Performance of Digitalized Heart During Halothane Anesthesia

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Halothane is used extensively to produce surgical anesthesia in patients with and without apparent heart disease although arterial hypotension and bradycardia are prominent clinical circulatory characteristics of halothane. Digitalis has been recommended as a therapeutic agent to combat arterial hypotension and as a prophylactic measure before operation. It was reported that digitalis preparations augment the contractile force of nonfailing human hearts and that deleterious effects on the hemodynamics of the cardiovascular system in subjects with normal hearts are not demonstrable. It became apparent that the recommendation for the use of the cardiac glycosides before anesthesia and operation was based solely on the findings that these drugs exert a positive inotropic effect on the normal heart. Recent findings regarding the influence of digitalis during halothane anesthesia were complicated by the effects of open pneumothorax and by open pericardium. The present study was designed to ascertain whether or not the positive inotropic and pressor effects of digitalis counteract the negative inotropic and depressor action of halothane in the intact, nonmedicated and nonoperated subjects.

Methods

The methods used to obtain ventricular function curve (VFC), tension-time index (TTI) and left ventricular stroke power (LVSP) in nonmedicated, nonoperated dogs with an intact thoracic cage and pericardium were similar to those described in previous publications (fig. 1).

The tracheas of 14 mongrel dogs (average weight 17.6 kg.) were intubated with a cuffed tube following the intravenous administration of succinylcholine chloride (40 mg.). Succinylcholine chloride, 0.1 per cent solution in 5 per cent dextrose, was infused throughout the procedure (3 mg./kg./hour). Procaine (1 per cent solution) was administered for local anesthesia. Respiration was controlled with 100 per cent oxygen by means of a volume-limited, pressure-variable respirator with a nonrebreathing system. The tidal volume and respiratory frequency were kept constant as soon as the arterial blood gases were within physiologic levels.

Following local anesthesia, the left femoral artery and vein were exposed, and a right and left heart catheterization was carried out under fluoroscopic control: via the femoral vein, the distal opening of a double lumen Courmand catheter was inserted into the pulmonary artery with proximal opening residing in the right ventricle for measurement of pulmonary arterial and right ventricular end diastolic pressure (RVEDP). A second double lumen catheter was inserted into the left femoral artery with the distal opening positioned in the left atrium and the proximal opening residing in the left ventricle for the measurement of left ventricular end diastolic pressure (LVEDP). A single lumen catheter (U. S. catheter no. 6, 40 cm. in length) was inserted into the ascending aorta through the right carotid artery for measurement of aortic pressure. Positions of catheters were verified by pressure tracings and rechecked at autopsy upon conclusion of the experiment. A small rubber balloon of the type described by Schilder, Hyatt and Fry was attached to a polyethylene catheter and introduced into midesophagus to record intra-
pleural pressure for determining the effective ventricular filling pressure (EVFP). A polyethylene catheter was inserted into the right femoral artery for recording systemic arterial pressure and for collection of arterial blood samples. Cardiac output was determined by the indicator dilution technique using tricarbocyanine dye diluted in plasma. The arterial blood was withdrawn to a cuvette of a Colson densitometer (model 103) by a motor driven syringe at a constant rate of 0.9 ml/second. Fifteen to 20 ml of the blood withdrawn for each output determination was rein infused into the animal immediately after the completion of each output determination.

Statham P23D and P23G pressure transducers were used to obtain ventricular, arterial and aortic pressures, and model P23B for the esophageal pressure. Continuous and simultaneous recordings of pressures in the left and right ventricles, the pulmonary and femoral arteries, aorta, esophagus, and electrocardiograms, were made on a Sanborn Poly-Viso recorder at a paper speed of 1.0 mm/second. Paper speeds of 5 and 100 mm per second were used for recording the indicator dilution curve and end diastolic ventricular pressures. The pressures of the two ventricles were recorded at the diastolic portion (0-40 cm of water). Mean systemic and pulmonary arterial pressures were obtained by electrical integration.

A reservoir containing the experimental animal's blood, collected ten days before the study and kept in acid citrate dextrose solution, was connected to the right femoral vein.
by means of Tygon tubing (fig. 1). The blood was kept at a temperature of 37° C. and was mixed continuously in the reservoir by a magnet stirrer. The rectal temperature of experimental animals was recorded and kept constant at 37° C. Increments of 50 to 100 ml. of blood were infused at regular intervals to obtain changes of the ventricular filling pressure. The cardiac output and the end diastolic ventricular pressures were obtained 60 seconds after each infusion. The stroke work of each ventricle in grammeters was calculated according to the following formula:

\[
\text{stroke work} = \frac{(\text{cm. } H_2O \text{ mean arterial pressure} - \text{cm. } H_2O \text{ EVFP}) \times \text{stroke volume}}{100}
\]

The effective filling pressure of each ventricle (EVFP) was determined as the difference between ventricular end diastolic pressure and mean esophageal pressure. Stroke volume in cubic centimeters was obtained by dividing cardiac output per minute by heart rate. The left and right VFC were constructed by plotting the calculated stroke work of each ventricle against the EVFP of the corresponding ventricle. LVSP was calculated as a ratio of the left ventricular stroke work to the duration of systole and expressed in watts. The conversion factor used was: 1 watt = 10,180 g.-cm./second. TTI per beat in millimeters Hg \times seconds was obtained from the area under the systolic portion of the aortic pressure pulse. The duration of systole was measured as the time from abrupt pressure rise to the incisural notch.

In nine dogs VFC, TTI and LVSP were determined prior to and following digitalization and during halothane anesthesia. At the completion of VFC determination, the total amount of infused blood minus the blood withdrawn for arterial gas analysis was withdrawn from the right femoral vein into the reservoir. After all pressures returned to the control level ouabain, in doses ranging from 0.03 to 0.05 mg./kg., was injected into the right femoral vein. Digitalizing dose of ouabain was determined by changes in the T wave and depression of the S-T segment of the electrocardiogram. None of the animals showed premature ventricular contraction after administration of the glycoside.

Measurements of VFC, TTI and LVSP were repeated after the assessment of digitalization. A Model II Fluotec vaporizer, fitted into the nonbreathing system, was calibrated by means of gas chromatography using a column of celite coated with silicone oil and helium as the carrier gas. Standard halothane-oxygen mixtures for calibration were prepared by weighing halothane and mixed with 100 per cent oxygen. Calibration was performed by injecting into the chromatograph a set volume of a standard gas mixture at room temperature and by calculating the area. It was found to deliver halothane in O\textsubscript{2} 0.5, 0.9, 1.3 and 1.8 in volume per cent (V/V) with the dial settings of 0.5, 1.0, 1.5 and 2.0 respectively. Although the output of the vaporizer may not represent the concentration of halothane in the venous blood, the experimental design and duration of exposure to the agent permitted the maintenance of consistent and constant values. Observations were made after 0.5 per cent halothane was administered for thirty minutes. These procedures were repeated with 1.0, 1.5 and 2.0 per cent halothane at 1.5 hour intervals. In one throracotomized animal, heart rate was controlled at 80 per minute by bipolar electrical stimulation of right ventricular wall following A-V block produced by the technique described by Bordius \textit{et al.}\textsuperscript{21} using 10 per cent formaldehyde. In two dogs digitalization was carried out during 2 per cent halothane anesthesia. In four dogs the cardiohemodynamic effects of digitalis and halothane were studied.

The slope of the VFC, the ratio of external ventricular stroke work in g.-m. to a unit of EVFP in cm. of water, was obtained from the initial linear portion of the curve, where ventricular stroke work is more readily augmented by a small change in filling pressure.\textsuperscript{25, 26} In each experiment the slope of the control VFC refers to zero, and the percentage changes in the slopes of VFC obtained during the administration of ouabain and halothane were calculated.

Arterial blood samples were analyzed for oxygen and total bicarbonate contents according to the method of Van Slyke and Neill.\textsuperscript{27} Arterial blood pH and P\textsubscript{CO\textsubscript{2}} were measured by means of a Sanz-Metrom pH electrode and a
Severinghaus $P_{CO_2}$ electrode using an Epsco Blood Parameter Analyzer.

**Results**

**Myocardial Contractility—Digitalis.** The effect of ouabain on myocardial contractility of nonmedicated, nonanesthetized dogs with intact thorax is illustrated in figure 2 which presents VFC obtained before and after administration of ouabain. The increase in myocardial contractility by ouabain is demonstrated by the increase in slope of VFC. There was also an increase in left ventricular stroke power from any given left ventricular end diastolic pressure (fig. 2). TTI per beat was unchanged by digitalization at any given left ventricular end diastolic pressure (fig. 2). VFC's obtained 15, 30 and 70 minutes after digitalization were essentially the same. Results similar to those shown in figure 2 were obtained in eight other animals.

**Myocardial Contractility—Halothane.** Depression of myocardial contractility was directly proportional to the inspired concentration of halothane. The VFC's were depressed as shown by the mean percentage changes in slopes during 0.5, 1.0, 1.5 and 2.0 per cent halothane anesthesia and were $-3$, $-13$, $-51$ and $-89$ per cent, respectively (table 1 and fig. 3). A significant linear relation was found between the percentage decrease in slope and the inspired concentration of halothane. The correlation coefficients relating the percentage change in slope of VFC to the halothane concentration were $-0.94$ on the left and $-0.94$ on the right.

**Myocardial Contractility—Halothane in Digitalized Heart.** During the administration of 0.5, 1.0, 1.5 and 2.0 per cent halothane in six dogs given digitalis prophylactically, the mean percentage changes in slopes of the left VFC were $0$, $-6$, $-34$ and $-56$ respectively (table 1). Changes observed in the right ventricle were similar to those in the left. Figure 3 demonstrates the mean percentage depression of the slopes of left VFC during
halothane anesthesia in nondigitalized and pre-digitalized dogs. During halothane anesthesia in all concentrations studied, there was an improvement of myocardial contractility as shown by the changes in slope of VFC in predigitalized dogs as compared with those obtained in nondigitalized dogs. Figure 4 illustrates the characteristic responses of VFC’s observed during halothane anesthesia in nondigitalized and digitalized dogs.

In dogs given digitalis during halothane anesthesia, there was an increase in myocardial contractility as indicated by the increase in slope of VFC. The increase of ventricular stroke work was accomplished primarily by an increase in stroke volume at a given ventricular end diastolic pressure. Mean arterial blood pressure was not influenced by the administration of digitalis during halothane anesthesia.

**Hemodynamic Effects—Digitalis and Halothane.** The administration of ouabain in nonmedicated, nonoperated dogs caused a reduction in cardiac output and an increase in arterial blood pressure. The calculated total peripheral resistance was markedly increased after digitalization (fig. 5).

In nondigitalized dogs during one hour of halothane anesthesia there was a reduction of cardiac output associated with a fall in arterial blood pressure. Total peripheral resistance was increased (fig. 5).

When the animal was digitalized prophylactically, the administration of halothane resulted in an elevation of cardiac output. Arterial blood pressure was reduced to the same level observed in those of nondigitalized animals (fig. 5). Arterial blood pH, total CO₂, P₅₀, oxygen saturation, and body temperature remained at physiological levels prior to and following digitalization and during halothane anesthesia. Hematocrit value was not altered throughout an experiment.

**Discussion**

Reduction of myocardial contractility as indicated by changes in slopes of the ventricular function curves was directly proportional to the inspired concentration of halothane.¹³,¹⁵ Myocardial oxygen consumption determined by the tension time index was also reduced, and the relationship of left ventricular stroke work to TTI was linear.¹³ These findings suggest that the mechanical efficiency of the heart, i.e., the ratio of external cardiac work to myocardial oxygen consumption, is not

% CHANGE

**Table 1. Change in Slope of Left Ventricular Function Curve**

<table>
<thead>
<tr>
<th>Halothane (percentage concentration)</th>
<th>Slope (percentage change)</th>
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<tbody>
<tr>
<td></td>
<td>Nondigitalized*</td>
</tr>
<tr>
<td>0.5</td>
<td>–3</td>
</tr>
<tr>
<td>1.0</td>
<td>–13</td>
</tr>
<tr>
<td>1.5</td>
<td>–51</td>
</tr>
<tr>
<td>2.0</td>
<td>–89</td>
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* Mean values of ten experiments.
† Mean values of six experiments.

**Fig. 3. Changes in the ventricular stroke work plotted against a unit of ventricular filling pressure in nondigitalized (left) and digitalized (right) preparations during halothane anesthesia.**
altered during halothane anesthesia. The ventricle operates at different functional levels during various concentrations of halothane in preserving its capacity to perform efficient external useful work in the presence of decreased myocardial contractility. It has been shown that ventricular contractile force, measured with a Walton strain

Fig. 4. Left and right ventricular function curves during halothane anesthesia in nondigitalized (A) and digitalized (B) dogs. C: Control observation.
gauge, is markedly diminished during halothane anesthesia. These studies were performed during extreme experimental conditions, i.e., premedication, respiratory acidosis, other induction anesthetic agents, and surgical trauma associated with thoracotomy, opening the pericardium and securing of a Walton strain gauge on the myocardium. All these factors may change the normal force of ventricular contraction. It was demonstrated that opening of the pericardium results in an impairment of myocardial contractility as indicated by a lowered VFC. Therefore, the reduction of ventricular contractile force does not necessarily indicate depressed myocardial contractility. Whereas, the preparation used in the present study is capable of analyzing changes of the performance of the heart in nonmedicated, nonoperated dogs with an intact thorax and pericardium prior to and during the administration of drugs.

Recent evidence supporting the concept that cardiac glycosides exert a positive inotropic effect on the normal heart has been presented by many investigators. Braunwald et al. found that the administration of cardiac glycosides augments the myocardial contractile force in the nonfailing human heart. Cotten and Stopp demonstrated that digitalis increases myocardial contractility as determined by VFC in the nonfailing heart in experiments on dogs with an open thorax. In the present study intravenous administration of ouabain to the normal heart of nonanesthetized, nonoperated and nonpremedicated dogs produced an increase in myocardial contractility as indicated by the elevation of VFC (fig. 2). Digitalization decreased the cardiac output and produced an elevation of arterial blood pressure (fig. 5). These observations on the effects of digitalis upon the normal heart were in accordance with the findings of other investigators.

It should be noted that digitalis increased myocardial contractility without altering TTI at any given end diastolic ventricular pressure. Since TTI is the principal hemodynamic determinant of myocardial oxygen at any given functional state of the heart, our findings support the concept that digitalis has no effect on myocardial qO₂, but aids in producing more effective external work and increases myocardial contractility.

It has been reported that digitalis can increase the arterial blood pressure in subjects with normal cardiovascular systems. The vasoconstrictor effect of cardiac glycosides on the arteriolar bed has been suggested as the basis for the increase in mean systemic pressure. In this study it was observed that the increase in arterial blood pressure and decrease in cardiac output following the administration of ouabain were associated with an increase of the calculated total peripheral resistance. Evidently, the cardiac glycosides exert a direct effect upon the arteriolar smooth muscle causing an increase in peripheral vascular resistance. Therefore, this peripheral action is the primary cause for the elevation of arterial blood pressure in normal subjects.

In view of the positive inotropic action of

**Fig. 5.** Hemodynamic effects of halothane anesthesia and digitalis. *Top:* Halothane. *Middle:* Ouabain 0.04 mg/kg. *Bottom:* Halothane in predigitalized dog.
digitalis and its pressor effect upon blood pressure in normal subjects, and in view of the negative inotropic action of halothane and its depressor effect, one is apt to infer that the prophylactic use of digitalis counteracts the depressant action of this anesthetic agent. The results obtained in the present study indicate that there was less depression of myocardial contractility in the digitalized preparation than those observed in the nondigitalized preparation during halothane anesthesia. However, the improvement of myocardial contractility in the digitalized heart was not complete.

In the predigitalized subject cardiac output was increased during halothane anesthesia and the arterial blood pressure remained at the same lowered level as observed in the nondigitalized preparation. Changes in cardiac output do not necessarily reflect the actual changes occurring in myocardial function. Cardiac output depends upon several factors including heart rate, effective ventricular filling pressure, myocardial contractility and blood pressure. According to the degree and direction of the changes in these factors, cardiac output may increase, decrease, or show no change in the presence of altered myocardial contractility. Tachycardia with heart rate of above 180 per minute or bradycardia with the rate below 60 per minute may cause shifting of the VFC. However, the heart rate, under the present experimental conditions, ranged from 80 to 160 per minute in all experiments and the responses of heart rate to the step-wise blood infusion for VFC determination were similar in each animal before and during halothane anesthesia with and without digitalization. The results obtained in an experiment where the heart rate was kept constant were approximately equal to those obtained when the heart rate was not controlled. Therefore, heart rate is not the critical determinant in effecting myocardial contractility in this study.

Improvement of myocardial contractility during halothane anesthesia with digitalization was not reflected by an increase in arterial blood pressure. This may indicate that halothane blocks the peripheral action of digitalis. This concept is based upon findings that digitalis acts directly on arteriolar smooth muscle and that halothane has antidiurenergic action upon the vessel wall and does not evoke a sympathoadrenal discharge. The action of halothane in suppressing the sympathetic nervous system responses to the cardiocirculatory depression is indicated by failure in observing a detectable increase in plasma catecholamine concentration in man. Recent studies in this laboratory revealed a significant reduction of myocardial epinephrine content with no change in norepinephrine content in dogs during halothane anesthesia. The chemical analyses of tissue catecholamines may determine the stored portion of catecholamines rather than the free form which is liberated and diluted into the systemic circulation. A decrease in epinephrine content of heart tissues is probably related to one or more of the following factors: (1) increased breakdown of epinephrine in the myocardium, (2) blockade of the methylation process from norepinephrine to epinephrine, and (3) increased utilization of epinephrine for supporting myocardial function during halothane anesthesia.

In view of these findings it is reasonable to state that digitalis increases myocardial contractility in the normal canine heart without changing the myocardial oxygen consumption, and partly protects myocardial contractility from being depressed during deep halothane anesthesia. However, there appears to be no justification for the use of digitalis in the treatment of hypotension, because the improvement of myocardial contractility is not complete, and the hypotension persists. It would seem more appropriate to decrease the inspired concentration of the anesthetic agent, thereby permitting a return of the myocardial function and arterial blood pressure within physiologic levels.

Summary

Determinations of left and right ventricular function curves, tension-time index and left ventricular stroke power were made in nonmedicated and nonoperated dogs prior to and following digitalization and during halothane anesthesia. In the nondigitalized subjects anesthetized with halothane, myocardial contractility as indicated by changes in slopes of the ventricular function curves was depressed in direct proportion to the inspired concentra-
tion of halothane. During 1.5 per cent halothane anesthesia the slope of the left ventricular function curve was depressed 51 per cent, and during 2 per cent halothane was depressed 89 per cent. The administration of digitalis alone resulted in a decrease of cardiac output and an increase in arterial blood pressure and myocardial contractility. In the digitalized preparation with halothane anesthesia, the slope of the left ventricular function curve was depressed 34 per cent with 1.5 per cent halothane and 56 per cent with 2 per cent halothane. Improvement of myocardial contractility was not reflected by an increase in arterial blood pressure.

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