Alterations of Normal Left Ventricular Performance by General Anesthesia

Bernard E. Filner, M.D.,* and Joel S. Kariiner, M.D.†

Serial invasive and noninvasive (systolic time interval) measurements of left ventricular performance were obtained in six healthy volunteers during general anesthesia employing the following sequence: thiopental induction, succinylcholine (prior to endotracheal intubation), and halothane—100 per cent oxygen at 1.25 and 1.75 MAC. Heart rate (HR), mean pulmonary arterial "wedge" pressure (PAW) and mean systemic arterial pressure (MAP) were measured continuously: cardiac index and systolic time intervals (STI’s) were measured during each intervention. At both levels of halothane, MAP and stroke work index decreased (both \( P < 0.02 \), while HR and systemic vascular resistance did not change. At 1.25 MAC halothane PAW was unchanged, but at 1.75 MAC PAW increased from 8 ± 4 (SD) to 11 ± 5 torr (\( P < 0.02 \)). Preload was altered at 1.25 MAC by administration of 600–1,000 ml lactated Ringer’s solution; PAW increased from 9 ± 4 to 17 ± 3 torr (\( P < 0.01 \)). At 1.75 MAC halothane, volume expansion increased PAW in a similar manner, but the resultant ventricular function curve was depressed compared with 1.25 MAC halothane. In addition, at each level of halothane anesthesia, the ventricular function curve was depressed compared with results obtained in awake normal subjects. Afterload was altered at 1.25 MAC halothane by infusion of phenylephrine sufficient to raise MAP by 30 per cent. This intervention resulted in a greater depression of cardiac performance than that observed at 1.75 MAC halothane alone. Although alterations in STI’s were directionally similar to changes observed in invasive hemodynamic measurements, STI’s were sensitive to acute alterations in loading conditions. It is concluded that the levels of halothane commonly employed for general anesthesia significantly depress left ventricular performance in normal subjects, as evidenced by abnormal responses to alterations in preload and afterload, and that STI’s should not be employed for routine measurement of left ventricular performance during anesthesia unless the afterload and the preload on the myocardium are known. (Key words: Heart, systolic time intervals; Heart, myocardial function; Anesthetics, volatile, halothane.)

In recent years, studies of cardiovascular effects of various inhalation anesthetic agents in healthy human volunteers have been reported. However, these carefully controlled studies intentionally omitted such drugs as premedicants, anticholinergics, thiopental, and succinylcholine. In contrast to administration of a pure inhalational anesthetic, a common anesthetic sequence is characterized by an induction dose of thiopental followed by succinylcholine, endotracheal intubation and then introduction of the inhalational agent. Therefore, previous studies employing inhalational agents only may not accurately define the changes occurring in patients. Also, these

<table>
<thead>
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<th>ABBREVIATIONS</th>
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<tbody>
<tr>
<td>BSA = body surface area</td>
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<tr>
<td>CI = cardiac index</td>
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<tr>
<td>CI = cardiac output</td>
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<tr>
<td>CVP = mean central venous pressure</td>
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<tr>
<td>HR = heart rate</td>
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<tr>
<td>LVET = left ventricular ejection time</td>
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<tr>
<td>MAP = mean systemic arterial pressure</td>
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<tr>
<td>PAW = mean pulmonary arterial &quot;wedge&quot; pressure</td>
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<tr>
<td>PEP = pre-ejection period</td>
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<tr>
<td>PEPI = pre-ejection period &quot;index&quot;</td>
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<td>Q-S2 = time from onset of the Q wave to the aortic component of the second heart sound</td>
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<td>STI = systolic time interval</td>
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<td>SV = stroke volume</td>
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<td>SVR = systemic vascular resistance</td>
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<td>SWI = stroke work index</td>
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previous studies did not contain data on changes in left-sided cardiac filling pressures (pulmonary arterial "wedge" pressures). Such measurements add another dimension to the characterization of the hemodynamic effects of these agents. In addition, anesthesia is not infrequently accompanied by hypotension, explained or otherwise, which may be treated by rapid fluid administration, vasopressors, or a combination of the two. While some information about the effects of acute changes in systemic arterial pressure (afterload) in anesthetized patients with heart disease is available, we are unaware of any study reporting the effects of acute changes in volume (preload) and afterload in anesthetized subjects who have normal cardiovascular function. Such acute alterations in loading conditions previously have proved highly useful in the study of cardiovascular function in conscious healthy animals, as well as in healthy conscious human subjects. We also previously emphasized that such interventions can provide a model for studying the clinical pharmacology of cardiovascular drugs, and in this study we have demonstrated that these techniques can also be used in the hemodynamic assessment of anesthetic agents.

Recently, there has been considerable interest in the use of noninvasive techniques, such as determination of systolic time intervals (STI's), for monitoring cardiovascular function in anesthetized patients. However, there are few data derived from human subjects undergoing general anesthesia in which STI's have been compared with the more widely used and accepted indices derived from invasive measurements of cardiovascular function.

Therefore, we designed a study to provide data concerning: 1) the validity of using STI's for measuring the cardiovascular effects of halothane; 2) the hemodynamic effects of drugs commonly used in anesthetic practice in premedicated healthy subjects; 3) the effects on myocardial performance of acute alterations in preload and afterload during such halothane anesthesia.

Methods

The study group consisted of six healthy male volunteer subjects ranging in age from 19 to 24 years. Prior to acceptance of a subject into the study, a complete history and physical examination were obtained. The following laboratory data were obtained for each subject (all results were within normal limits): STI's, resting electrocardiogram, chest x-ray, pulmonary function studies, complete blood count, blood urea nitrogen, serum creatinine, serum sodium, potassium, bicarbonate and chloride, and serum lactate dehydrogenase, glutamic-oxidase, and glutamic-pyruvate transaminases. The study protocol and consent forms were approved by the Committee on Human Research and Investigations of the University of California, San Diego. Each subject was interviewed and allowed at least a week to review the consent form before signing it.

Each subject was premedicated with 0.1 mg/kg diazepam and 0.5 mg atropine, given intramuscularly, one-half hour prior to arrival in the study area (an operating room) in the postabsorptive state. Using local infiltration anesthesia, appropriate catheters were placed for intravenous infusion, and arterial (radial artery), central venous, and pulmonary capillary ("wedge") pressure measurements. A balloon-tipped, flow-directed catheter (size 5F) was inserted percutaneously into the right or left median basilic vein and passed into the pulmonary artery, using the pulse contour recognition method.

After all catheters were in place, baseline measurements (STI's, central venous pressure [CVP], mean pulmonary arterial "wedge" pressure [PAW], systemic arterial pressure, and cardiac output were recorded. All pressure measurements were referred to atmospheric pressure, and all were made at end-expiration. The subjects then breathed 100 per cent oxygen for 10 minutes, and another set of measurements was made. During this period, as well as for the remainder of the study, airway pressure was measured, and values of PAW, CVP and MAP were obtained when airway pressure had fallen to zero. This was true during periods of spontaneous as well as mechanical ventilation. Positive end-expiratory pressure was not applied to the airway during any part of this study. Induction of anesthesia was accomplished with thiopental, 5 mg/kg, iv., succinylcholine, 100 mg, was administered intra-
venously. Measurements after thiopental and succinylcholine were made within one minute of the onset of drug effects. After the post-
sucinylcholine measurements were made, an
endotracheal tube was placed and each subject
was given halothane in 100 per cent oxygen,
administered via a semiclosed circle absorp-
tion system. An end-tidal concentration of 1.05
per cent halothane (1.25 MAC in this age
group) was maintained for 20 minutes. Volume
expansion sufficient to increase FAW 5–7
torr was carried out (5 per cent dextrose in
lactated Ringer’s solution, 600–1,000 mL given
over 10 minutes). The level of anesthesia was
deepened to 1.47 per cent end-tidal halothane
concentration (1.75 MAC) and equilibrium
maintained for 20 minutes. A fluid load was
again administered as described above. The
end-tidal concentration of halothane was then
reduced to 1.05 per cent (1.25 MAC) and main-
tained at that level for 20 minutes. The final
phase of the study was the intravenous infu-
sion of phenylephrine sufficient to raise mean
arterial pressure to 30 per cent above the level
at the start of infusion. The phenylephrine infu-
sion lasted an average of 20 minutes (range
15–25) and was administered only at the 1.25
MAC level. All subjects were mechanically
ventilated to maintain PaO₂ in the normal
range (33–37 torr). Measurements of all vari-
ables recorded during baseline studies were
made after each of the steps in the above
outline of the anesthetic sequence. Arterial
blood gases, body temperature and hematocrit
were also measured at each step. There was no
significant differences in these variables be-
tween any sets of measurements.

When the study was completed, anesthetic
administration was terminated, all catheters
were removed, and the subjects returned to
the recovery room. Each subject remained in
the hospital overnight and was discharged the
next day. Each was examined by the principal
investigator a week after the study was com-
pleted. No subjective or objective evidence of
any morbidity was found in any subject.

All pressures were measured using physio-
logic transducers.† Piezoelectric crystal mi-
crophones§ were employed in the recording of
the heart sounds and the carotid arterial pulse
contour. A standard three-lead ECG was rec-
corded continuously. End-tidal halothane and
CO₂ concentrations were measured using infra-
red analyzers. Cardiac output was deter-
mined by the dye-dilution method. Indo-
cyanine green (1 mL of 2.5 mg dye/mL) was
injected through the central venous catheter
and blood was withdrawn from a radial artery.
Cardiac output was calculated using a Lyons
densitometer–computer.** Arterial Blood
gases were measured with the appropriate
electrodes.†† Temperature was monitored con-
tinuously with an esophageal thermistor
probe.†† All pressures, the ECG, phonocar-
diogram, carotid arterial pulse tracing, and
end-tidal halothane and CO₂ concentrations
were recorded on an eight-channel paper
recorder§ and on an FM magnetic tape recorder.§
† The STIs were calculated using the meth-
ods of Weisssler et al.††† Indices were calcu-
lated from standard regression equations.††† All
recordings were obtained at 100 mm/sec
paper speed, and 10 cycles were averaged for
each measurement.

The paired t-test was used to determine
statistical significances of the changes ob-
served.

Results

Table 1 lists the derivations employed in the
data analysis. Table 2 lists mean values ± 1
standard deviation for the derived and meas-
ured data. Table 3 shows the paired statistical
comparisons in outline form.

Thiopental

The only significant change was an increase
in HR (P < 0.01) compared with values ob-
tained while the subjects were breathing 100
per cent oxygen.

Succinylcholine

Compared with values obtained after ad-
ministration of thiopental, there was a sig-

† Model LB-2, Beckman Instruments, Schiller
Park, Ill.

** Physiotronics, Burbank, Ca. Presently Elec-
tronics for Medicine, White Plains, N.Y.

†† Radiometer, Copenhagen.

††† Yellow Springs Instruments, Yellow Springs,
Ohio.
Stroke volume (ml)
Stroke work index (g-m/beat/m²)
Systemic vascular resistance (dynes·sec·cm⁻⁵)
Cardiac index (l/min/m²)
Pre-ejection period (ms)
Pre-ejection period "index" (ms)

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<tr>
<td>[ SV = \frac{CO}{HR} ]</td>
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<tr>
<td>[ SWI = \frac{(MAP - PAW) \times 1.36}{100 \times BSA} ]</td>
</tr>
<tr>
<td>[ SVR = \frac{(MAP - CVP)}{CO \times 0.8} ]</td>
</tr>
<tr>
<td>[ CI = \frac{CO}{BSA} ]</td>
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<tr>
<td>[ PEP = (Q-S_t) - \text{LVET} ]</td>
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<tr>
<td>[ PEPI = PEP + (HR \times 0.4) ]</td>
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</tbody>
</table>

\* SV = stroke volume; CO = cardiac output; HR = heart rate; SWI = stroke work index; MAP = mean systemic arterial pressure; PAW = mean pulmonary arterial "wedge" pressure; BSA = body surface area; CVP = mean central venous pressure; PEP = pre-ejection period; (Q-S_t) = time from onset of the Q wave to the aortic component of the second heart sound; LVET = left ventricular ejection time, measured from a simultaneously obtained radial arterial pressure tracing; PEPI = pre-ejection period "index."

A significant increase in HR (P < 0.01). However, one subject developed ventricular bigeminy and none hypotension after the administration of succinylcholine. When this subject is omitted from the data analysis, an increase in MAP (P < 0.05) is also evident. Compared with values obtained during breathing of 100 per cent oxygen, there were significant increases in CI (P < 0.01), MAP (P < 0.05), and HR (P < 0.01).

**HALOTHANE**

1.25 MAC compared with 100 per cent O₂ alone. Significant decreases in CO (P < 0.05), MAP (P < 0.05), and SWI (P < 0.01) were accompanied by increases in PEP, PEPI, and PEPI/LVET, with decreases in 1/PEP² and 1/PEP² (all P values <0.01). No significant change in SVR was found.

1.75 MAC compared with 100 per cent O₂ alone. Significant decreases in CI (P < 0.05), MAP (P < 0.01), and SWI (P < 0.01) were again accompanied by increases in PEP, PEPI, and PEPI/LVET and decreases in 1/PEP² and 1/PEP². Also observed was a significant increase in PAW (P < 0.02). Again, no significant change in SVR was found.

1.75 MAC compared with 1.25 MAC. No significant change in any of the STI data was found. Decreases in MAP (P < 0.05), SWI (P < 0.05), and CI and CO (P < 0.01) were observed, with an increase in PAW (P < 0.05).

1.25 MAC compared with values after succinylcholine. HR (P < 0.01), SWI (P < 0.02), SVR (P < 0.05), MAP, CI, 1/PEP², and 1/PEP² (all P < 0.01) decreased, while PEP, PEPI and PEPI/LVET increased (all P < 0.01).

**VOLUME EXPANSION DURING HALOTHANE ANESTHESIA**

At 1.25 MAC, fluid administration resulted in significant increases in PAW, CI, 1/PEP² and 1/PEP², with decreases in PEP, PEPI, PEPI/LVET and SVR (all P < 0.01). No significant change in MAP, SWI or HR was found.

At 1.75 MAC, fluid administration resulted in no significant change in any variable except PAW, which increased (P < 0.01).

Composite ventricular function curves for all subjects were constructed after fluid administration at 1.25 and 1.75 MAC. Figure 1 depicts these curves constructed from all points during fluid administration at both MAC multiples of halothane. Compared with values obtained when the subjects were awake, the curves showed displacement downward and to the right with increasing halothane concentration.

**PHENYLEPHRINE INFUSION**

1.25 MAC halothane + phenylephrine compared with 1.25 MAC halothane alone. The pressor infusion resulted in significant increases in SVR, PAW, MAP and SWI (all
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<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>CO (l/min)</th>
<th>CI (l/min/m^2)</th>
<th>PPA (mm Hg)</th>
<th>SWI (g/cm^2/m^2)</th>
<th>SWV (artery)</th>
<th>PEPI (mm Hg)</th>
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<td>± 27</td>
<td>± 166</td>
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<td>92.8</td>
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<td>± 7.5</td>
<td>± 5.5</td>
<td>± 2.27</td>
<td>± 0.95</td>
<td>± 3.8</td>
<td>± 30</td>
<td>± 220</td>
<td>± 7.9</td>
<td>± 8.1</td>
<td>± 12</td>
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<td>Thiopental</td>
<td>82.5</td>
<td>93.3</td>
<td>8.80</td>
<td>4.32</td>
<td>10.0</td>
<td>59.3</td>
<td>837</td>
<td>112.7</td>
<td>145.7</td>
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<td>± 4.2</td>
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<td>± 1.90</td>
<td>± 0.82</td>
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<td>± 230</td>
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<td>± 8.9</td>
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<td>± 12.1</td>
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<td>Halothane, 1.25 MAC, + volume expansion</td>
<td>74.7</td>
<td>61.9</td>
<td>6.07</td>
<td>3.00</td>
<td>17</td>
<td>26.1</td>
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<td>± 17.3</td>
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<td>± 0.80</td>
<td>± 0.53</td>
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<td>± 13</td>
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<td>77.5</td>
<td>58.3</td>
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<td>152.5</td>
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<td>± 91</td>
<td>± 33.4</td>
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<td>5.24</td>
<td>2.62</td>
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<td>± 172</td>
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* For statistical analysis, see table 3.
1 Mean ± 1 standard deviation.
|                          | Number | HR  | MAP | CO  | CI  | F2W | SW1 | SVH | PEP | PEPI | TPEP | TPEPI | TPEPIE
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<td>NS</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>100 per cent O₂/halothane 1.75 MAC</td>
<td>5</td>
<td>NS</td>
<td>P &lt; .01</td>
<td>P &lt; .05</td>
<td>P &lt; .02</td>
<td>NS</td>
<td>NS</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
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<td>P &lt; .01</td>
<td>P &lt; .01</td>
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<tr>
<td>Halothane 1.75 MAC halothane 1.75 MAC + volume expansion</td>
<td>4</td>
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<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<td>NS</td>
<td>NS</td>
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</tr>
<tr>
<td>Halothane 1.25 MAC halothane 1.25 MAC + phenylephrine</td>
<td>6</td>
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<td>P &lt; .01</td>
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<td>P &lt; .01</td>
</tr>
<tr>
<td>Halothane 1.75 MAC halothane 1.25 MAC + phenylephrine</td>
<td>5</td>
<td>NS</td>
<td>P &lt; .01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
</tr>
</tbody>
</table>

* For actual data, see Table 2.
† One patient became hypotensive during 1.75 MAC halothane and was excluded from the data analysis.
‡ One additional patient developed ventricular bigeminy during fluid administration, which responded to intravenous administration of lidocaine. Because of the arrhythmia he was excluded from the data analysis.
Fig. 1. Composite left ventricular function curves at two levels of halothane anesthesia compared with a left ventricular function curve derived from data obtained in normal awake subjects by Sanghvi et al. Left ventricular “filling” pressure for the awake subjects refers to left ventricular end-diastolic pressure, and for the anesthetized subjects to mean pulmonary capillary (“wedge”) pressure (PAW). For the anesthetized subjects the ventricular function curve at each anesthetic level was constructed by averaging the slopes and the intercepts from each curve for each subject and then constructing the composite curves shown.

\[ P < 0.01 \], while HR (\( P < 0.05 \)) and CI (\( P < 0.01 \)) decreased. PEP, PEPI and PEP/LVET increased, while 1/PEP\(^2\) and 1/PEPF showed corresponding decrements (all \( P < 0.01 \)).

1.25 MAC halothane + phentylephrine compared with 1.75 MAC halothane alone. CI and HR were not significantly different. MAP, SVR, SWI, and PAW were higher after phentylephrine infusion at 1.25 MAC (all \( P < 0.01 \)). PEP, PEPI, and PEP/LVET were increased, and 1/PEP\(^2\) and 1/PEPF decreased (all \( P < 0.02 \)).

Discussion

Hemodynamic Measures of Left Ventricular Performance Obtained by Invasive Means

In this study, we did not attempt to isolate specific effects of the premedicants. Nitrous oxide, which is usually administered during halothane anesthesia, was not added to the sequence, since we felt that this would significantly increase the number of pharmacologic variables as well as the subjects’ total time of anesthetic exposure. As has been indicated by others in previous reports employing unpremedicated subjects, our data should be interpreted in the light of differences between our prospectively controlled study conditions in healthy human subjects and those occurring during the usual conditions of clinical practice.

Thiopental

Our data indicate that thiopental had little net hemodynamic effect in the subjects investigated. The increase in HR appears to have been the result of a baroreceptor reflex response. Thus, a slight decrease in systemic arterial pressure was associated with an augmented HR and subsequent return of the systemic arterial pressure to a level close to the initial values. An example of this response is shown in figure 2. Such responses account for the apparent stability of the circulation in this group after thiopental administration. The possibility that patients unable to respond to thiopental with an increase in HR should be given this agent with great care should be considered. Such situations may arise when the baroreceptor response is blunted during halothane anesthesia, when beta-adrenergic blockade is established, or when the patient has insufficient myocardial reserve to sustain an augmented heart rate.

In contrast to our observations, most previously published information (especially in the case of thiopental) is based on animal or in vitro experiments, rather than on human studies. In one of the few reported human studies, Prystowsky and colleagues examined the effects of thiopental induction in treated and untreated hypertensive patients and observed decreases in systemic arterial pressure, with or without declines in SVR (depending on whether the patients were receiving antihypertensive medication). In a prior report, the same group had commented on markedly decreased baroreceptor activity in their hypertensive patients, and this could account for the divergent data.
Succinylcholine

This drug produced an increase in HR beyond that observed with thiopental, as well as increases in CI and MAP, while PAW, SVR, and SWI were unchanged. These changes all occurred prior to laryngoscopy and endotracheal intubation. It is possible that all observed changes resulted from the increase in HR. It is well known that an increase in HR alone can act as a positive inotropic stimulus to the myocardium, but the possible influence of succinylcholine-induced sympathetic ganglionic stimulation should also be considered.

Halothane

The data obtained during halothane administration are similar to those reported by Eger et al. The absolute changes in CI and SWI at both levels of halothane anesthesia were greater in our subjects, possibly due to the prior administration of thiopental. That our subjects had body temperatures 0.5 to 1.0 degree C lower than those of Eger et al. may also account in part for these differences. The increase of PAW in the face of decreasing CI and SWI as anesthesia was deepened from 1.25 to 1.75 MAC is further evidence for the additional myocardial depression that occurs with greater depth of halothane anesthesia in man (fig. 1). These observations are in agreement with the conclusions of Eger et al. concerning the myocardial depressant effects of halothane. Our results are also consistent with data obtained in dogs that showed that halothane is a potent depressor of left ventricular performance. No recovery of myocardial function was observed during the relatively brief exposure of our subjects to halothane anesthesia.

It should be emphasized that the majority of hemodynamic comparison detailed in tables 2 and 3 were performed while the subjects were being mechanically ventilated. As mentioned previously, all data obtained after the subjects began breathing 100 per cent oxygen were measured at zero airway pressure. Thus, all such comparisons were obtained under identical conditions with respect to intrapleural pressure. We are aware that there are difficulties in comparing values of PAW (referred to atmospheric pressure) measured in spontaneously breathing subjects with data obtained from subjects being mechanically ventilated. However, it is well known that in closed-chest animals all circulatory changes arising from imposed positive pressure reverse promptly once the lungs are vented to atmosphere (zero intratracheal pressure). Therefore, the pressures we measured at zero intratracheal pressure should be true transmural pressures rather than purely luminal pressures. We believe that under these conditions the comparisons with the data obtained during breathing of 100 per cent oxygen are valid.

Our data demonstrate that administration of halothane did not result in any significant alteration in SVR. Others have reported that SVR decreases with induction of halothane anesthesia, but does not change significantly as depth of halothane anesthesia increases.
the present study, the latter observation was confirmed. SVR remaining unaltered as the halothane level was increased from 1.25 to 1.75 MAC. The lack of change in SVR with induction in our study is perhaps attributable to the initially low SVR’s of our subjects, which may have been the result of diazepam premedication.

**Volume Expansion**

The rapid administration of fluid was employed to assess the effect of halothane on the response of the left ventricle to acute changes in preload. At 1.25 MAC halothane, the effects of volume expansion included a significant decrease in SVR with a small but significant increase in CI, and no change in MAP, SW1, or HR. At 1.75 MAC halothane, every subject manifested a decrease in SVR but, probably due to the small sample size, the change was not statistically significant. The decrease in SVR with volume expansion may be due to opening of peripheral vascular “channels” and/or the inability of a depressed myocardium to respond to the fluid loading with a normal increase in cardiac output. Volume expansion was not performed in our subjects while they were awake, but recent information concerning the effects of acute alterations in preload in the normal subject are available. Sanghvi *et al.* reported that administration of an average of 387 ml of low-molecular-weight dextran to normal subjects increased the left ventricular end-diastolic pressure from 8 to 18 torr, increased CI from 3.2 to 4.0 l/min/m², and increased SW1 from 46 to 54 g-m/beat/m² with no change in HR or MAP. These results differ from our data, which showed (at both levels of halothane anesthesia) no significant change in SW1 despite an increase in PAW. These observations are further evidence that halothane anesthesia reduces the ability of the normal left ventricle to utilize the Frank-Starling mechanism in response to an acute alteration in preload. Composite ventricular function curves during volume expansion at both levels of halothane anesthesia are compared with the data of Sanghvi *et al.* in figure 1.

**Increase in Systemic Arterial Pressure**

Phenylephrine, an alpha-adrenergic agonist with virtually no beta-adrenergic effect, was infused to determine the effect of increasing afterload during halothane anesthesia. All subjects had significant increases in MAP, SVR, SW1, and PAW. Accompanying these changes, CI and HR decreased. Phenylephrine infusion at 1.25 MAC halothane resulted in greater depression of cardiac performance than that observed with 1.75 MAC halothane alone. Fourcade *et al.* recommended the use of phenylephrine infusion to maintain systemic hypertension during carotid endarterectomy performed using halothane anesthesia. However, it has recently been demonstrated that in patients who have coronary-artery disease, acute increases in afterload may result in abrupt increases in PAW and may lead to ischemic ST-segment depression on the electrocardiogram. Such patients may have minimal myocardial reserve, and any decline in cardiac output or increase in myocardial oxygen consumption that ensues when systemic arterial pressure is raised by pharmacologic means can result in acute myocardial ischemia. Therefore, this particular technique may be inappropriate for some patients.

**Hemodynamic Measures of Left Ventricular Performance Obtained by Analysis of STIs**

The second and perhaps most important aspect of this study involved the assessment of a noninvasive method for measuring cardiovascular function in man. Systolic time intervals (STIs) were chosen because they have been extensively studied and because they have been proposed as useful measures of "myocardial contractility" during general anesthesia. However, it has been argued that "contractility" cannot be measured by STI's since the latter are affected by loading conditions. Further, the use of STI's has not been validated in controlled studies in anesthetized man, although experimental studies in animals are available. For example, the inverse square of the pre-ejection period (1/PEP²) correlates with peak aortic acceleration in dogs.

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et al. reported that when $\bar{PAW}$ exceeded 12 torr in anesthetized dogs, externally measured STI's correlated poorly with internally measured STI's and other measures of cardiac performance such as left ventricular $dP/dt$.27 These investigators also reported a significant effect of afterload on PEP, the latter increasing as afterload was augmented.27 Several studies4,25,28 have indicated that HR per se has little effect on PEP (and therefore, PEP does not have to be converted to PEPi to correct for HR). Thus, an alteration in PEP would be expected only during an inotropic intervention regardless of the effect on HR, but such a formulation is complicated by the well-known positive inotropic effects of an increase in HR.*

Previous studies of STI's in man have been performed under "static" conditions. During such experiments, the patients or subjects were exercised or drugs were administered, and then an isolated measurement of the altered cardiovascular status was made. It has been claimed that $1/PEPi$ reflects changes in "myocardial inotropy" induced by changes in $P_{a}_{ox}$ in man.29 This study represents an attempt to use STI's as a measure of myocardial function in a "dynamic" situation, i.e., the relatively unstable hemodynamic system that occurs in anesthetized man. Recently, Forrest et al. used STI's to measure the hemodynamic effects of lumbar epidural blockade.11 They also described the differential effects of methoxamine and ephedrine (used as pressors after epidural block) on the STI's.

Our preanesthetic and baseline measurements of STI's yielded values that were in agreement with the normal values reported by Weissler and colleagues.11 Although tachycardia was found after induction of anesthesia with thiopental, no significant change in STI's was seen in these subjects.

After succinylcholine was administered, there were increases in HR, MAP, and CI, with a decrease in PEP and an increase in $1/PEPi$, compared with control values. Thus, these data indicate a positive inotropic response associated with succinylcholine administration.

Compared with control values at both levels of halothane anesthesia, the changes in the STI's suggested that myocardial depression occurred during administration of this agent. All of the noninvasive variables indicated some recovery of myocardial function (with the accompanying increase in CI) when fluid was administered at 1.25 MAC halothane. They also indicated that recovery occurred at the 1.75 MAC level after volume expansion.

### Table 4. Correlation Coefficients for Selected Invasive vs. Noninvasive Variables

<table>
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<tr>
<th></th>
<th>High $\bar{PAW}$</th>
<th>Low $\bar{PAW}$</th>
<th>High SVR</th>
<th>Low SVR</th>
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<td></td>
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<tr>
<td>CH vs. PEP</td>
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</tr>
<tr>
<td>CH vs. PEPi</td>
<td>0.81</td>
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<td></td>
</tr>
<tr>
<td>CH vs. $1/PEPi$</td>
<td>0.81</td>
<td>0.80$^4$</td>
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<td></td>
</tr>
<tr>
<td>CH vs. PEPi$1/2$</td>
<td>0.81</td>
<td>0.80$^4$</td>
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<td>CH vs. PEPi$1/2$</td>
<td>0.81</td>
<td>0.80$^4$</td>
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<tr>
<td>CH vs. PEPi$1/2$</td>
<td>0.81</td>
<td>0.80$^4$</td>
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<tr>
<td><strong>Part B</strong></td>
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<tr>
<td>SWH vs. PEP</td>
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<tr>
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<td>0.77$^4$</td>
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<tr>
<td>SWH vs. PEPi$1/2$</td>
<td>0.84</td>
<td>0.77$^4$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^*$ indicates correlation coefficient derived by least-squares regression analysis. 

$^4$ $n = 57$. 

$^6$ $n = 25$. 

$^8$ $n = 32$. 

$^{10}$ $n = 12$. 

$^{12}$ $n = 45$. 

$H$ Phenylephrine data not included.
These observations are consistent with the hypothesis that STI's are sensitive to alterations in preload. Thus, although pump function under these circumstances is improved, experimental data indicate that muscle function as measured by left ventricular dP/dt and mean rate of internal diameter shortening may remain unchanged.6 Despite significant decreases in CI, SWL, and MAP, accompanied by increases in FAW as anesthesia was deepened from 1.25 MAC to 1.75 MAC, no further change in the already abnormal STI's was seen. Possible explanations for this observation include the influence of alterations in left ventricular filling pressure on STI's,7 the order of anesthetic levels in the protocol, and the small sample size.

The highest values of PEP, PEPI, and PEP/ LVET and the lowest values of 1/PEPI2 and 1/PEPI1, together with the lowest values of CI, were found after infusion of phenylephrine at 1.25 MAC halothane. Although these data are consistent with a state of severe myocardial depression produced by this combination of drugs, it should be realized that the increased afterload would be expected to lengthen the PEP, since the aortic valve opens at a higher pressure under the above described conditions.20 Thus, the fact that PEP remained elevated (indeed higher than at 1.75 MAC halothane alone) could have resulted solely from an alteration in loading conditions, and therefore, STI's may not be a valid method for evaluating myocardial function in this setting.

Correlation coefficients for selected pairs of invasive vs. noninvasive variables are shown in table 4. These correlations were obtained using pooled data from all subjects. The data indicate that with respect to the correlation of CI with 1/PEPI and 1/PEPI1, an increased FAW or SVR results in a better correlation than a low FAW or SVR. This is in contrast to previously published experimental observations.55 Inspection of table 4 reveals that while some of these correlations are quite good, considerable scatter exists, and it is not possible to employ 1/PEPI2 or the other STI values as a direct predictor of CI or SWI, although the correlations might tend to improve with a larger sample size.

These observations concerning changes in STI's during alterations of preload and afterload are consistent with the observed hemodynamic trends, and serve to underscore the dependence of measures of left ventricular pump performance and STI's on loading conditions. Thus, while alterations in STI's appear to be directionally similar to changes in values obtained by invasive hemodynamic measurements, they are not independent measures of left ventricular "contractility." Therefore STI's should not be employed for routine measurement of cardiac performance during general anesthesia unless both the afterload and the preload on the myocardium are known. In the future, perhaps another noninvasive measure of myocardial function that is not dependent on loading conditions will be proposed and can reliably be added to the anesthesiologist's armamentarium. Certainly further research is desirable and justified.

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