Ventricular Function in Children during Halothane Anesthesia: An Echocardiographic Evaluation

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The effect of halothane on ventricular function in normal children was studied with the aid of echocardiography, which offers a noninvasive method to obtain these measurements safely. Thirteen healthy children ranging in age from 19 months to 12 years (mean = 6 years), undergoing elective non-cardiac surgical procedures, were studied. Secobarbital, 4 mg/kg, and morphine, 0.1 mg/kg, were administered intramuscularly an hour prior to induction of general anesthesia. Echocardiographic measurements were obtained while the patients breathed room air (control) and following nitrous oxide, 60 per cent, and concentrations of halothane ranging from 0.5 to 2 per cent. Increasing inspired concentrations of halothane significantly altered ventricular function in a dose-dependent fashion. At halothane, 2 per cent, systolic blood pressure, pulse rate, and cardiac output decreased to 82, 94, and 72 per cent of control values, respectively. Measurements of ventricular performance, ejection fraction (EF), left ventricular end-diastolic volume (LVEDV), and mean normalized rate of circumferential fiber shortening (V_{ef}) showed parallel decreases. Following atropine, 0.02 mg/kg, intravenously, improvement in cardiac output and all rate-dependent variables was observed. Although V_{ef} improved by 18 per cent, other indices of myocardial performance (EF, LVEDV, PEP/LVET) still showed depression. It is concluded that halothane can significantly decrease ventricular function in children undergoing surgical procedures. The accompanying decrease in cardiac output was completely offset by the administration of atropine. (Key words: Anesthesia, pediatric. Anesthesiology, volatile: halothane. Parasympathetic nervous system: atropine. Heart: echocardiography; myocardial function; contractility.)

The myocardial depressant effects of halothane have been well demonstrated in isolated muscle preparations, animal studies, and adult man.1-4 However, studies of the effects of halothane on myocardial function in children have been limited by the lack of adequate noninvasive techniques. For example, McGregor et al. used an invasive indicator-dilution technique to obtain cardiovascular data from children during halothane anesthesia.5 Echocardiography provides a useful, safe, noninvasive method for assessing left ventricular performance in man. Utilizing this modality, estimations of cardiac output, ejection fraction, mean circumferential fiber shortening rate, end-diastolic volume, and systolic time intervals can be obtained, with excellent correlation between echocardiographic data of angiographic determinations of these variables in adults and children.6-11 Accordingly, these indices, derived from echocardiographic data, were used to evaluate left ventricular function during halothane-nitrous oxide anesthesia in children without cardiac disease who were undergoing surgical procedures.

Methods

Thirteen children without cardiac disease, ranging in age from 19 months to 12 years (mean age = 6 years; mean weight = 22 kg, range = 12-41 kg), undergoing elective operations (e.g., herniorrhaphy, tonsillectomy), were studied. Premedication with secobarbital, 4 mg/kg, and morphine, 0.1 mg/kg, was administered intramuscularly an hour prior to the induction of general anesthesia. Following arrival of the patient in the operating suite, a blood pressure cuff, precordial stethoscope, and electrocardiographic and echocardiographic leads were applied. With the patient breathing room air a set of control ventricular function data was obtained. These measurements were repeated with the patients breathing nitrous oxide:oxygen, 60:40 per cent, alone via a semiclosed circle absorption system or Jackson-Rees nonrebreathing pediatric circuit and following the addition of halothane in concentrations of 0.5, 1.0, 1.5, and 2.0 per cent. Halothane concentrations were changed at 2-minute intervals (fig. 1). While at halothane, 2 per cent, ten patients received atropine, 0.02 mg/kg, intravenously, and ventricular function data were again obtained. Succinylcholine, 1 mg/kg, was then administered intravenously. Observations were then made.

**Abbreviations**

dP/dt = time rate change of pressure
LPWV = posterior left ventricular wall
LVET = left ventricular ejection time
PEP = pre-ejection period
PRP = pressure-rate product
RVO = right ventricular outflow tract
STI = systolic time intervals
V_{ef} = mean normalized rate of circumferential fiber shortening

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79
during intubation (halothane 0.5 per cent) and prior to surgical incision (≈20 min after obtaining control value with halothane, 1.0 per cent). Concentrations of all gases are expressed as percentages of inflow gas delivered to the anesthetic circuit. The patients showed no clinical sign of hypercarbia. Each patient served as his own control, with ventilation assisted at halothane, 1 per cent, and controlled at halothane concentrations of 1.5 per cent or more. During the study period, dextrose, 5 per cent, with 0.45 physiologic saline solution was administered intravenously at a rate of 1–2 ml/kg/hr.

The following hemodynamic values were obtained: blood pressure, pulse rate, cardiac output, ejection fraction, left ventricular end-diastolic volume (LVEDV), mean normalized rate of circumferential fiber shortening (Vcf), and pre-ejection period/left ventricular ejection time (PEP/LVET). Blood pressure was monitored via the standard arm-cuff occlusion method. Pulse rate was obtained from the electrocardiographic tracing. The indices of left ventricular performance were calculated from echocardiographic measurements of the end-diastolic and end-systolic dimensions.

The echocardiograms were recorded with a Unirad 132c echoscope interfaced with a Honeywell 1856 fiberoptic strip-chart recorder. Either a 2.25-MHz or a 5-MHz transducer was placed parastermally in the fourth left intercostal space and angled inferiorly and laterally until the posterior mitral valve apparatus was located. A standardized recording technique was employed using external and intracardiac landmarks to minimize any possible error in serial recordings. This location was used to obtain left ventricular measurements (fig. 2). The transducer was then angled superiorly and medially until the aortic valve was located for measurement of systolic time intervals.

End-diastolic dimensions (EDD) were measured from inner surfaces of the endocardium of the interventricular septum and posterior left ventricular wall (LPW), respectively, with end-diastole taken as the peak of the “R” wave of the simultaneously recorded electrocardiogram. End-systolic dimensions (ESD) were similarly measured, with end-systole taken as the point of maximum anterior motion of the LPW.

End-diastolic volume (EDV) and ejection fraction (EF) were estimated from echocardiographic dimensions using the regression equation of Meyer, et al.⁴:

\[
EDV = -19.1 + 14.6 \times EDD + 0.62 \times EDD^3
\]

\[
EF = \frac{ESD}{EDD} = \frac{1 - \text{EF}}{A_{ESD}} \sqrt{\frac{A_{EDD}}{A_{ESD}}}
\]

Cardiac output (ml/min) = EDV x EF x pulse

Vcf was calculated according to the method of Fortuin.¹¹ Ejection time (ET) was determined from an aortic valve tracing (fig. 3) with the same R-R interval (electrocardiogram) used in measuring the ventricular dimensions.

\[
V_{cf} = \frac{EDD - ESD}{EDD \times ET}
\]

Systolic time intervals (STI) were obtained from echocardiographic tracings (100 mm/sec) of the aortic valve (fig. 3). The pre-ejection period (PEP) was measured from the onset of the Q wave (electrocardiogram) to the initiation of the opening of the aortic valve. Left ventricular ejection time (LVET) was measured from opening to complete coaptation of the leaflets of the aortic valve.¹⁰ The ratio, PEP/LVET, was computed and used as an index of left ventricular function.¹³ All cardiovascular measurements obtained from the echocardiogram were averaged for three consecutive

⁴ Meyer has derived a mathematical equation for ejection fraction in children relating shortening in both the minor axis (ESD/EDD) and the major axis A_{ESD}/A_{EDD}.⁸
Fig. 2. Echocardiogram of left ventricle and mitral valve apparatus during control period (A) and halothane (B) administration. Note increase in end-systolic dimension (ESD) at halothane, 2 per cent, with end-diastolic dimension (EDD) remaining virtually unchanged. This is consistent with a decrease in stroke volume (see discussion). (RV = right ventricle, LV = left ventricle, EKG = electrocardiogram).

Fig. 3. Echocardiogram of aorta (AO) and left atrium (LA) used for measurement of systolic time intervals. PEP = pre-ejection period, LVET = left ventricular ejection time, RVO = right ventricular outflow tract.
cardiac cycles. Results of all variables evaluated are expressed as percentage changes from the control value (table 1). Statistical analysis was done using a t test for paired data and significant P values from a two-tailed distribution.

Results

Increasing concentrations of halothane were associated with decreases in systolic blood pressure (fig. 4). At halothane, 2 per cent, an 18 per cent decrease in blood pressure occurred. Atropine did not cause a significant increase in blood pressure. Pulse rate was not significantly affected until a concentration of halothane, 1.5 per cent, was achieved, at which time there was a mean decrease of 6 per cent. Following atropine administration pulse rate increased 49 per cent of the control. Following intubation, the pulse rate increased further (63 per cent above control).

No significant change in cardiac output from control was seen with nitrous oxide, but a significant decrease (19 per cent) occurred at halothane, 1 per cent. At halothane, 2 per cent, a decrease of 28 per cent was observed. Following atropine, cardiac output increased by 47 per cent compared with the immediate pre-atropine value.

A dose-dependent decrease in ejection fraction was seen with the largest depression (74 per cent of control) occurring at halothane, 2 per cent (fig. 5). No significant dose-dependent alteration in left ventricular end-diastolic volume was observed at any level of halothane administration, prior to or following atropine.

Of all variables studied, V\text{se} showed the greatest dose-related depression (fig. 6). At halothane, 0.5 per cent, a mean decrease of 15 per cent was seen. A progressive, almost linear decrease was observed with increasing concentrations of halothane. The most significant decrease, 36 per cent, occurred at halothane, 2 per cent. Although an increase of 18 per cent in fiber performance was observed following atropine (compared with pre-atropine values), there was still marked depression compared with the control value. With tracheal intubation and decrease in halothane concentration, V\text{se} returned to the control value. At halothane, 1 per cent, a significant increase in the PEP/LVET of 14 per cent was observed, compared with control (PEP increased and LVET decreased). At halothane, 2 per cent, a further increase to 18 per cent above the control value was observed. No change occurred after administration of atropine compared with the immediate pre-atropine value.

Since direct measurement of myocardial oxygen consumption could not be made, an indirect correlation could be seen using the pressure–rate product (PRP). At halothane, 2 per cent, a 23 per cent decrease in PRP was observed (fig. 7). Following atropine, PRP increased to 26 per cent above control, and after intubation, to a maximum of 55 per cent above control.

Discussion

Methodology for assessment of ventricular function should take into account the following determinants: preload, afterload, inotropic and chronotropic state of the myocardium. Due to the risks and limitations of invasive monitoring of cardiac function, attention has...
recently been directed toward noninvasive techniques for evaluation of left ventricular performance. Of the methods currently available (phonocardiography, impedance cardiography, systolic time intervals and echocardiography), echocardiography has been deemed to have great potential. Until recently, echocardiography, developed by Edler and Hertz in 1953, was limited in clinical practice to assessment of mitral stenosis, atrial tumors, and ball-valve thrombosis. In the past few years, extensive investigation has expanded its applications to diagnosis and dynamic evaluation of cardiac function. The correlation between cineangiographic and echocardiographic estimates of left ventricular volumes and performance appears to be highly significant.

Using echocardiographic monitoring in pediatric patients, we were able to confirm the myocardial depressant effects of halothane that have been extensively reported to occur under various experimental conditions. Rusy et al., using cineradiography to measure preload in dogs, observed no significant change until an end-tidal halothane concentration of 2 percent was achieved. They also found a significant decrease in left ventricular contractility as measured by $Q_{max}$ (acceleration of blood ejected by left ventricle). Goldberg and Pheur, using rat left ventricular trabeculae, demonstrated proportionate decreases in $V_{max}$ (velocity of shortening of the unloaded muscle) with increasing concentrations of halothane. Merin et al., utilizing chronically catheterized dogs, found a
dose-dependent effect of halothane on ventricular function. In adult human volunteers, using ballistocardiography, Eger et al. found a decrease in cardiac output with significant myocardial depression. Under the conditions of our study, halothane caused dose-related depression of cardiac performance. When echocardiographic measurements are used for serial assessment of left ventricular performance, however, the level of heart rate and systemic arterial pressure at which studies are obtained must be considered. Following administration of halothane, in our subjects, heart rate declined, as did systemic arterial pressure (afterload), although end-diastolic volume (preload) did not change. A large decrease in heart rate would be expected to diminish \( V_{\text{et}} \) but in the range observed in this series (6 per cent decrease) little alteration in \( V_{\text{et}} \) would be likely. Further, a decline in afterload would be expected to result in an increase in \( V_{\text{et}} \), which was not seen in any of the patients studied. The most likely explanation for our observations is the direct depression of the inotropic state of the myocardium by halothane, as has been demonstrated in experimental animals. This observation is corroborated by a decrease in ejection fraction (fig. 2). Further confirmation of alteration of the inotropic state was obtained utilizing measurement of the systolic time intervals. Systolic time intervals have been used as an index of myocardial function, with close correlation shown between changes in the systolic time intervals, PEP/LVET ratio, and left ventricular function. A progressive increase in PEP associated with a decrease in LVET resulted in increase of PEP/LVET ratio, which also indicates deterioration of ventricular performance.

In addition to the effects of halothane on ventricular function, other therapeutic interventions may have affected the results. Although the patients were premedicated with secobarbital and morphine, they were awake and cooperative during the control period. Furthermore, control values of all the variables were within normal limits for unanesthetized children (table 1). Our results also may have been affected by variations in carbon dioxide concentrations, which were not measured. However, each patient served as his own control, with maintenance of consistent respiratory rates and tidal volumes as monitored by auscultation during the study period. Clinically, there was no sign of hypoventilation or hypoxemia. Finally, the addition of nitrous oxide may have modified circulatory function. In this regard, Smith et al. reported that nitrous oxide added to halothane caused peripheral vasoconstriction, with myocardial function remaining unchanged.

Modulation of the response to halothane by atropine administration focuses on the role of heart rate in ventricular function. There has been interest in the effect on ventricular performance of an acute augmentation of pulse rate. The classic studies of Woodworth demonstrated that acute increases in pulse rate exerted a positive inotropic action. Depending on the model used, various investigators have reported minimal to profound increases in cardiac contractility following increases of pulse rate. Noble et al., using the conscious dog, observed no inotropic effect from an increased pulse rate. Higgins et al., using both awake and anesthetized (pentobarbital) dogs, found only a slight inotropic action of increased heart rate in the conscious dog. However, in anesthetized dogs, increasing the frequency of contraction was associated with a severalfold increase in inotropic effect per unit increase in heart rate. Recently, Hirschleifer et al., using parenterally administered atropine, found a significant increase in the ejection phase (\( V_{\text{et}} \) and mean posterior wall velocity). In our study, although \( V_{\text{et}} \) improved, the absence of any change in either PEP/LVET ratio or ejection fraction after atropine would support the presence of continued impairment of myocardial performance.

In addition to the sustained depression of ventricular function following atropine administration, it is interesting that the pressure–rate product outstripped cardiac output by 20 per cent. The clinical implications of increased myocardial oxygen consumption as reflected by the pressure–rate product are obvious when considering the management of patients with coronary-artery disease. This factor might assume similar importance in the anesthetic management of the pediatric patient with congenital heart disease.

At present, from an anesthesiologist's point of view, there are several limitations to the more widespread use of echocardiography in the operating room. The machinery itself is large, cumbersome and requires a specially trained technician for operation. Pattern recognition can be complex and not amenable to the rapid interpretation that is necessary for the critically ill in an operating room setting. There can be difficulty in obtaining an adequate trace from an adult patient receiving mechanical ventilation with a large tidal volume. These probably represent only temporary limitations. With more advanced units, interfaced with a dedicated computer system, rapid continuous online recording of indices of ventricular performance can be obtained. At present, caution must be used in estimations of ventricular size and performance with echocardiography. It is implicit in the technique that certain geometric and physiologic assumptions are made in converting a two-dimensional echocardio-
graphic measurement to an estimate of left ventricular volume. Nevertheless, the technique offers the possibility of adding a new dimension to the intraoperative assessment of the anesthetized patient.

In conclusion, halothane anesthesia produces significant depression of cardiac performance in children, as demonstrated by echocardiography. The accompanying decrease in cardiac output can be reversed by atropine. Echocardiography, offering a precise method of evaluating cardiovascular performance, has the potential to be a useful tool for clinical anesthesiology that may supplant the invasive monitoring currently available.

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