Effects of phenylephrine and prostaglandin E₁ on ventriculo–arterial matching during halothane anaesthesia

S. HOKA, T. KAWASAKI, H. OKAMOTO, T. OKUYAMA AND S. TAKAHASHI

Summary
We have investigated the effects of phenylephrine alone and combined with prostaglandin E₁ (PGE₁) on ventriculo–arterial matching during halothane anaesthesia in dogs. The ratio of left ventricular end-systolic elastance (Ees) to effective arterial elastance (Ea) was used as an index of ventriculo–arterial matching. In group 1 (n = 7), measurements were performed at control, 1.5% halothane, halothane + phenylephrine 1–10 μg kg⁻¹ min⁻¹, and halothane + phenylephrine + PGE₁ 0.2–1.0 or 1.0–2.0 μg kg⁻¹ min⁻¹. In group 2 (n = 5), dobutamine 2 and 5 μg kg⁻¹ min⁻¹ was infused during halothane anesthesia. Halothane 1.5% decreased mean arterial pressure (MAP), cardiac output and Ees. Phenylephrine restored MAP, but further decreased cardiac output. The decrease in Ees produced by halothane was reversed by phenylephrine. PGE₁ increased cardiac output and reversed the decreases in Ea and Ea/Ees during phenylephrine infusion. Dobutamine also reversed halothane-induced decreases in MAP, cardiac output and Ees, and improved Ea/Ees. Our results indicate that combined use of PGE₁ with phenylephrine can eliminate the vasoconstrictive property of phenylephrine, resulting in an improvement in ventriculo–arterial matching. (Br. J. Anaesth. 1995; 74: 438–442)

Key words

Volatile anaesthetics cause a concentration-dependent negative inotropic effect in humans, experimental animals, and in isolated atria and ventricles of a variety of mammalian species [1, 2]. They also cause vasodilatation and a decrease in vascular resistance [3]. In addition to their direct actions, negative inotropy and vasodilatation are associated also with inhibition of the sympathetic nervous system [4].

Exogenous and endogenous catecholamines are considered to be beneficial in restoring the circulatory depression produced by volatile anaesthetics [5]. However, phenylephrine is not recommended usually because it increases systemic vascular resistance, resulting in a further decrease in cardiac output [6]. It has been shown that bolus administration of phenylephrine in patients during isoflurane-induced hypotension caused a transient im-

Summary
We have investigated the effects of phenylephrine alone and combined with prostaglandin E₁ (PGE₁) on ventriculo–arterial matching during halothane anaesthesia in dogs. The ratio of left ventricular end-systolic elastance (Ees) to effective arterial elastance (Ea) was used as an index of ventriculo–arterial matching. In group 1 (n = 7), measurements were performed at control, 1.5% halothane, halothane + phenylephrine 1–10 μg kg⁻¹ min⁻¹, and halothane + phenylephrine + PGE₁ 0.2–1.0 or 1.0–2.0 μg kg⁻¹ min⁻¹. In group 2 (n = 5), dobutamine 2 and 5 μg kg⁻¹ min⁻¹ was infused during halothane anesthesia. Halothane 1.5% decreased mean arterial pressure (MAP), cardiac output and Ees. Phenylephrine restored MAP, but further decreased cardiac output. The decrease in Ees produced by halothane was reversed by phenylephrine. PGE₁ increased cardiac output and reversed the decreases in Ea and Ea/Ees during phenylephrine infusion. Dobutamine also reversed halothane-induced decreases in MAP, cardiac output and Ees, and improved Ea/Ees. Our results indicate that combined use of PGE₁ with phenylephrine can eliminate the vasoconstrictive property of phenylephrine, resulting in an improvement in ventriculo–arterial matching. (Br. J. Anaesth. 1995; 74: 438–442)

Key words

Volatile anaesthetics cause a concentration-dependent negative inotropic effect in humans, experimental animals, and in isolated atria and ventricles of a variety of mammalian species [1, 2]. They also cause vasodilatation and a decrease in vascular resistance [3]. In addition to their direct actions, negative inotropy and vasodilatation are associated also with inhibition of the sympathetic nervous system [4].

Exogenous and endogenous catecholamines are considered to be beneficial in restoring the circulatory depression produced by volatile anaesthetics [5]. However, phenylephrine is not recommended usually because it increases systemic vascular resistance, resulting in a further decrease in cardiac output [6]. It has been shown that bolus administration of phenylephrine in patients during isoflurane-induced hypotension caused a transient im-
aortic flow probe. To measure left ventricular pressure, another microtipped pressure transducer was inserted through the apex of the left ventricle. These pressure transducers were attached to an amplifier (Polygraph type 361, San-ei Instrument Co., Tokyo). Continuous electrocardiographic monitoring was performed throughout the experiment and all haemodynamic measurements were taken during the resting expiratory phase of respiration. All data were recorded and digitized by a computer interfaced with an analogue-to-digital converter (Mac Lab, Analogue Digital Instruments Pty Ltd, Australia).

Figure 1  Ventriculo-arterial coupling in the pressure-volume plane. The diagram shows left ventricular (LV) end-systolic elastance (Ees) as the slope of the end-systolic pressure-volume relationship. Vo = end-systolic unstressed volume. The effective arterial elastance (Ea) is the slope of the end-systolic pressure-stroke volume relation. Ees can be approximated by the ratio of arterial resistance to one cardiac cycle length. The diagonal line that runs from end-diastolic volume (Ved) represents the Ea line. The intersection between the Ees and Ea line gives the end-systolic volume (Ves). Stroke volume is the difference between Ved and Ves. The hatched area indicates the stroke work (SW) of the ventricle, which represents the external work done by the ventricle against the arterial system. Maximal SW is established, from a given end-diastolic volume, under optimal coupling when the slopes of both the ventricular and arterial end-systolic-stroke volume relationships are the same, that is $Ea/Ees = 1$.

We treated both the ventricle and arterial systems as elastic chambers while applying the concept described by Sunagawa, Maughan and Sagawa [11] (fig. 1): end-systolic elastance (Ees) represents ventricular properties and the effective arterial elastance (Ea) represents arterial loading properties [11]. Ees is the slope of the end-systolic pressure-volume relation, while Ea is the slope of the end-systolic pressure-stroke volume relation.

We used a single-beat estimation technique to evaluate $Ees$ without altering the loading conditions of the left ventricle [12]. Details of the single-beat estimation of $Ees$ have been described previously [12, 13]. Briefly, we predicted isovolumetric left ventricular pressure (LVP) using the Grauss-Newton non-linear curve-fitting technique to fit its isovolumetric portion to the sinusoidal function that follows, and thus determined the constants A, B, C and D:

$$LVP = A \sin(Bt + C) + D$$

where $t =$ time. Drawing a tangential line from the predicted isovolumetric peak left ventricular press-ure to the left corner of the pressure-ejected volume loop yields the end-systolic pressure-volume relation line. The slope of this line represents $Ees$. By definition, $Ea$ is determined by the ratio of end-systolic pressure to stroke volume. Since end-systolic pressure determined by the single-beat estimation was close to mean arterial pressure (MAP), we approximated $Ea$ as the ratio of MAP to stroke volume.

Stroke work (SW) is defined as the area of the pressure-volume loop for each cardiac cycle. According to the framework of ventriculo-arterial matching (fig. 1), end-systolic pressure ($Pes$) can be expressed as

$$Pes = SV \cdot Ea = (Ved - Vo - SV) \cdot Ees$$

where $SV =$ stroke volume, $Ved =$ end-diastolic volume, and $Vo =$ end-systolic unstressed volume. Rearranging this equation yields

$$SV = (Ved - Vo)/(1 + Ea/Ees)$$

and

$$Pes = (Ved - Vo) \cdot Ea/(1 + Ea/Ees)$$

Assuming isobaric contraction at a pressure of $Pes$, SW can thus be approximated as

$$SW = Pes \cdot SV = (Ved - Vo)^2 \cdot Ea/(1 + Ea/Ees)^2 \quad (1)$$

By differentiating equation (1) with respect to $Ea$, one can show that SW becomes maximal when $Ees$ equals $Ea$ [11]. It has been shown also that mechanical efficiency, which is defined as the ratio of SW to myocardial oxygen consumption, is maximized when $Ea/Ees$ is approximately 0.5 [14]. Under physiological conditions, it has been demonstrated that ventriculo-arterial matching operates between an $Ees/Ea$ of 0.5 and 1.0 [11, 13]. Thus we used the $Ea/Ees$ ratio as an index for assessment of ventriculo-arterial coupling.

After an equilibrium period of 30 min, haemodynamic data were obtained under basal anaesthesia (control). Thereafter, animals were allocated to two groups. In group 1 ($n = 7$), after 1.5 % halothane was inhaled for 30 min, phenylephrine was infused at 1–10 μg kg$^{-1}$ min$^{-1}$ to restore MAP to a level similar to control. Subsequently, PGE$_2$ was infused at 0.2–1.0 μg kg$^{-1}$ min$^{-1}$ until MAP decreased by approximately 15 %, and then at 1.0–2.0 μg kg$^{-1}$ min$^{-1}$ until MAP decreased by approximately 30 %. All haemodynamic data were obtained under stable conditions. In group 2 ($n = 5$), after 1.5 % halothane was inhaled for 20 min, dobutamine was infused at two doses, 2 and 5 μg kg$^{-1}$ min$^{-1}$.

The halothane vaporizer was calibrated over the appropriate range of concentrations using an anaesthesia–respiratory gas monitor (Raman Scattering Gas Monitor, Rascal, Albion Instruments). The ability of the vaporizer to maintain 1.5 % halothane over the time course of the study had been established previously.

All values are given as mean (SEM). Statistical analysis was performed by analysis of variance (ANOVA) with repeated measures, followed by Student's $t$ test with Bonferroni's correction. $P < 0.05$ was considered significant.
Table 1 Changes in mean arterial pressure (MAP), cardiac output (CO) and heart rate (HR) in group 1 (n = 7), subjected to 1.5% halothane (Hal.), phenylephrine (Phe.) and a low and high dose of prostaglandin E₁ (PGE₁₁, PGE₁₂) (mean (SEM)). * P < 0.05 compared with control; † P < 0.05 compared with Hal; ‡ P < 0.05 compared with Phe.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>102 (10)</td>
<td>61 (6)*</td>
<td>107 (6)†</td>
<td>88 (5)†</td>
<td>75 (2)‡</td>
</tr>
<tr>
<td>CO (litre min⁻¹)</td>
<td>1.49 (0.18)</td>
<td>1.04 (0.15)*</td>
<td>0.83 (0.012)*</td>
<td>1.43 (0.24)‡</td>
<td>1.66 (0.30)‡</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>113 (7)</td>
<td>102 (7)*</td>
<td>104 (10)</td>
<td>108 (10)</td>
<td>108 (10)</td>
</tr>
</tbody>
</table>

Figure 2 Changes in Ea (••••) and Ees (○○○○) and the Ea/Ees ratio in group 1 (n = 7), subjected to 1.5% halothane (Hal.), phenylephrine (Phe.), and a low and high dose of prostaglandin E₁ (PGE₁₁, PGE₁₂). Note that Hal. decreased Ees; this was restored by Phe. Phe. increased Ea markedly, while the increase was reversed by PGE₁. Phe. increased Ea/Ees, while the combined use of PGE₁ reversed the change. Since Ea/Ees was considered an index of ventriculo-arterial matching, the combination of Phe. and PGE₁ appeared to improve ventriculo-arterial matching. * P < 0.05 vs control; † P < 0.05 vs Hal.; ‡ P < 0.05 vs Hal. + Phe. C = Control.

Results

Table 1 and figure 2 show the haemodynamic changes in group 1. Halothane 1.5% decreased MAP, cardiac output and heart rate. Halothane also decreased Ea and Ees from 8.5 (0.9) to 6.9 (0.8) mm Hg ml⁻¹ and from 8.2 (0.8) to 5.5 (0.8) mm Hg ml⁻¹, respectively (figure 2). Ea/Ees changed from 1.07 (0.11) to 1.33 (0.22) during halothane anaesthesia. Phenylephrine restored MAP, whereas it decreased cardiac output and increased Ea to 16.0 (2.5) mm Hg ml⁻¹ (fig. 2). The decrease in Ees produced by halothane was reversed by phenyl-

Table 2 Changes in mean arterial pressure (MAP), cardiac output (CO) and heart rate (HR) in group 2 (n = 5), subjected to 1.5% halothane (Hal.) and dobutamine (DOB-2 (2 μg kg⁻¹ min⁻¹) and DOB-5 (5 μg kg⁻¹ min⁻¹)) (mean (SEM)). * P < 0.05 compared with control; † P < 0.05 compared with Hal.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hal.</th>
<th>DOB-2</th>
<th>DOB-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>102 (6)</td>
<td>55 (5)*</td>
<td>86 (8)†</td>
<td>98 (9)†</td>
</tr>
<tr>
<td>CO (litre min⁻¹)</td>
<td>1.19 (0.05)</td>
<td>0.82 (0.08)*</td>
<td>1.18 (0.09)†</td>
<td>1.48 (0.01)†</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>121 (4)</td>
<td>96 (6)*</td>
<td>107 (7)</td>
<td>118 (9)</td>
</tr>
</tbody>
</table>
Phenylephrine and prostaglandin E,

ephrine. \( \text{Ea/} \text{Ees} \) increased significantly to 2.26 (0.29) during infusion of phenylephrine. Both low and high doses of \( \text{PGE}_1 \) decreased MAP. Cardiac output increased at low and high \( \text{PGE}_1 \) infusion rates. \( \text{PGE}_1 \) reversed the increases in \( \text{Ea} \) and \( \text{Ea/} \text{Ees} \) produced by phenylephrine.

Table 2 and figure 3 show the haemodynamic changes in group 2. The observed changes during halothane anaesthesia were similar to those in group 1. The decreases in MAP and cardiac output were reversed by infusion of dobutamine during halothane anaesthesia. Dobutamine 2 and 5 \( \mu \)g kg\(^{-1} \) min\(^{-1} \) increased \( \text{Ea} \) from 6.7 (0.6) to 11.0 (2.0) mm Hg ml\(^{-1} \) and 15.4 (3.1) mm Hg ml\(^{-1} \), and decreased \( \text{Ea/} \text{Ees} \) from 1.07 (0.15) to 0.81 (0.16) and to 0.56 (0.08), respectively.

Discussion

We found that phenylephrine restored arterial pressure with a further decrease in cardiac output and impairment of ventriculo-arterial matching during halothane anaesthesia. The combined use of \( \text{PGE}_1 \) reversed the decrease in cardiac output and improved ventriculo-arterial matching. Low-dose dobutamine produced a similar effect on cardiac output and ventriculo-arterial matching.

Our results suggest that phenylephrine restored halothane-induced depression of left ventricular contractility, as demonstrated by recovery of \( \text{Ees} \), and caused also a marked increase in afterload, as demonstrated by the increase in \( \text{Ea} \). In addition, infusion of phenylephrine during halothane anaesthesia may evoke an afterload mismatch, which overrides left ventricular contractility, leading to a reduction in stroke volume and thus cardiac output. The finding that phenylephrine by itself produced a detrimental effect on cardiac performance is consistent with previous reports [6–8]. The use of \( \text{PGE}_1 \), which has a potent vasoconstrictor effect on resistance vessels but no significant effect on cardiac contractility [15, 16], eliminated the vasoconstrictive actions of phenylephrine, as demonstrated by attenuation of the increased level of \( \text{Ea} \). Therefore, the inotropic effect of phenylephrine on left ventricular contractility emerged and impairment of ventriculo-arterial matching was improved. \( \text{PGE}_1 \) has been used for intraoperative arterial pressure control during anaesthesia in Japan. It dilates resistance vessels mainly, in contrast with other vasodilators that have effects on both resistance and capacitance vessels (e.g. sodium nitroprusside and nitroglycerin).

MAP decreased by 50% with 1.5% halothane but was restored by phenylephrine, and then decreased to 85% and 70% by \( \text{PGE}_1 \) (table 1). MAP during infusion of \( \text{PGE}_1 \) was greater than with halothane alone; cardiac output increased by approximately 30–50% compared with halothane alone. Thus the combination of phenylephrine and \( \text{PGE}_1 \) appeared to maintain ventriculo-arterial matching, but did not restore arterial pressure during halothane anaesthesia.

Phenylephrine has been found to exert a positive inotropic effect via \( \alpha \_1 \) adrenoceptor-mediated mechanisms, independent of any \( \beta \) adrenoceptor response [9]. This has been reported to be associated with an increase in \( \text{Ca}^{2+} \) influx through the myocardial cell membrane, an increase in the calcium sensitivity of myofilaments [17, 18] or acceleration of phosphatidylinositol metabolism [19, 20]. Although the underlying molecular mechanisms remain incompletely understood, this study suggests that the positive inotropic action of phenylephrine is capable of overcoming the negative inotropic effect of halothane.

The positive inotropic effects of \( \alpha \_1 \) adrenoceptor stimulation vary among mammalian species. It has been demonstrated clearly in rats, rabbits and humans [21], but in the in vitro dog heart preparations, \( \alpha \_1 \) adrenoceptor stimulation did not elicit a positive inotropic effect, although \( \alpha \_1 \) adrenoceptor binding sites were present [21]. In the present in vivo study, we demonstrated that phenylephrine reversed anaesthetic-induced depression of contractility.\n
\( \text{Ea/} \text{Ees} \) was used in this study as an index of ventriculo-arterial matching. Sunagawa, Maughan and Sagawa [11] theoretically predicted and experimentally validated, in the isolated physiologically loaded canine heart, that maximization of left ventricular stroke work occurs when ventricular contractility and simulated arterial input impedance are matched to each other, that is when \( \text{Ea/} \text{Ees} = 1 \) [11]. In contrast, the theoretical analysis of Burkhoff and Sagawa [14] indicates that maximal efficiency in ventriculo-arterial matching is achieved when \( \text{Ea/} \text{Ees} \) is approximately 0.5. Therefore, it is likely that physiological ventriculo-arterial matching may exist between an \( \text{Ea/} \text{Ees} \) of 0.5 and 1.0.

We have shown that halothane tended to increase, but not significantly, \( \text{Ea/} \text{Ees} \) from 1.07 to 1.33, whereas our previous study demonstrated a significant increase in \( \text{Ea/} \text{Ees} \) during 1.5% halothane in comparison with no change during 2.5% isoflurane [22]. The deleterious effect of phenylephrine on ventriculo-arterial matching and its reversal by \( \text{PGE}_1 \) are obvious when based on changes in \( \text{Ea/} \text{Ees} \).

The results of this study have to be interpreted with caution. We estimated \( \text{Ees} \) using a single-beat estimation technique which analyses only the isovolumetric phases of ventricular pressure. Thus the estimated \( \text{Ees} \) would be relatively insensitive to changes in ventricular pressure during ejection [13]. We have assumed a linear relationship between end-systolic pressure and volume in the left ventricle. Several studies have shown this relationship to be somewhat curvilinear as one approaches the volume intercept [23]. However, we believe that this curvilinearity would not alter greatly the interpretation of our data.

We investigated dogs with intact baroreflexes. A decrease in MAP produced by \( \text{PGE}_1 \) could have caused an increase in cardiac contractility as a result of a baroreflex-induced increase in sympathetic tone. However, this is unlikely because \( \text{Ees} \) did not change significantly during the \( \text{PGE}_1 \)-induced decrease in MAP. We did not investigate the effects of \( \beta \) blockers on the phenylephrine-induced changes in haemodynamics in this study. Therefore, it is possible that the effect of phenylephrine on cardiac contractility may be caused by \( \beta \) adrenoceptor stimulation. In
addition, we used dogs which were anaesthetized with α-chloralose and pentobarbitone; our data may not reflect the situation during the conscious state.

Acknowledgement

This study was supported by a grant-in-aid for scientific research (05671269), the Ministry of Education, Science and Culture, Japan.

References