Effects of isoflurane–nitrous oxide and halothane–nitrous oxide anaesthesia on myocardial contractility assessed by transoesophageal echocardiography

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SUMMARY

In order to evaluate the direct effect of isoflurane–nitrous oxide and halothane–nitrous oxide anaesthesia on cardiac contractility in 20 adults, we have used a method based on left ventricular end-systolic wall stress (LVESWS) vs velocity of circumferential fibre shortening with corrected heart rate (v_{fsc}), obtained by transoesophageal echocardiography. We found that LVESWS (index of afterload) decreased significantly with isoflurane–nitrous oxide (n = 10) in concentrations of 1.5–1.95 MAC, but there were no significant changes in LVESWS with halothane–nitrous oxide (n = 10). v_{fsc} decreased significantly with halothane–nitrous oxide in concentrations of 1.5–1.95 MAC, but this index did not change significantly with isoflurane–nitrous oxide. However, there was no significant difference between the two groups in LVESWS or v_{fsc}. In the analysis of the LVESWS–v_{fsc} relationship, myocardial contractility associated with isoflurane–nitrous oxide anaesthesia did not differ significantly from that associated with halothane–nitrous oxide anaesthesia at equiMAC concentrations. The results suggest that halothane–nitrous oxide anaesthesia, at 1.5–1.95 MAC, maintained myocardial contractility in similar anaesthetic concentrations to isoflurane–nitrous oxide. (Br. J. Anaesth. 1994; 72: 315–320)

KEY WORDS


Reports on humans [1–4] and animals [5–8] suggest that both isoflurane and halothane depress myocardial contractility, and that isoflurane does so to a lesser extent than halothane. Because of the difficulty of assessing contractility in humans, the negative inotropic actions of isoflurane and halothane have previously been investigated indirectly, by observing either haemodynamic changes or load-dependent contractile indices, which are influenced by changes in preload and afterload. However, few studies have examined the direct effect of inhaled anaesthetics on contractile state in humans. Several studies in vivo have demonstrated a greater negative inotropic action of halothane, compared with isoflurane [5, 6, 8]. In one study, Coetzee, Fourie and Badenhorst [7] used a load-independent index in dogs and found that the negative inotropic effect of halothane did not differ from that of isoflurane at 1.0 MAC. Furthermore, the concurrent use of nitrous oxide with isoflurane or halothane attenuated the haemodynamic depression caused by the same MAC value of volatile anaesthetic alone [2,4]. Thus substitution of 0.6 MAC of nitrous oxide for 0.6 MAC of a volatile agent may reduce haemodynamic depression and preserve myocardial contractility in humans. A direct assessment of the myocardial contractile state in humans would allow reliable evaluation of volatile agents that alter ventricular performance. Such a direct assessment is available using echocardiography to examine the slope of left ventricular end-systolic wall stress (LVESWS) vs velocity of circumferential fibre shortening corrected for heart rate (v_{fsc}) [9]. The present study was conducted to assess the effects of isoflurane–nitrous oxide and halothane–nitrous oxide anaesthesia on myocardial contractility, as evaluated by echocardiographical assessment of contractile index in humans.

SUBJECTS AND METHODS

After obtaining informed consent, we studied 20 ASA I or II subjects, 37–58 yr of age, before elective surgery. This study was approved by the department medical Ethics Committee. Patients with clinically significant respiratory, cardiovascular, hepatic, renal, haematological, neurological or metabolic diseases were excluded, together with patients on long-term medications. The patients were allocated randomly into two groups. The isoflurane group consisted of 10 patients anaesthetized with isoflurane or 1.5% nitrous oxide and either 1.5 litre min⁻¹ was given i.v. before induction of anaesthesia. Anaesthesia was induced with thiopentone 4–5 mg kg⁻¹ i.v. and vecuronium bromide 0.15 mg kg⁻¹ was given i.v. to produce neuromuscular block. After induction of anaesthesia, ventilation of the lungs was controlled manually using a face mask for 3–5 min, with oxygen 6 litre min⁻¹ and either 2% isoflurane or 1.5%
halothane until tracheal intubation. After tracheal intubation with a cuffed tube, anaesthesia was maintained with oxygen and 1% end-tidal isoflurane with 60% nitrous oxide in oxygen (total of 1.5 MAC) in the isoflurane group or 0.7% end-tidal halothane with 60% nitrous oxide in oxygen (total of 1.5 MAC) in the halothane group. Ventilatory frequency and tidal volume were controlled so that end-tidal carbon dioxide concentration was maintained at 4.6–5.3 kPa. Inspired and end-tidal anaesthetic concentration and end-tidal carbon dioxide were measured frequently and adjusted with a calibrated infra-red multigas anaesthetic gas analyser (Capnomac, Datex, Finland) and quadrupole mass spectrometer (MGA-2000SP, Airspec, U.K.) to maintain end-tidal concentrations at predetermined levels. Body temperature and lead 2 of the electrocardiogram were monitored continuously. Systolic, diastolic and mean arterial pressures were measured by automated oscillometry (CBM7000, Colin, Japan) every 2.5 min from before induction of anaesthesia to the end of the study. Lactated Ringer’s solution was infused i.v. at 2–4 ml kg⁻¹ h⁻¹ throughout the study. After tracheal intubation, a gastrointestinal scope tipped with a 5-MHz ultrasonic transducer (Hewlett-Packard, Andover, MA) was inserted into the oesophagus and positioned behind the left ventricle to obtain a short axis view at the level of the midpapillary muscles. The transducer was connected to an ultrasonograph (77020AC, Hewlett-Packard, Andover, MA) focused to 12 cm. Two-dimensional echocardiograms were recorded on videotapes while arterial pressure and heart rate measurements were obtained.

After end-tidal anaesthetic concentrations had reached a total of 1.5 MAC and were maintained constant for 15 min, data for heart rate, arterial pressure and transoesophageal echocardiography (TOE) were obtained. End-tidal concentrations of isoflurane or halothane were then increased to 1.6% or 1.0%, respectively (total of 1.95 MAC with 60% nitrous oxide in oxygen) and held constant for 15 min. The measurements were then repeated. For safety reasons the concentration of inhaled anaesthetics was increased in steps in both groups. The TOE probe was manipulated only at the time of recording, for approximately 60 s, to prevent haemodynamic reactions caused by oesophageal stimulation. A left ventricular short axis view at the level of the midpapillary muscles was confirmed at each recording of an echocardiogram. Rate–pressure product (RPP) was determined as:

\[ \text{RPP} \text{ (beat \cdot mm Hg)} = \text{heart rate} \cdot \text{systolic arterial pressure} \]

Echocardiographical and haemodynamic data were analysed after completion of surgery.

**Transoesophageal echocardiographic analysis**

TOE analysis was performed as follows. We traced the left ventricular short axis endocardium at end-diastole to obtain end-diastolic area (LVEDA) and end-diastolic circumference (LVEDC) and traced the endocardium and epicardium at end-systole to obtain end-systolic area (LVESA) with papillary muscles included, end-systolic circumference of endocardium (LVESC) and the total area (A) enclosed by the left ventricular epicardium and right side of the septum. Leading–leading methods were used to trace the endocardium and epicardium [10]. Left ventricular ejection time (LVET) was determined using the number of frames (one every 33 ms) from end-diastole to end-systole. Ventricular end-diastole was identified by the peak of the R wave and end-systole by minimal left ventricular dimension. The mean of three consecutive beats at end-expiration was used for analysis. Each echocardiogram was analysed by 77020AC ultrasonograph system. Systolic fractional area change (FAC) and systolic circumferential fibre shortening (CFS) were determined as follows [11]

\[ \text{FAC } (\%) = \frac{\text{LVEDA} - \text{LVESA}}{\text{LVEDA}} \times 100 \]

\[ \text{CFS } (\%) = \frac{\text{LVEDC} - \text{LVESC}}{\text{LVEDC}} \times 100 \]

We determined left ventricular end-systolic wall stress (LVESWS, an index of afterload) and velocity of circumferential fibre shortening with heart rate corrected (v_{e_{t+d}}) as follows [9, 12]:

\[ \text{LVESWS} = \frac{1.35 \cdot \text{Pcuff} \cdot \text{LVESA}}{(A - \text{LVESA})} \]

where LVESWS is expressed as g cm⁻²; Pcuff = cuff systolic arterial pressure (mm Hg); LVEDA and LVESA are expressed as cm²; and 1.35 = a factor to convert mm Hg to g cm⁻² [12].

\[ v_{e_{t+d}}(\text{LVEDC} - \text{LVESC})/(\text{LVEDC} - \text{LVET}) \cdot (\text{RR})^3 = \text{CFS(\%)} \cdot (\text{RR})^3/(\text{LVET} \times 100) \]

where RR is the interval between cardiac cycles, determined as the number of frames from the peak of the R wave to the next peak of the R wave and LVEDC and LVESC are expressed in cm [9].

**Statistical analysis**

Effects of isoflurane and halothane, both with nitrous oxide, on heart rate, arterial pressures and variables analysed by echocardiography were compared by one-way and two-way analysis of variance (ANOVA) followed by Bonferroni multiple comparison test. We plotted LVESWS on the X-axis and v_{e_{t+d}} on the Y-axis and calculated the linear regression equation of the LVESWS—v_{e_{t+d}} relationship with simple linear regression by the least squares method in each of the experimental conditions. In this LVESWS—v_{e_{t+d}} relationship, v_{e_{t+d}} was greater for any given value of LVESWS in increased inotropic state and smaller in depressed contractile state. A change in contractility reflected by a change in the LVESWS—v_{e_{t+d}} relationship at each anaesthetic concentration was compared by analysis of covariance (covariant ANOVA). Statistical analysis was conducted using the Statistical Analysis System (SAS Institute, Cary, NC, U.S.A.). P < 0.05 was considered statistically significant. All data are expressed as mean (sd).

**RESULTS**

Patients in both groups were similar in age, gender, body weight and height (table I). There were no significant differences in heart rate, arterial pressures or RPP before induction of anaesthesia in each
anaesthetic group (table II). There was no significant change in heart rate during anaesthesia in both groups. Increasing concentrations of isoflurane and halothane caused progressive decreases in systolic, diastolic and mean arterial pressures, but there was no significant difference in arterial pressures between the two groups. RPP decreased significantly from the awake state to 1.95 MAC in each of the two groups. In the halothane group, RPP decreased significantly from that at 1.5 MAC to that at 1.95 MAC (P < 0.05), but no significant change in RPP was observed during anaesthesia in both groups.

A left ventricular short axis view at the level of the midpapillary muscles was obtained satisfactorily in all subjects. No segmental wall motion abnormality, ST-segment change, arrhythmia or influence on haemodynamic state was caused by probe manipulation. There was no significant change in in the isoflurane group and from the awake state to 1.5 and 1.95 MAC in the halothane group, but no significant change in RPP was observed during anaesthesia in each of the two groups (table II).

Increases in isoflurane and halothane concentrations progressively decreased LVESWS and rate-pressure product (RPP). Significant changes compared with equiMAC anaesthetic concentrations were observed in the isoflurane group. There was no significant change in LVESWS between the two groups at equiMAC anaesthetic concentrations. Percent changes in v_{v}c were from those at 1.5 MAC in each group are shown in figure 1. Ejection time corrected for heart rate did not change significantly in the isoflurane group, but was increased significantly from that at 1.5 MAC to that at 1.95 MAC in the halothane group (P < 0.05). Rate-corrected ejection time was significantly greater at 1.95 MAC in the halothane group than that in the isoflurane group. There was no significant change in EDA, A or A minus ESA in each group.
We examined the effects of isoflurane and halothane, both with nitrous oxide on the LVESWS-$v_{cfc}$ relationship as a direct assessment of myocardial contractility. In the isoflurane group, the regression equations were $v_{cfc} = -0.00143$ LVESWS + 0.547 ($r = -0.57$, $P < 0.1$) at 1.5 MAC and $v_{cfc} = -0.00153$ LVESWS + 0.500 ($r = -0.56$, $P < 0.1$) at 1.95 MAC. In the halothane group, the regression equations were $v_{cfc} = -0.00372$ LVESWS + 0.776 ($r = -0.40$, $P < 0.5$) at 1.5 MAC and $v_{cfc} = -0.00209$ LVESWS + 0.586 ($r = -0.26$, $P < 0.5$) at 1.95 MAC. Figures 2 and 3 show the individual plots and regression lines of the isoflurane and halothane groups, respectively. Downward shifts of the regression lines between LVESWS and $v_{cfc}$ were observed from those at 1.5 MAC to those at 1.95 MAC in both groups. In both groups, however, there was no significant change in contractile state between values at 1.5 and 1.95 MAC.

Comparison of the two groups indicated that the myocardial contractility associated with isoflurane and nitrous oxide did not differ significantly from that associated with halothane and nitrous oxide.

**DISCUSSION**

We have found that both isoflurane and halothane depressed systolic and diastolic arterial pressures, in a dose-dependent manner, but assessment of the LVESWS-$v_{cfc}$ relationship, derived from TOE, indicated that halothane preserved myocardial contractility to the same extent as isoflurane during 1.5 and 1.95 MAC anaesthesia in the presence of 60% nitrous oxide in oxygen.

The haemodynamic effects of isoflurane observed in this study were similar to those reported previously in humans [1,2]. Dolan and colleagues [2] observed a significant increase in heart rate with isoflurane at increasing concentrations from 1.10 to 2.08 MAC. However, there was no significant change in heart rate with isoflurane in the present study. The haemodynamic effects of halothane in our study were similar to those reported previously in humans [3,4]. We found no significant difference in arterial pressures between the two groups.

Previous in vivo studies [5,6,8] have reported that isoflurane depressed myocardial contractility to a lesser degree than halothane. Pagel and colleagues [8] used a load-independent contractile index in dogs and reported that halothane depressed contractility significantly more than isoflurane at 1.5 and 2.0 MAC. This difference in depression of the contractile state produced by these anaesthetics has also been noted in studies in humans [1—4]. However, in humans, the observed haemodynamic changes may have been influenced by changes in preload, afterload, and therefore the inotropic effects were not assessed directly. Few studies have reported on the direct myocardial effects of isoflurane and halothane in humans. Earlier studies [2,4] indicated that concomitant use of nitrous oxide with inhaled anaesthetics reduced haemodynamic depression which might preserve myocardial contractility. Therefore, we have attempted to assess contractile state directly using the LVESWS-$v_{cfc}$ relationships during isoflurane—nitrous oxide and halothane—nitrous oxide anaesthesia.

The LVESWS-$v_{cfc}$ relationship was reported by Colan, Borow and Neumann [9] as a load-independent index of myocardial contractility. They found that the LVESWS-$v_{cfc}$ relationship was inversely linear and $v_{cfc}$ was greater for any given value of LVESWS in the increased inotropic state and smaller for any given value of LVESWS in the depressed contractile state. This relationship shifted upwards with positive inotropic influences and downwards with negative inotropic influences. It was found that this relationship was independent of preload and incorporated both afterload and heart rate.

There are several limitations in the present study with the use of the LVESWS-$v_{cfc}$ relationship as a contractile index. First, we did not obtain control echocardiographic data in the conscious state. Therefore, we could not demonstrate depression of...
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myocardial contractility during isoflurane–nitrous oxide and halothane–nitrous oxide anaesthesia compared with the conscious state. Second, we did not measure contractile state in individual patients because combining echocardiographic data from several subjects is necessary to obtain the LVESWS–$v_{ctc}$ relationship. Third, LVESWS and $v_{ctc}$ did not correlate significantly at each anaesthetic level in both groups. Thus poor correlation between LVESWS and $v_{te}$ limits our ability to use the slope of the LVESWS–$v_{te}$ relationships as a contractile index. We applied covariant ANOVA to compare the LVESWS–$v_{te}$ relationship quantitatively and this statistical analysis assumes that the regression lines are parallel straight lines [13]. If the data do not violate these assumptions, covariant ANOVA can be performed even when the correlation coefficient is not significant [13]. As our data did not violate these assumptions, it was possible to undertake this analysis.

In the present study, we used meridional wall stress as a measure of LVESWS rather than circumferential wall stress, because the latter depends on the left ventricular major axis, which must be approximated from the short axis. Thus meridional wall stress is independent of the major axis and requires no such approximation [12, 14]. To calculate circumferential wall stress, the major axis is assumed to be twice as long as the short axis, based on an ellipsoid model. Circumferential wall stress may thus possibly involve error when the ratio of the major axis to the minor axis changes to less, or more than, two under changing conditions of left ventricle volume (as exist during administration of volatile anaesthetics). Reichek and colleagues [15] observed that in humans, non-invasive cuff systolic arterial pressure correlated closely with end-systolic micro-manometer left ventricular pressure ($r = 0.89$) and non-invasive end-systolic left ventricular wall stress with cuff systolic pressure; invasive stress correlated to an even greater extent with end-systolic left ventricular pressure ($r = 0.97$). Thus in our study, cuff systolic arterial pressure was considered appropriate for non-invasive estimation of LVESWS. $v_{te}$ may be an afterload-dependent contractile index, but independent of preload, whereas ejection fraction may be altered significantly by a large change in preload [16].

Haendchen and co-workers [17] determined FAC and CFS as indices of contractile function in two-dimensional echocardiography. The use of FAC and CFS facilitates assessment of cardiac function, as does ejection fraction, but both are preload– and afterload-dependent and thus cannot reflect accurately left ventricular contractile state. Therefore, we used direct assessment of contractility with the LVESWS–$v_{te}$ relationship.

Changes in the LVEDA and LVESA of echocardiography are considered to reflect changes in left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV), respectively [18]. Thus in our study, the absence of significant changes in EDA indicated absence of change in LVEDV or left ventricular preload during isoflurane or halothane anaesthesia.

LVESWS decreased significantly from the value at 1.5 MAC to that at 1.95 MAC in the isoflurane group, although it did not change significantly in the halothane group. In previous reports [1,2], isoflurane was found to decrease systemic vascular resistance dose-dependently in humans, although halothane did not decrease systemic vascular resistance [3,4]. In the present study, the effects of isoflurane on LVESWS may have been caused primarily by the effects on systemic vascular resistance. Using the LVESWS–$v_{te}$ relationship, there was no significant difference in contractile depression between the isoflurane and halothane groups in our study.

REFERENCES


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