l'AP thoraco-lombaire, seule, a diminué l'Ets de 49 % ($P < 0,05$). Dans le groupe d'AP, l'injection péridurale a entraîné une baisse de 85 % de la concentration d'adrénaline ($P < 0,05$) et une baisse de 39 % de noradrénaline ($P < 0,05$), même pendant l'acidose hypercapnique. Cependant, dans le groupe témoin, l'acidose hypercapnique n'a pas modifié la concentration plasmatique d'adrénaline, mais a augmenté de 74 % la concentration de noradrénaline ($P < 0,05$).

Conclusion : La combinaison d'acidose hypercapnique et d'AP réduisent de façon marquée la contractilité ventriculaire gauche d'une manière additive chez des lapins sous anesthésie générale.

From the Department of Anesthesiology and Intensive Care Medicine,* and the Department of Emergency and Critical Care Medicine,† Kanazawa University School of Medicine, Kanazawa, Japan.

Address correspondence to: Dr. Yuzo Mizukoshi, Department of Anesthesiology and Intensive Care Medicine, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa 920-8641, Japan. Phone: +81-76-265-2434; Fax: +81-76-234-4267; E-mail: ymizkosi@med.kanazawa-u.ac.jp

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THE cardiovascular responses to hypercapnic acidosis result from the direct effects of carbon dioxide on the myocardium and peripheral vasculature, and the indirect effects on the sympathetic nervous system.¹ Hypercapnic acidosis directly reduces contractility in isolated heart muscle preparations,² causes peripheral vasodilation, and indirectly increases the release of catecholamines from sympathetic nerve endings and adrenal glands.^{3,4} We have previously observed that thoracolumbar epidural anesthesia (EA) in dogs abolishes the physiologic increase in circulating catecholamine concentrations and reduces cardiac output (CO) and mean arterial blood pressure (MAP) during marked hypercapnic acidosis.⁵ However, CO is also influenced by loading conditions and is not a suitable index of left ventricular contractility. Therefore we could not differentiate the direct and indirect effects of CO₂ during hypercapnic acidosis. Our objective was to determine whether a combination of marked hypercapnic acidosis and EA depresses left ventricular contractility. Left ventricular contractility was assessed by measuring the slope of the left ventricular end-systolic pressure-volume relationship, [i.e., end-systolic elastance (Ees)], because it reflects the contractile state and is relatively insensitive to loading conditions.⁶⁻⁸

Methods

This investigation was approved by our institutional Animal Care Committee.

Preparations

Twenty-two Japanese white rabbits 3.3 to 4.0 kg were anesthetized by inhalation of isoflurane. An epidural catheter (0.6 mm outer diameter, Hakko, Tokyo, Japan) was then inserted percutaneously, employing the loss-of-resistance technique.⁹ A space between the fifth and seventh lumbar vertebra was chosen as the site of puncture. The catheter was advanced 8 to 10 cm cephalad into the epidural space. Correct placement of the catheter and spread of contrast medium were verified radiographically using 0.5 mL·kg⁻¹ of iopamidol. An ear vein was cannulated to infuse Ringer's acetate solution at a rate of 10 mL·kg⁻¹·hr⁻¹. Anesthesia was maintained with 2.0% isoflurane during the surgical procedures. The trachea was intubated and the animal mechanically ventilated to maintain an arterial CO₂ tension (PaCO₂) between 35 and 45 mmHg. The carotid artery was cannulated to monitor the MAP and to sample blood. Lead II of the electrocardiogram was recorded continuously.

Pressure-volume relationship

The chest was opened along the sternum, and a 6-electrode conductance catheter (2Fr, Unique Medical,

Tokyo, Japan) was inserted into the left ventricle from the apex toward the aortic valve to measure ventricular volume. A catheter-tipped micromanometer (4Fr, Keller, Winterthur, Switzerland) was inserted into the left ventricle from the apex to determine left ventricular pressure. Specific blood conductance was measured on samples placed in a cuvette. The conditioning amplifier (Integral 3 model-VPR-1002, Unique Medical), which converts the voltages from the conductance catheter to volume, was then calibrated and all of the signals, including left ventricular pressure and volume and the electrocardiogram, were digitized (AD12-8, Contec, Osaka, Japan) at a sampling rate of 480 Hz. They were sent to a dedicated laboratory computer system (ThinkPad 600, IBM Japan, Tokyo, Japan) for instantaneous left ventricular pressure-volume loop monitoring and subsequent analysis (VPS-101, Unique Medical). Correct positioning of the catheters was verified by monitoring the pressure-volume loops. The conductance method used to determine left ventricular volume is based on measuring the conductivity of the blood inside the left ventricular cavity.¹⁰ Ees was determined from multiple pressure-volume loops obtained during partial occlusion of the pulmonary artery and was calculated using an iterative linear regression method.¹¹ The effective arterial elastance (Ea) was defined as the ratio of end-systolic pressure to stroke volume (SV). The end-diastolic volume (EDV) and Ea represent indices of preload and afterload,¹² respectively.

Experimental protocol

After placement of the catheters, the concentration of inspired isoflurane was decreased to 1.0%, and at least 20 min was allowed for blood gases and hemodynamic parameters to stabilize. The animals were randomly assigned to two groups according to the absence (control group, *n*=11) or presence (EA group, *n*=11) of thoracolumbar EA. Arterial blood was sampled for blood gas analysis and for determining plasma catecholamine concentrations. Hemodynamic variables, including MAP, heart rate (HR), left ventricular volume and pressure were measured. CO, SV, Ees, and Ea were calculated. After baseline measurements were obtained, either 0.5 mL·kg⁻¹ of 0.9% saline (control group) or 1% mepivacaine (EA group) was injected *via* the epidural catheter. Biochemical analysis and hemodynamic measurements were performed 15 min after the epidural injection and 15 min after the start of hypercapnic challenge. Switching the inspired gas from 50% O₂/50% N₂ to a hypercapnic gas mixture (50% O₂ / 10% CO₂ / 40% N₂) induced hypercapnic acidosis. Arterial blood gases were measured using an automated blood gas

analyzer (ABL-3, Radiometer, Copenhagen, Denmark). Blood used for the determination of catecholamines was placed in 5 mL sodium ethylenediaminetetraacetic acid vacuum tubes on ice prior to centrifugation for 15 min at $2,000 \times g$ and 4°C . Plasma was decanted and stored at -20°C until analysis.

Statistical analysis

Data are presented as the mean $\pm$ SD. Between-group differences and within-group changes over time were analyzed by two-way analysis of variance with repeated measures using Super ANOVA (Abacus Concepts, Berkeley, USA). A value for $P < 0.05$ was considered statistically significant. When the analysis of variance detected a significant between-group or within-group difference, unpaired *t* test and the least-squares means contrast was performed, respectively.

Results

There was no significant difference between the control and EA group with respect to weight (3.8 ± 0.2 and 3.7 ± 0.2 kg, respectively). Radiographic studies indicated that the contrast medium spread from the T2 $\pm$ 3 level to L3 $\pm$ 1 level and from the T2 $\pm$ 3 level to L4 $\pm$ 1 level, in the control and the EA groups, respectively.

Blood gas analysis

The mean PaCO_2 increased to 84–85 mmHg in the control and EA groups 15 min after the start of hypercapnic challenge (Table I). There were no significant between-group differences at any point during the experimental period.

Hemodynamics

There were no significant differences in the baseline hemodynamic variables between the two groups (Table II). After epidural injection, the control group had no change in any of the hemodynamic variables. In contrast, the EA group had a 49% decrease in Ees and a 17% decrease in CO, compared with the baseline values. After the subsequent hypercapnic challenge, the control group had a 16% decrease in Ees and a 26% decrease in CO. In contrast, the EA group had a 65% decrease in Ees and a 20% decrease in CO, compared with baseline values. Thus, the impact of hypercapnic acidosis and thoracolumbar EA on the CO was not additive, but that on the Ees was additive.

Plasma catecholamine concentrations

There were no significant differences in the baseline plasma concentrations of epinephrine and norepinephrine between the two groups (Table III). Before

TABLE I Blood gas analysis in the control and EA groups

		Baseline	Post-EA	Hypercapnia
pH	Control	7.40 ± 0.05	7.40 ± 0.03	$7.12 \pm 0.05^{\dagger}$
	EA	7.40 ± 0.03	7.41 ± 0.03	$7.11 \pm 0.04^{\dagger}$
PaCO_2 (mmHg)	Control	38 ± 3	38 ± 2	$85 \pm 6^{\dagger}$
	EA	38 ± 3	36 ± 3	$84 \pm 3^{\dagger}$
PaO_2 (mmHg)	Control	272 ± 26	260 ± 34	274 ± 38
	EA	263 ± 21	262 ± 21	271 ± 29
HCO_3^- (mmol·L $^{-1}$)	Control	23 ± 2	23 ± 2	27 ± 2
	EA	23 ± 2	22 ± 2	26 ± 2

Values are reported as the mean $\pm$ SD; $n=11$ /group. Post-EA=15 min after epidural injection and just before hypercapnic challenge; Hypercapnia=15 min after the start of hypercapnic challenge.

$^{\dagger}P < 0.05$ vs baseline values.

TABLE II Hemodynamic data in the control and EA groups

		Baseline	Post-EA	Hypercapnia
MAP (mmHg)	Control	94 ± 9	95 ± 11	95 ± 12
	EA	97 ± 11	$55 \pm 20^{*\dagger}$	$53 \pm 20^{*\dagger}$
HR (beats·min $^{-1}$)	Control	213 ± 25	215 ± 28	$152 \pm 25^{\dagger}\$$
	EA	211 ± 29	$195 \pm 33^{\dagger}$	$178 \pm 41^{\dagger}\$$
CO (mL·min $^{-1}$)	Control	294 ± 66	306 ± 65	$217 \pm 46^{\dagger}\$$
	EA	283 ± 49	$236 \pm 63^{*\dagger}$	$227 \pm 59^{\dagger}$
SV (mL)	Control	1.4 ± 0.3	1.4 ± 0.3	1.5 ± 0.3
	EA	1.3 ± 0.2	1.2 ± 0.3	1.3 ± 0.3
Ees (mmHg·mL $^{-1}$)	Control	97 ± 21	94 ± 27	$81 \pm 19^{\dagger}\$$
	EA	85 ± 25	$43 \pm 16^{*\dagger}$	$30 \pm 11^{*\dagger}\$$
EDV (mL)	Control	5.9 ± 0.7	6.0 ± 0.6	$6.8 \pm 0.8^{\dagger}\$$
	EA	6.2 ± 0.9	$5.7 \pm 1.1^{\dagger}$	$6.4 \pm 0.9^{\dagger}\$$
Ea (mmHg·mL $^{-1}$)	Control	84 ± 29	79 ± 17	$91 \pm 33^{\dagger}\$$
	EA	86 ± 20	$62 \pm 19^{*\dagger}$	$58 \pm 23^{*\dagger}$

Values are reported as the mean $\pm$ SD; $n=11$ /group. EA=epidural anesthesia; MAP=mean arterial pressure; HR=heart rate. CO=cardiac output; SV=stroke volume; Ees=end-systolic elastance; EDV=end-diastolic volume; Ea=effective arterial elastance. * $P < 0.05$ vs control group; $^{\dagger}P < 0.05$ vs baseline values; $\$P < 0.05$ vs post-EA values.

the hypercapnic challenge, the plasma concentrations of both catecholamines were significantly lower in the EA group. Hypercapnic acidosis caused no significant change in the epinephrine concentration but resulted in a 74% increase in the norepinephrine concentration in the control group. In contrast, hypercapnia caused an 85% decrease in the epinephrine concentration and

TABLE III Plasma catecholamine concentrations in the control and EA groups

	Baseline	Post-EA	Hypercapnia
Epinephrine (pg·mL ⁻¹)			
Control	360 ± 220	330 ± 190	410 ± 430
EA	470 ± 260	96 ± 60*†	72 ± 53*†
Norepinephrine (pg·mL ⁻¹)			
Control	690 ± 260	750 ± 290	1200 ± 390†
EA	640 ± 150	260 ± 130*†	390 ± 190*†

Values are reported as the mean ± SD; *n*=11/group. EA=epidural anesthesia; **P*<0.05 *vs* control group; †*P*<0.05 *vs* baseline values.

a 39% decrease in the norepinephrine concentration in the EA group compared with the baseline values.

Electrocardiogram

Neither elevation nor depression of ST-segment was observed in lead II of the electrocardiogram during the experimental period.

Discussion

The major finding of this study was that the combination of hypercapnic acidosis and thoracolumbar EA caused a 65% reduction in left ventricular contractility. Furthermore, the effects of EA and hypercapnic acidosis were additive.

We have previously demonstrated that hypercapnic acidosis alone increases CO and MAP in dogs.⁵ Hypercapnia induces both direct and indirect cardiovascular effects. It directly depresses myocardial contractility, dilates the peripheral arterioles, and stimulates the sympathetic nervous system at several levels. Therefore, the cardiovascular responses to hypercapnia result from a direct effect of CO₂ as well as indirect effect on the sympathetic nervous system. However, no direct indices of left ventricular contractility were measured in our previous study. Therefore we could not differentiate the direct and indirect effects of CO₂ during hypercapnic acidosis.

There are many conventional measures of left ventricular performance, including ejection fraction, maximum rate of change of left ventricular pressure,^{1,3} circumferential fibre shortening,¹⁴ fractional area change,¹⁵ and pressure-dimension indices.^{6,16,17} All of these measures are influenced not only by the contractile state but also by loading conditions.^{8,18,19} However, Ees reflects the contractile state and is relatively insensitive to loading conditions.^{6-8,18} We therefore compared left ventricular contractility by measuring Ees.

Studies in isolated myocardial muscle and excised hearts have demonstrated that hypercapnic acidosis directly depresses contractility.²⁰⁻²⁴ Walley *et al.* reported that hypercapnic acidosis (PaCO₂ 92 mmHg) decreases Ees by 19% in dogs anesthetized with fentanyl.²⁵ In contrast to previous studies in humans or dogs, hypercapnic acidosis caused bradycardia and reduced CO in our study of rabbits. We hypothesize that this finding is due to activation of compensatory reflexes.²⁶ We also found no increase in the epinephrine concentration during hypercapnia, and this may contribute to the bradycardia observed during hypercapnic acidosis in rabbits. Although the changes in HR and CO can vary based on the animal studied, we confirmed that hypercapnic acidosis during general anesthesia reduces left ventricular contractility *in vivo*.

In spite of several previous clinical and experimental studies, questions remain about the effect of EA on left ventricular contractility, which has variously been reported to be unchanged,^{27,28} decreased,^{29,30} or even increased.^{31,32} This variability is attributable to differences in study design, the subjects studied, and the measures used to assess left ventricular contractility. Our results demonstrate that thoracolumbar EA reduced Ees by 49% compared with the baseline value. The contrast medium spread extensively and circulating catecholamines decreased in the EA group. Therefore, the decreased contractility appears to be the result of both sympathetic denervation of the heart and blockade of the humoral sympathetic system. Goertz *et al.* reported that high thoracic EA decreases Ees in humans by 50%.³⁰ The decrease in Ees in humans is similar to that observed during thoracolumbar EA in the present study. Thoracolumbar EA causes the blockade of afferences and efferences between the heart and the central nervous system (cardiac denervation). This results in a decreased norepinephrine level in the circulation. If, in addition, lumbar denervation is obtained, the adrenal gland will not release epinephrine (humoral aspect of the sympathetic system).

We previously found that the combination of hypercapnic acidosis and thoracolumbar EA decreased CO and MAP in dogs.⁵ We assumed that sympathetic blockade and cardiac denervation caused by thoracolumbar EA unmasked the direct effects of CO₂ on left ventricular contractility and vascular tone. However, there was no direct evidence of reduced left ventricular contractility in our previous study. The present study evaluated directly the effect of combined hypercapnic acidosis and thoracolumbar EA on left ventricular contractility, and demonstrated that this combination reduced contractil-

ity in an additive fashion. Miyabe *et al.* previously reported that thoracic EA reduces the time to cardiac arrest in apneic rabbits.^{3,3} Because apnea causes not only hypercapnia but also hypoxia, we cannot directly compare their results with ours. However, the markedly reduced left ventricular contractility demonstrated in our study may have contributed to this reduced time to cardiac arrest.

With regard to CO, the impact of hypercapnic acidosis and thoracolumbar EA are not additive. Therefore, from the standpoint of “non-cardiac organs”, the combination of hypercapnic acidosis and thoracolumbar EA has potentially no major impact in patients without heart failure.

There are several limitations to the current study. First, there are species differences with respect to the cardiovascular responses to hypercapnic acidosis. Acute hypercapnic acidosis causes increased HR and CO in dogs^{5,25} and humans,⁴ but decreases HR and CO in rabbits. Therefore, it may not be appropriate to simply extrapolate our results to humans. Second, our findings may not have direct clinical applicability because hypercapnic acidosis was induced acutely by inhalation of high concentration of CO₂, a situation unlikely to occur during clinical anesthesia. Third, the general anesthesia technique used in our study may have influenced results.⁸ However, the minimum alveolar concentration for isoflurane in rabbits is 2.05%,^{3,4} and the effect of light anesthesia, such as that used in the current study, is most likely minor.

In summary, the current study shows that, in anesthetized rabbits, the combination of marked hypercapnic acidosis and EA reduces left ventricular contractility in an additive fashion. Inasmuch as extrapolation to the clinical setting is feasible, our findings suggest that, during the combined administration of epidural and general anesthesia, it is specially important to avoid hypercapnia.

References

- 1 Cullen DJ, Eger, II, EI. Cardiovascular effects of carbon dioxide in man. *Anesthesiology* 1974; 41: 345–9.
- 2 Foëx P, Fordham RMM. Intrinsic myocardial recovery from the negative inotropic effects of acute hypercapnia. *Cardiovasc Res* 1972; 6: 257–62.
- 3 Davidson D, Stalcup SA, Mellins RB. Systemic hemodynamics affecting cardiac output during hypercapnic and hypercapnic hypoxia. *J Appl Physiol* 1986; 60:1230–6.
- 4 Rasmussen JP, Dauchot PJ, DePalma RG, *et al.* Cardiac function and hypercarbia. *Arch Surg* 1978; 113: 1196–200.
- 5 Shibata K, Futagami A, Taki Y, Kobayashi T. Epidural anesthesia modifies the cardiovascular response to marked hypercapnia in dogs. *Anesthesiology* 1994; 81: 1454–60.
- 6 Suga H, Sagawa K, Shoukas AA. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res* 1973; 32: 314–22.
- 7 Mehmel HC, Stockins B, Ruffmann K, Olshausen KV, Schuler G, Kübler W. The linearity of the end-systolic pressure-volume relationship in man and its sensitivity for assessment of left ventricular function. *Circulation* 1981; 63: 1216–22.
- 8 Declercq C, Hillel Z, Shih H, Kuroda M, Connery CP, Thys DM. A comparison of left ventricular performance indices measured by transesophageal echocardiography with automated border detection. *Anesthesiology* 1998; 89: 341–9.
- 9 Taguchi H, Murao K, Nakamura K, Uchida M, Shingu K. Percutaneous chronic epidural catheterization in the rabbit. *Acta Anaesthesiol Scand* 1996; 40: 232–6.
- 10 Baan J, van der Velde ET, Hein MS, *et al.* Continuous measurement of left ventricular volume in animals and human by conductance catheter. *Circulation* 1984; 70: 812–23.
- 11 Kono A, Maughan WL, Sunagawa K, Hamilton K, Sagawa K, Weisfeldt ML. The use of left ventricular end-ejection pressure and peak pressure to estimate the end-systolic pressure-volume relationship. *Circulation* 1984; 70: 1057–65.
- 12 Kelly RP, Ting C-T, Yang T-M, *et al.* Effective arterial elastance as index of arterial vascular load in humans. *Circulation* 1992; 86: 513–21.
- 13 Hillidge CJ, Lees P. The rate of rise of intraventricular pressure as an index of myocardial contractility in conscious and anaesthetised ponies. *Res Vet Sci* 1976; 21: 176–83.
- 14 Karliner JS, Gault JH, Eckberg D, Mullins CB, Ross J Jr. Mean velocity of fibre shortening. A simplified measure of left ventricular myocardial contractility. *Circulation* 1971; 44: 323–33.
- 15 Konstadt SN, Thys D, Mindich BP, Kaplan JA, Goldman M. Validation of quantitative intraoperative transesophageal echocardiography. *Anesthesiology* 1986; 65: 418–21.
- 16 Little WC. The left ventricular dP/dt_{max}-end-diastolic volume relation in closed-chest dogs. *Circ Res* 1985; 56: 808–15.
- 17 Glower DD, Spratt JA, Snow ND, *et al.* Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation* 1985; 71: 994–1009.
- 18 Kass DA, Maughan WL, Guo ZM, Kono A, Sunagawa K, Sagawa K. Comparative influence of load versus inotropic states on indexes of ventricular contractility:

- experimental and theoretical analysis based on pressure-volume relationships. *Circulation* 1987; 76: 1422–36.
- 19 Maughan WL, Sunagawa K, Burkhoff D, Sagawa K. Effect of arterial impedance changes on the end-systolic pressure-volume relation. *Circ Res* 1984; 54: 595–602.
 - 20 Solaro RJ, Lee JA, Kentish JC, Allen DG. Effects of acidosis on ventricular muscle from adult and neonatal rats. *Circ Res* 1988; 63: 779–87.
 - 21 Poole-Wilson PA, Langer GA. Effects of acidosis on mechanical function and Ca^{2+} exchange in rabbit myocardium. *Am J Physiol* 1979; 236: H525–33.
 - 22 Cingolani HE, Mattiazzi AR, Blesa ES, Gonzalez NC. Contractility in isolated mammalian heart muscle after acid-base changes. *Circ Res* 1970; 26: 269–78.
 - 23 Ng ML, Levy MN, Zieske HA. Effects of changes of pH and of carbon dioxide tension on left ventricular performance. *Am J Physiol* 1967; 213: 115–20.
 - 24 Steenbergen C, Delecuw G, Rich T, Williamson JR. Effects of acidosis and ischemia on contractility and intracellular pH of rat heart. *Circ Res* 1977; 41: 849–58.
 - 25 Walley KR, Lewis TH, Wood LDH. Acute respiratory acidosis decreases left ventricular contractility but increases cardiac output in dogs. *Circ Res* 1990; 67: 628–35.
 - 26 Stekiel TA, Stekiel WJ, Tominaga M, Stadnicka A, Bosnjak ZJ, Kampine JP. Effects of halothane and isoflurane on in situ diameter responses of small mesenteric veins to acute graded hypercapnia. *Anesth Analg* 1996; 82: 349–57.
 - 27 Ottesen S, Renck H, Jynge P. Thoracic epidural analgesia. An experimental study in sheep of the effects on central circulation, regional perfusion and myocardial performance during normoxia, hypoxia and isoproterenol administration. *Acta Anaesthesiol Scand* 1978; 69(suppl): 1–16.
 - 28 Saada M, Catoire P, Bonnet F, et al. Effect of thoracic epidural anesthesia combined with general anesthesia on segmental wall motion assessed by transesophageal echocardiography. *Anesth Analg* 1992; 75: 329–35.
 - 29 Hotvedt R, Refsum H, Platou ES. Cardiac electrophysiological and hemodynamic effects of β -adrenoceptor blockade and thoracic epidural analgesia in the dog. *Anesth Analg* 1984; 63: 817–24.
 - 30 Goertz AW, Seeling W, Heinrich H, Lindner KH, Schirmer U. Influence of high thoracic epidural anesthesia on left ventricular contractility assessed using the end-systolic pressure-length relationship. *Acta Anaesthesiol Scand* 1993; 37: 38–44.
 - 31 Blomberg S, Emanuelsson H, Kvist H, et al. Effects of thoracic epidural anesthesia on coronary arteries and arterioles in patients with coronary artery disease. *Anesthesiology* 1990; 73: 840–7.
 - 32 Kock M, Blomberg S, Emanuelsson H, Lomsky M, Strömblad S-O, Ricksten S-E. Thoracic epidural anesthesia improves global and regional left ventricular function during stress-induced myocardial ischemia in patients with coronary artery disease. *Anesth Analg* 1990; 71: 625–30.
 - 33 Miyabe M, Takahashi S, Sato S, Toyooka H. Thoracic epidural block attenuates cardiovascular response to apnea in rabbits. *Can J Anaesth* 1998; 45: 373–6.
 - 34 Drummond JC. MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit: and a test for the validity of MAC determinations. *Anesthesiology* 1985; 62: 336–8.