Halothane anaesthesia does not modify the cardiovascular response to phenylephrine in man

Daniel F. Grum MD, Shafik S. Azmy MD

Conflicting results exist regarding the ability of halothane to alter the vascular response to α_1 adrenergic agonists in animals. Because data from humans are lacking, we studied the haemodynamic response to phenylephrine (PHE) in eight patients about to undergo coronary artery bypass surgery before and during halothane anaesthesia. After obtaining baseline measurements in patients while awake, the responses to PHE infusion at 30, 40, and 50 $\mu\text{g} \cdot \text{min}^{-1}$ were determined. New baseline measurements were made following stabilisation during anaesthesia with halothane, one per cent inspired in oxygen, prior to surgical incision. Then the responses to identical PHE doses were measured again. Halothane did not influence the cardiovascular response to PHE: there was no dose-response shift for any cardiovascular variable. No arrhythmias or signs of ischaemia were observed. We conclude that one per cent halothane anaesthesia does not attenuate PHE-induced vasoconstriction in man.

Des études contradictoires existent concernant la capacité de l'halothane d'altérer la réponse vasculaire aux agonistes α_1 adrénérgique chez l'animal. A cause d'un manque de donnée chez l'humain, on a étudié la réponse hémodynamique au phényléphrine (PHE) chez huit patients devant subir un pontage aorto-coronarien avant et pendant à l'anesthésie à l'halothane. Après l'obtention des mesures de base chez les patients

réveillés, les réponses à la perfusion de PHE à 30, 40 et 50 $\mu\text{g} \cdot \text{min}^{-1}$ ont été déterminées. De nouvelles mesures de base ont été faites après stabilisation pendant l'anesthésie avec l'halothane un pour cent inspiré avec l'oxygène avant l'incision chirurgicale. Puis les réponses aux doses équivalentes de PHE ont été mesurées de nouveau. L'halothane n'a pas influencé la réponse cardio-vasculaire au PHE : il n'y avait aucune translocation de la courbe de dose-réponse pour aucune des variables hémodynamiques. Aucune arythmie et aucun signe d'ischémie n'a été observé. On conclut qu'un pour cent d'halothane lors de l'anesthésie n'atténue pas la vasoconstriction induite par le PHE chez l'homme.

Halothane has been demonstrated to attenuate α_2 - but not α_1 -adrenergic vasoconstriction *in vivo* and *in vitro* using a rat saphenous vein preparation.¹ However, this finding is at variance with the halothane-mediated dose-dependent reduction in phenylephrine-induced contraction of rat aortic strips described by others.² Furthermore, the influence of halothane on vasoconstriction induced by phenylephrine (PHE) in man has not been described. Phenylephrine, a selective α_1 -adrenoceptor agonist, is commonly utilized to support systemic pressures during coronary artery bypass surgery (CABG). To evaluate the possibility that its haemodynamic effects might be attenuated by halothane, we examined the cardiovascular response to PHE of patients scheduled for CABG prior to and during halothane anaesthesia before the commencement of surgery.

Methods

After approval of the protocol by the institutional Human Research Projects Committee and Institutional Review Board, and after obtaining written informed consent from all subjects, eight male patients without systemic disease and with normal left ventricular function who were scheduled for elective coronary artery bypass graft surgery (CABG) were studied. The patients were not taking any medications other than occasional sublingual nitrates

Key words

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From the Department of Cardiothoracic Anesthesiology, The Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44106.

Address correspondence to: Dr. D. F. Grum, Department of Anesthesiology, University of Tennessee, Memphis, 877 Jefferson Avenue, Chandler Building FG-023, Memphis, Tennessee 38103.

as needed for angina pectoris. Premedication consisted of morphine sulfate ($0.1 \text{ mg} \cdot \text{kg}^{-1}$, IM), scopolamine (0.4 mg , IM), and transderm nitroglycerin (5 mg) administered one hour before arrival in the operating room suite. No patient had taken sublingual nitrates within the previous 12 hr. Oxygen, $3 \text{ L} \cdot \text{min}^{-1}$ by nasal prongs, was administered to all patients upon arrival. The electrocardiogram (standard and augmented limb leads, and V_5), heart rate, and intra-arterial blood pressure at the radial artery were monitored, and a pulmonary artery catheter was inserted via the right internal jugular vein for determination of pulmonary artery pressures and cardiac index.

The following haemodynamic variables were measured and calculated in patients while awake before and after PHE infusions at 30, 40, and $50 \text{ } \mu\text{g} \cdot \text{min}^{-1}$: heart rate (HR), diastolic and systemic arterial blood pressures (DBP, MAP), diastolic and mean pulmonary artery pressures (PAD, PAM), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), cardiac index (CI), and systemic and pulmonary vascular resistances (SVR, PVR). The endpoint for each rate of infusion of PHE, after which haemodynamic measurements were made, was stabilisation of the response of the systemic arterial blood pressure (5–10 min). Upon completing the measurements following each rate of infusion, the effects of PHE were allowed to subside and the haemodynamic variables returned to pre-PHE baseline in all patients. Anaesthesia was induced with thiopentone ($2\text{--}3 \text{ mg} \cdot \text{kg}^{-1}$), utilizing a pancuronium-metocurine mixture ($0.4 \text{ mg} \cdot \text{ml}^{-1} + 1.6 \text{ mg} \cdot \text{ml}^{-1}$; $1 \text{ ml} \cdot 10 \text{ kg}^{-1}$) for neuromuscular blockade during and following tracheal intubation. Lidocaine (100 mg) was used to attenuate the haemodynamic response to tracheal intubation. Anaesthesia was maintained with halothane, one per cent inspired, in oxygen. The ventilator was adjusted to maintain normal acid–base status and PaCO_2 in each patient. After cardiovascular stability was achieved during halothane administration (approximately 20–30 min), new baseline haemodynamic measurements were obtained and the cardiovascular responses to PHE infusions at 30, 40 and $50 \text{ } \mu\text{g} \cdot \text{min}^{-1}$. Data were analyzed by paired *t* tests and by analysis of variance (ANOVA) for differences between the two study periods (before and during anaesthesia).

Results

The mean age of the patients was 57 ± 8 yr and their mean weight was $80 \pm 11 \text{ kg}$. Blood pressures and heart rates upon arrival in the operating room suite did not differ from those recorded in the hospital rooms. No arrhythmias or signs and symptoms of ischaemia (ST-T segment changes, sudden large increase in PCWP, nor angina pectoris or other symptoms while awake) were observed in any

TABLE I Comparison of baseline haemodynamic data before (awake) and following anaesthesia (halothane)

	Awake	Halothane
HR ($\text{beats} \cdot \text{min}^{-1}$)	67 ± 5	73 ± 3
MAP (mmHg)	94 ± 6	$74 \pm 4^*$
DBP (mmHg)	76 ± 4	$64 \pm 3^*$
SVR ($\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$)	1440 ± 177	1400 ± 176
PAM (mmHg)	18 ± 2	15 ± 1
PAD (mmHg)	13 ± 2	11 ± 1
PVR ($\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$)	118 ± 46	110 ± 23
PCWP (mmHg)	10 ± 1	10 ± 1
CVP (mmHg)	7 ± 1	7 ± 1
CI ($\text{L} \cdot \text{min}^{-1} \cdot \text{meter}^{-2}$)	$2.8 \pm .3$	$2.2 \pm .2^*$

Values are mean $\pm$ SD ($n = 8$). HR = heart rate; MAP = mean systemic arterial pressure; DBP = systemic diastolic blood pressure; SVR = systemic vascular resistance; PAM = mean pulmonary artery pressure; PAD = pulmonary artery diastolic pressure; PVR = pulmonary vascular resistance; PCWP = pulmonary capillary wedge pressure; CVP = central venous pressure; CI = cardiac index.

*Significant ($P < 0.05$) difference from awake value.

patient at any time during the study. Arterial blood gas analyses prior to and during halothane anaesthesia were normal.

The baseline haemodynamic measurements in patients both awake and anaesthetized are summarized in Table I. Following stabilisation under halothane anaesthesia, the new baseline MAP and DBP were significantly decreased from the unanaesthetized state. This was accompanied by a significant decrease in CI, without any significant change being noted in PAM, PAD, CVP, PCWP, SVR, or PVR. The increase in HR was not statistically significant.

The cardiovascular responses to PHE prior to and after halothane anaesthesia are summarized in Table II. In awake patients, PHE caused significant increases in MAP, DBP (except at PHE: $30 \text{ } \mu\text{g} \cdot \text{min}^{-1}$), SVR (except at PHE: $30 \text{ } \mu\text{g} \cdot \text{min}^{-1}$), and PAD compared with baseline. These changes were accompanied by significant reductions in HR and CI, with significant increases in PCWP and PVR (except at PHE: $30 \text{ } \mu\text{g} \cdot \text{min}^{-1}$). The increases in DBP at PHE 40 and $50 \text{ } \mu\text{g} \cdot \text{min}^{-1}$ and the reductions in HR with each increase in PHE dose were significant when compared with the preceding value, but the changes in CI were not.

During halothane anaesthesia, MAP, DBP, SVR, CVP, and PCWP increased significantly from baseline values following infusion of PHE, with correspondingly significant decreases in CI and HR (Table II). PVR did not change significantly in anaesthetized patients in response to PHE.

ANOVA was used to compare the differences in haemodynamic variables from baseline measurements with values found at the various PHE infusion rates before

TABLE II Haemodynamic response to phenylephrine before and after halothane anaesthesia

	Before halothane PHE dose ($\mu\text{g} \cdot \text{min}^{-1}$)			After halothane PHE dose ($\mu\text{g} \cdot \text{min}^{-1}$)		
	30	40	50	30	40	50
Δ HR	-7 ± 4	$-10 \pm 5^\dagger$	$-13 \pm 6^\dagger$	-10 ± 7	$-15 \pm 9^\dagger$	-18 ± 10
Δ DBP	$2 \pm 4^*$	$5 \pm 6^\dagger$	$8 \pm 6^\dagger$	7 ± 7	$12 \pm 5^\dagger$	13 ± 7
Δ MAP	5 ± 6	10 ± 8	15 ± 9	10 ± 11	$16 \pm 10^\dagger$	19 ± 13
Δ SVR	$116 \pm 229^*$	255 ± 311	413 ± 416	$444 \pm 163^\dagger$	522 ± 325	526 ± 326
Δ PAD	2 ± 2	2 ± 2	3 ± 3	2 ± 2	3 ± 4	4 ± 5
Δ PAM	3 ± 2	4 ± 4	5 ± 3	$1 \pm 2^\dagger$	3 ± 3	5 ± 5
Δ PVR	$10 \pm 52^*$	43 ± 51	45 ± 45	$-2 \pm 37^*$	10 ± 46	$35 \pm 43^*$
Δ PCWP	2 ± 1	3 ± 1	3 ± 2	2 ± 2	4 ± 2	4 ± 3
Δ CVP	2 ± 2	2 ± 3	3 ± 5	3 ± 3	3 ± 3	4 ± 2
Δ CI	-0.2 ± 0.3	-0.3 ± 0.4	-0.4 ± 0.4	-0.4 ± 0.3	-0.5 ± 0.4	-0.5 ± 0.5

Values are mean $\pm$ SD changes (Δ) from baseline ($n = 8$). See Table I for abbreviations. All changes significant ($P < 0.05$) when compared with baseline except *.

† Significant change ($P < 0.05$) compared with preceding value.

‡ Significant differences ($P < 0.05$) at comparable doses, before vs after halothane.

No differences are significant at $P < 0.01$ (refer to text for discussion).

and during halothane anaesthesia. None of the differences were statistically significant at this level: the overall cardiovascular response of patients to PHE infusion was not influenced by the presence of halothane anaesthesia.

Discussion

Phenylephrine is an alpha-agonist drug which preferentially stimulates the α_1 -adrenoceptor³ and is commonly utilized to support blood pressure at various times during CABG surgery. The important finding in our study was the demonstration that halothane anaesthesia did not alter the overall cardiovascular response to infusion of PHE at dosages commonly administered during CABG. Thus, a normal pressor response to PHE can be expected under these conditions. This has not been previously reported in humans.

To determine whether halothane influences the cardiovascular response to alpha-agonists in the clinical setting, we studied patients about to undergo CABG surgery with normal left ventricular function, who were otherwise free from chronic illness and who took no chronic, daily medications other than occasional nitrates for relief of angina pectoris. However, preoperative medication was administered because it was felt to be a necessary part of each patient's preparation for the stress of surgery and anaesthesia.⁴ Although the use of nitroglycerin (NTG) with premedication introduced a known vasodilator, plasma levels from transdermal patches at one and two hours are extremely low (0.2 – $0.3 \text{ ng} \cdot \text{ml}^{-1}$).⁵ Since plasma concentrations of 1 – $2 \text{ ng} \cdot \text{ml}^{-1}$ are required to produce venodilatation,⁶ it is unlikely that transdermal nitroglycerin had any effect on vascular responsiveness to PHE.

The decrease in MAP that we measured after stabilisation of anaesthesia with one per cent halothane was secondary to depression of cardiac output and a slight decrease in SVR, accompanied by a small but significant increase in HR. This is similar to the finding by Eger *et al.*⁷ In contrast to those results we found no change in CVP. Also, PCWP did not change in our patients after halothane anaesthesia. This differs from the results of Delaney *et al.*, measured after 20–30 minutes of $1/2$ MAC halothane anaesthesia or at $3/4$ MAC in patients with coronary artery disease who were similarly premedicated, except for transdermal NTG.⁸ They found significant increases in CVP and PCWP. Their methodology differed from ours: their patients were given a halothane anaesthetic induction and assisted ventilation by mask, whereas our patients underwent thiopentone induction, neuromuscular blockade, tracheal intubation and positive-pressure ventilation during halothane anaesthesia.

Halothane increases venous compliance⁹ and, in patients with high sympathetic tone, decreases systemic vascular resistance.¹⁰ Various central and peripheral actions play a role in halothane-mediated vascular smooth muscle relaxation,¹ including the inhibition of vasoconstrictor actions of catecholamines, both *in vivo*¹¹ and *in vitro*.^{12,13} In order to determine more specifically the cause of halothane's antivasoconstrictor action against catecholamines, various studies in animals have been done utilizing nonspecific as well as selective agonists of postjunctional α_1 and α_2 adrenoceptors.^{1,2,14,15} Results have not been consistent, possibly secondary to differences in methodology, differences in species, non-specific versus selective agonist effect, and the types of blood vessels studied.

Since halothane decreases blood pressure, other investigators have attempted to compensate pharmacologically for this depression and to eliminate any indirect reflex-induced actions of alpha agonists. Larach *et al.* titrated arginine vasopressin (AVP) in their anaesthetized animal preparation to examine whether halothane-induced hypotension reduced vascular responsiveness in rats.¹ Kenny *et al.* studied the haemodynamic response to pressors in anaesthetized dogs following ganglionic, cholinergic, and beta adrenergic blockade in doses appropriate to block reflex change in heart rate.¹⁴ Because we attempted to measure vascular responsiveness to PHE in a realistic clinical situation, we did not undertake any of the above measures. As expected, halothane did decrease baseline systemic blood pressures before PHE administration, and PHE caused a reflex slowing of HR in our patients. However, the cardiovascular response curves to PHE during halothane did not differ significantly from those obtained prior to anaesthesia. Unlike the study of Kenny *et al.*,¹⁴ we were unable to demonstrate a significant shift to the right of the dose-response curve for any haemodynamic parameter.

Acid-base abnormalities can influence alpha₁-adrenoceptor responses.¹⁶ Acid-base status was normal in all our subjects while unanaesthetized. During anaesthesia, ventilation was adjusted to maintain acid-base normality and to keep arterial PCO₂ unchanged from control. No patient required pharmacological therapy for correction of a metabolic abnormality.

Phenylephrine infusion (mean = $78 \pm 22 \mu\text{g} \cdot \text{min}^{-1}$) has been demonstrated to reverse the improvement in ST-segment depression observed during nitroglycerin administration in patients with acute myocardial infarction¹⁸ and with heart failure.¹⁸ Our patients, all of whom had coronary artery disease with normal left ventricular function, without remote or acute infarction, were free from angina pectoris while awake during PHE infusion and did not demonstrate electrocardiographic evidence of ischaemia while awake. We also did not observe any evidence of ischaemia (evidenced by ST-segment, T-wave, or acute changes in PCWP) with PHE infusion during halothane anaesthesia.

Phenylephrine has been shown to increase guinea pig SA nodal pacemaker firing,¹⁹ which may be the result of a direct action on beta adrenergic receptors^{20,21} and from secondary release of norepinephrine.^{20,22} In our patients a reflex bradycardia predominated. We observed statistically significant decreases in HR at each level of PHE infusion in both awake and anaesthetized patients. We did not observe arrhythmias at any time with increasing doses of PHE and resulting increases in blood pressure, neither before nor during halothane anaesthesia. Although concluding that both myocardial alpha₁-adrenoceptors and

elevation of blood pressure are involved in the arrhythmogenic action of PHE, other investigators have similarly noted in dogs the failure of PHE alone to induce arrhythmias during halothane anaesthesia.²³

In conclusion, we found that halothane, one per cent inspired, in oxygen did not alter the overall haemodynamic response to phenylephrine in patients who were not taking chronic cardiovascular medications, even though alone it did lower systemic blood pressure and depress cardiac output. The response to PHE infusion, in doses commonly used during anaesthesia for CABG, was an increase in systemic and pulmonary blood pressures and a reduction in cardiac output that paralleled and was not significantly different from the response found in unanaesthetized patients. In addition, PHE in the doses employed, did not cause myocardial ischaemia and was not arrhythmogenic when given during anaesthesia with halothane in oxygen in patients with coronary artery disease and normal left ventricular function.

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