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On-line Systolic Time Intervals during Anesthesia in Patients with and without Heart Disease

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Twenty-four patients with severe, 24 with moderate, and 24 without heart disease were selected for measurements of systolic time intervals (STI) and blood pressure before and during anesthesia. In all patients anesthesia was induced with thiopental, 4 mg/kg. After tracheal intubation, 12 patients from each heart-disease class received halothane–N_2O–O_2 (halothane) and 12 patients from each class morphine–*d*-tubocurarine–N_2O–O_2 (MS-*d*Tc). Thiopental increased the pre-ejection period (PEP), decreased left ventricular ejection time (LVET), and accelerated heart rate (HR). These changes were similar in patients with and without heart disease. Halothane and MS-*d*Tc lowered systolic blood pressure and increased PEP/LVET. With halothane but not with MS-*d*Tc these changes were more pronounced in patients who had heart disease. Changes of the PEP/LVET ratio during halothane anesthesia were a better discriminating variable among patients without, with moderate, and with severe heart disease than were changes in systolic blood pressure. (Key words: Heart, systolic time intervals; Blood pressure, anesthesia; Analgesics, narcotic, morphine; Neuromuscular relaxants, *d*-tubocurarine; Anesthetics, intravenous, thiopental; Anesthetics, volatile, halothane.)

ANESTHESIA relying on morphine sulfate–nitrous oxide–oxygen and *d*-tubocurarine (MS-*d*Tc) has gained popularity because it appears to cause little cardiovascular depression.[1,2] Halothane, on the other hand, is a cardiac depressant, and arterial hypotension during halothane anesthesia is well recognized.

Systolic time intervals (STI) are said to provide particularly useful information in the noninvasive assessment of cardiac function.[3–6] Hence, STI might reveal cardiovascular changes during anesthesia, particularly in patients who have heart disease that alterations in arterial pressure fail to show. We, therefore, measured blood pressure and STI in patients with and without heart disease during halothane and MS-*d*Tc anesthesia to determine whether the measurement of STI can improve the evaluation of the cardiovascular status during anesthesia.

Methods

Seventy-two patients scheduled for major abdominal procedures were studied after informed consent was obtained. Their ages ranged from 25 to 76 years. Medical history, physical examination, routine laboratory data, bedside respiratory function tests, arterial blood gases during breathing of room air and 100 per cent inspired oxygen, electrocardiography, and chest radiograms were obtained preoperatively. Each patient was then classified in one of three classes: Class I, no heart disease; Class II, moderate heart disease;

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Class III, severe heart disease. This classification paralleled that of the New York Heart Association[7] but combined the latter's classes III and IV into a single class, severe heart disease. Thirty-six men (mean age 56 years) were assigned to a halothane treatment group, while 24 men and 12 women (mean age 50 years) were assigned to a MS-*d*Tc treatment group. Each treatment group was made up of 12 patients with severe, 12 with moderate, and 12 without heart disease.

Patients in the MS-*d*Tc group had radial arterial cannulas placed using local anesthesia before induction of general anesthesia. In all patients systolic time intervals (STI) were computed from the simultaneous processing of lead II of the ECG, phonocardiogram, and carotid arterial pulse contours. A microphone was placed in the fourth intercostal space to the left of the sternum for detection of the initial high-frequency component of the second heart sound (S_2). A piezoelectric transducer was secured over the carotid artery using an elastic and Velcro collar 6 inches wide. The resultant analog waveforms were sampled 250 times per second in 4-millisecond intervals by an analog-to-digital converter and processed on-line in real time with a PDP 11/20 computer using 16 K of core memory.[8] The onsets of the four events (the QRS wave of the ECG, the start of the carotid upstroke, the dicrotic notch, and the S_2) were determined by computing first and second derivatives. The accuracy of the detection algorithms was monitored by the computer operator, who visually scanned waveforms that were intermittently displayed with cursors marking the computer-detected onsets of the four events.

Heart rate (HR) was determined from R-R intervals, whereas the pre-ejection period (PEP) was measured as the interval from Q to the start of the carotid upstroke minus the S_2-to-dicrotic notch time interval. Left ventricular ejection time (LVET) was computed as the time interval from the start of the carotid upstroke to the dicrotic notch.

HR, PEP, LVET, and PEP/LVET were computed beat-by-beat for 15 seconds and then averaged so as to damp out the effects of the respiratory cycles. These values, as well as internal measures of quality control such as the standard deviations and the number of successfully processed STI versus the number of heart beats per 15-second interval, were then stored on disk. These processed data were presented numerically via a teletypewriter and graphically via a Gould 4800 electrostatic printer and a Computek 300 CRT display terminal for both the computer operator and the anesthesiologist and surgeon in the operating room using a slave TV monitor.

Arterial blood pressure was measured every minute with an Avionics Ultrasonic Arteriosonde Monitor placed on the upper arm or directly when an arterial line was available. The triple product (TP) was computed as LVET × systolic blood pressure (SBP) × HR in the halothane study alone. Arterial blood-gas analyses were performed intermittently. All intraoperative events were noted by the anesthesiologist upon his records, as well as reported on the voice channel of a multichannel analog tape recorder.

After placement of the monitoring sensors, baseline data were obtained and 0.6 mg atropine sulfate injected intravenously. This was followed by 4 mg/kg sodium thiopental, iv. Five minutes later, 100 mg succinylcholine was injected iv and the trachea intubated. Ventilation was controlled with an Air-Shields ventilator delivering 50 per cent oxygen with nitrous oxide in the halothane group and a mixture of 30 per cent oxygen and 70 per cent nitrous oxide in the MS-*d*Tc group. In the halothane group, all patients received halothane via a Fluotec vaporizer at 1.5 vol per cent inspired concentration for the initial 15 minutes of anesthesia. Later inspired halothane concentrations varied between 1.5 and 0.5 vol per cent as determined by the clinical judgment of the anesthesiologist.

In the MS-*d*Tc group, after intubation, all patients received morphine sulfate, 0.2 mg/kg, iv. Five minutes later an initial dose of *d*-tubocurarine, 0.4 mg/kg, was injected iv. Additional doses of *d*Tc were added as needed for muscle relaxation.

In both groups, data were collected throughout the operation and the pre-atropine data were used as baseline (control) data. In the halothane group, only data from the first 15 minutes of halothane anesthesia were used for analysis and averaged. In the MS-*d*Tc group, several periods following the injection of *d*Tc were examined: an early period (0–5 min), middle period (10–20 min), and late

period (35–40 min). These times refer to the minutes after injection of dTc. The data of each individual period were averaged.

For each group, all data were statistically analyzed by analysis of variance and by stepwise discriminant analysis. The significance of the observed difference between patient classes and times was assessed by the Scheffé method of multiple comparison. The BMD programs 08V and 07M[9] were employed in the analysis, using a PDP 11/45 computer.

Results

Halothane

The results for the halothane group are summarized in tables 1 and 2. Table 1 shows the control data before induction of anesthesia for the three cardiac classes. Patients with heart disease (Class II and Class III) had significantly higher SBP's and TP's than patients without heart disease. Patients who had severe heart disease had significantly greater pulse pressures (PP) than the healthy patients. There was no significant difference among the classes for HR or STI.

Table 2 shows the responses to thiopental and halothane expressed as percentage deviations from pre-anesthesia control values in the three patient classes. Thiopental caused significant increases in HR, PEP, and the PEP/LVET ratio and a significant shortening of LVET in each of the three classes. A decrease in PP with thiopental reached statistical significance in Class I only.

Inhalation of 1.5 per cent halothane resulted in a significant reduction in PP and significant increases in HR, PEP and PEP/LVET ratio in all classes. In addition to this, SBP and LVET decreased significantly in Classes II and III, while the TP decreased significantly in Class III only.

A discriminant analysis was employed to examine the question whether systolic time intervals contribute information about cardiac

TABLE 1. Halothane Group, Baseline Data before Induction of Anesthesia

	Class I No Heart Disease 12 Patients	Class II Moderate Heart Disease 12 Patients	Class III Severe Heart Disease 12 Patients
Number of patients taking drugs*	1	2	9
Age (years), mean and range	53 32–68	57 28–73	58 25–76
Pre-ejection period (PEP) (msec)	86 (3)†	83 (5)	84 (4)
Left ventricular ejection time (LVET) (msec)	287 (5)	286 (8)	299 (10)
PEP/LVET	0.30 (0.01)	0.29 (0.01)	0.28 (0.01)
Systolic blood pressure (SBP) (mm Hg)	127 (4)	150‡ (6)	157‡ (8)
Pulse pressure (PP) (mm Hg)	47 (3)	57 (7)	69‡ (6)
Heart rate (HR) (min^{-1})	78 (2)	80 (4)	75 (3)
Triple product (TP)	2808 (132)	3402‡ (188)	3491‡ (214)

* Number of patients taking one or more drugs for treatment of cardiovascular disease (includes antihypertensives, diuretics, antiarrhythmics, vasodilators, glycosides, beta blockers).

† Figures in parentheses are standard errors.

‡ Significantly different from Class I ($P < .05$), by Scheffé's method.

See text for abbreviations and methods.

TABLE 2. Halothane Group, Changes in Cardiovascular Variables Induced by Anesthesia

	Thiopental (4 mg/kg)	Halothane (1.5 Per Cent)
Class I: Twelve patients without heart disease		
Pre-ejection period (PEP)	117 (3)*	116 (6)*
Left ventricular ejection time (LVET)	84 (3)†	95 (2)
PEP/LVET	141 (8)†	122 (6)†
Systolic blood pressure (SBP)	94 (3)	97 (4)
Pulse pressure (PP)	79 (6)*	72 (4)†
Triple product (TP)	100 (3)	115 (7)
Heart rate (HR)	128 (7)†	122 (6)†
Class II: Twelve patients with moderate heart disease		
Pre-ejection period (PEP)	121 (4)†	141 (6)†
Left ventricular ejection time (LVET)	82 (2)†	91 (2)*
PEP/LVET	146 (5)†	152 (6)†
Systolic blood pressure (SBP)	91 (6)	79 (4)†
Pulse pressure (PP)	83 (11)	52 (4)†
Triple product (TP)	94 (8)	86 (8)
Heart rate (HR)	123 (7)†	117 (7)*
Class III: Twelve patients with severe heart disease		
Pre-ejection period (PEP)	126 (6)†	151 (6)†
Left ventricular ejection time (LVET)	86 (2)†	89 (2)†
PEP/LVET	149 (8)†	172 (5)†
Systolic blood pressure (SBP)	90 (4)	70 (5)†
Pulse pressure (PP)	83 (9)	48 (6)†
Triple product (TP)	99 (5)	76 (9)†
Heart rate (HR)	123 (5)†	120 (8)*

All responses (mean ± SE) are percentages of data shown in Table 1.
* $P < .05$, significant difference from control, by the Scheffé method.
† $P < .01$, significant difference from control.

function not available through "standard monitoring" (BP, HR, PP). First, using the baseline data and the percentage changes of all the recorded variables during the first 15 minutes of inhalation of 1.5 per cent halothane, a stepwise discriminant analysis was performed. Changes in SBP offered the best discrimination of all the standard monitoring (*i.e.*, HR, SBP, DBP, PP) variables during inhalation of halothane, 1.5 per cent. Adding to SBP another "standard" variable did not significantly improve the discrimination. The best discriminating variable obtainable from all monitored modalities, including the STI, was the change in PEP/LVET ratio during inhalation of halothane, 1.5 per cent. Adding any other recorded modality to the PEP/LVET ratio did not significantly improve this discrimination. Table 3 shows how these two discriminant functions separate patients with no (Class I), moderate (Class II), and severe (Class III) heart disease.

Next, we considered the question whether STI could be used to identify correctly, among the 36 patients, the 12 patients with severe, the 12 with moderate, and the 12 without heart disease. If the cardiovascular classifications of these 36 patients were not known intraoperatively and rather the patients were assigned randomly, equally, to the three classes of heart disease, each patient would have a 33% chance of being classified correctly. With the percentage change in SBP during halothane, 1.5 per cent, as a discriminating variable, the probability of a correct assignment improved from 33 to 67 per cent for the healthy patients (Class I) and from 33 to 58 per cent for the patients who had severe heart disease (Class III). The changes in SBP alone did not improve the

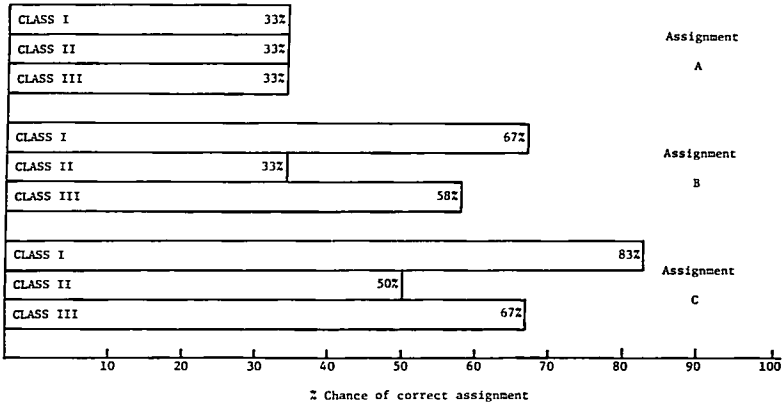

FIG. 1. Halothane group, probability of correct assignment based upon: *A*, random assignment; *B*, assignment using percentage change in systolic blood pressure as the intraoperative discriminant variable; *C*, assignment using percentage change in PEP/LVET ratio as the intraoperative discriminant variable.

chance of correct assignment of patients with moderate heart disease (Class II). For the whole population, the probability of correct assignment increased only from 33 to 53 per cent, using SBP changes during halothane. STI offered better information, because if the anesthesiologist had available the percentage change in PEP/LVET ratio during halothane anesthesia as the intraoperative discriminant variable, the chances of correct assignment increased from 33 to 83 per cent for the unknown Class I patient, from 33 to 50 per cent for the Class II patient, and from 33 to 67 per cent for the Class III patient. For the population as a whole, the probability of correct classification was doubled, from 33 to 67 per cent, by using STI changes during halothane anesthesia. The probabilities of correct assignment are summarized in figure 1.

MORPHINE-*d*-TUBOCURARINE

Table 4 summarizes the control data. Recumbent resting blood pressures measured by the Riva-Rocci method in the right arm on the evening before operation were not different from those recorded via radial arterial manometry in Classes II and III, but tended to be elevated after radial cannulation in Class I. Heart rates did not change with arterial cannulation, but pulse pressure tended to be greater when measured invasively. There was no significant difference among classes in terms of any of the baseline values.

Tables 5 and 6 summarize the effects of anesthesia. The data are expressed as percentages of "after cannulation of radial artery" baseline values. There was no difference among the classes in their responses to anes-

TABLE 3. Halothane Group, Discriminant Functions

	DF 1*	DF 2†
Class I: No heart disease	$x < 11.8\%$	$y < 37.6\%$
Class II: Moderate heart disease	$11.8\% \leq x < 24.6\%$	$37.6\% \leq y < 63.5\%$
Class III: Severe heart disease	$x \geq 24.6\%$	$y \geq 63.5\%$

* Discriminant Function 1, in which x represents the percentage decrease from baseline in SBP during inhalation of halothane, 1.5 per cent.

† Discriminant Function 2, in which y represents the percentage increase from baseline in PEP/LVET ratio during inhalation of halothane, 1.5 per cent.

thesia. Patients who had severe heart disease responded generally as did the patients without heart disease to thiopental, morphine sulfate, and *d*Tc. The differences reported as statistically significant all refer to the different times after drug injection. Thus, after thiopental injection, heart rates increased, LVET was shortened, and PEP and PEP/LVET increased. MS and *d*Tc injections were followed by similar changes, but now SBP and PP also decreased. The SBP and LVET effects were short-lived. The PEP effect developed more slowly and was largely responsible for the sustained increase in PEP/LVET ratio.

Discussion

In most other studies reported in the literature, measurement of systolic time intervals has been done manually, using high-speed paper tracings, a time-consuming and retrospective maneuver. Several computerized systems for off-line detection of systolic time intervals have been developed. Our system offers an opportunity to use systolic time intervals in a real-time setting. This application may become important for operating room monitoring only if these techniques offer the anesthesiologist new information that is clinically useful.

Many studies have confirmed the close relationship between the duration of systolic time intervals and various physiologic and pharmacologic alterations of cardiac function.[10–12] In general, these studies have established that a decrease in stroke volume or ejection fraction is accompanied by an increase in the PEP/LVET ratio, that an acute increase in afterload will result in prolongation of PEP,[13] and that an increase in heart rate induced by atropine or atrial pacing will be accompanied by a shortening of LVET without change in PEP.[10] Additionally, drugs associated with either positive or negative inotropic effects, such as isoproterenol and propranolol, are associated with either shortening or lengthening of PEP. These changes in PEP have been shown to correlate closely

TABLE 4. Morphine–*d*-Tubocurarine Group, Baseline Data before Induction of Anesthesia

	Class I No Heart Disease 12 Patients	Class II Moderate Heart Disease 12 Patients	Class III Severe Heart Disease 12 Patients
Number of patients taking drugs*	0	6	7
Age (years), mean and range	45 31–68	54 35–66	60 50–72
Pre-ejection period (PEP) (msec)	83 (5)†	92 (5)	86 (5)
Left ventricular ejection time (LVET) (msec)	284 (7)	283 (9)	293 (10)
PEP/LVET	.29 (.02)	.32 (.03)	.29 (.03)
Systolic blood pressure (SBP) (mm Hg) (after cannulation of radial artery)	161 (12)	153 (9)	152 (4)
Pulse pressure (PP) (mm Hg) (after cannulation of radial artery)	67 (8)	71 (8)	70 (5)
Heart rate (HR) (min^{-1})	80 (4)	76 (4)	74 (3)
Systolic blood pressure (SBP) (mm Hg) (evening before operation)	135 (5)	150 (6)	147 (7)
Pulse pressure (PP) (mm Hg) (evening before operation)	50 (5)	55 (6)	56 (6)

* Number of patients taking one or more drugs for treatment of cardiovascular disease (includes antihypertensives, diuretics, antiarrhythmics, vasodilators, glycosides, beta blockers).
† Figures in parentheses are standard errors.

TABLE 5. Morphine–*d*-Tubocurarine Group, Thiopental-induced Changes in Cardiovascular Variables in Percentages of Baseline Data*

	Systolic Blood Pressure (SBP)	Pulse Pressure (PP)	Pre-ejection Period (PEP)	Left Ventricular Ejection Time (LVET)	PEP/LVET	Heart Rate (HR)
Thiopental, 4 mg/kg†						
Class I	98	95	111‡	86‡	130‡	128‡
Class II	87	80‡	112‡	89‡	129‡	128‡
Class III	96	86	121‡	86‡	147‡	124‡

* See table 4.
† Data recorded at peak PEP/LVET response to thiopental.
‡ $P < .05$: The response differed significantly from the baseline response.

TABLE 6. Morphine–*d*-Tubocurarine Group, Anesthesia-induced Changes in Cardiovascular Variables in Percentages of Baseline Data*

	Systolic Blood Pressure (SBP)	Pulse Pressure (PP)	Pre-ejection Period (PEP)	Left Ventricular Ejection Time (LVET)	PEP/LVET	Heart Rate (HR)
Early†						
Class I	88	73	111	94	121	121
Class II	87	66	108	93	116	125
Class III	86	80	106	93	117	126
	‡	‡		‡	‡	‡
Middle						
Class I	93	64	130	95	135	113
Class II	95	80	117	99	119	111
Class III	84	70	123	97	131	111
		‡	‡		‡	
Late						
Class I	90	66	122	98	124	109
Class II	98	85	116	98	122	113
Class III	99	94	126	98	131	110
		‡	‡		‡	

* See table 4.
† Data were averaged for patients during the first 5 minutes (early), and 10–20 minutes (middle) and 35–40 (late) minutes after injection of *d*Tc.
‡ $P < .01$: The responses of all three groups differed significantly from the baseline responses, by the Scheffé method.

with changes in the first derivative of left ventricular pressure (dP/dt), a well-accepted invasive measurement of myocardial contractility.[11,12,14]

Anesthetic agents generally have a depressant action upon the myocardium, as shown by changes in left ventricular force, stroke volume, and STI.[15,16] Thiopental in doses of 2 to 5 mg/kg body weight has been shown to decrease myocardial function, as expressed by a prolongation of PEP and an increase in the PEP/LVET ratio.[15] This is in agreement with our findings in that the thiopental inductions in all three classes of patients were followed by the same qualitative responses.

The depressant action of halothane upon the cardiovascular system appears to be upon the myocardium, the peripheral vascular beds, and the autonomic nervous system.[17–20] Halothane substantially alters myocardial contractility and changes regional blood flow and resistance by a direct vasodilating action as a function of concentration of anesthetic and duration of administration. The negative inotropic action of halothane upon the heart was shown previously to prolong PEP,[5] and this was confirmed in our patients, in that the initial inhalation of 1.5 per cent halothane produced a lengthening of PEP and an increase in the PEP/LVET ratio.

Since the responses to anesthesia differed with the two types of anesthesia (halothane versus MS-*d*Tc) we must ask whether the two populations were comparable. In the halothane group, control group pressures immediately before induction of anesthesia were obtained by auscultation. In that group, patients in Class I had pressures of 127/80 mm Hg, whereas those in Class III were 157/88 mm Hg. These pressures are similar to the control blood pressures obtained by auscultation on the evening before operation in the MS-*d*Tc group (see table 1).

In the latter population, after cannulation of the artery, the systolic values determined invasively increased in Class I but changed little or not at all in Classes II and III (see table 4). Thus, the distinction (normotensive versus slightly hypertensive) between the Class I and Classes II and III was lost at the beginning of anesthesia. Nevertheless, the responses to 4 mg/kg thiopental, iv, were similar in the two studies. SBP changed little, pulse pressure fell, but not consistently, PEP increased, LVET decreased, and the PEP/LVET ratio increased. These effects were similar in all three classes. That the relatively large doses of thiopental (4 mg/kg) did not result in a pattern indicative of more profound cardiac depression, particularly in patients who had severe heart disease, was unexpected. Thiopental is recognized as a myocardial depressant,[21,22] with expected effects on systolic time intervals[15] as described above. Digitalization appears to counteract some of the effect of thiopental on STI,[23] supporting indirectly the assumption of a myocardial, rather than peripheral, thiopental effect.

After the injection of MS and *d*Tc (table 6), an early but short-lived shortening of LVET (present for less than 10 minutes after injection of *d*Tc) and a late but persistent lengthening of PEP (insignificant for the first 10 minutes, fully developed after 10 minutes and lasting more than 35 minutes) were observed. Histamine release (presumably short-lived) associated with a brief episode of mild hypotension and tachycardia[24] may have accounted for the early shortening of LVET.

Munger reported that injection of *d*-tubocurarine (12 mg/m^2) is immediately followed by a decrease in l/PEP^2, hypotension, and transient tachycardia when anesthesia is maintained with 60 per cent nitrous oxide and halothane, 0.75 per cent alveolar.[25] A decrease in l/PEP^2 corresponds to a lengthening of PEP. The fact that, in our study, PEP started to lengthen significantly only 10 minutes after injection of *d*-tubocurarine may have resulted from the different anesthetic regimen. The longer-lasting changes of PEP seen in our study are not readily explained, as several mechanisms may have been at work. Prominent among them may be ganglionic inhibition by *d*Tc,[26] and the cardiovascular effects of MS,[27,28] nitrous oxide,[29,30] and surgical stimulation during light anesthesia.

The study allows two general statements about STI: 1) These noninvasively obtainable indicators of cardiac function can offer information about anesthetic effects on the heart that is not available to the clinician who has to rely on the electrocardiogram and noninvasively obtained blood pressure recordings. 2) During halothane—but not during MS-*d*Tc—anesthesia, patients who had heart disease showed significantly greater changes in STI than patients without heart disease.

These observations raise the question whether systolic time intervals would provide the anesthesiologist with clinically valuable information about the cardiovascular system of the anesthetized patient. We have shown that the changes in STI during halothane anesthesia are more reliable indicators of existing heart disease than are the changes of SBP during halothane anesthesia. Yet, we do not know whether such information will lead to changes in anesthetic management or postoperative care that would lessen the morbidity and mortality of the perioperative period. Until it has been demonstrated that information provided by STI reduces perioperative morbidity and mortality, these measurements have to be accepted as a promising but not yet established monitoring technique for the surgical patient under anesthesia.

Neither do these studies suffice to draw the conclusion that anesthetic management with MS-*d*Tc is superior to that with halothane. While changes in STI as well as SBP were more pronounced during halothane than during MS-*d*Tc anesthesia, particularly in patients with heart disease, the significance of such changes has not been assessed in this study. An evaluation of the intra- and postoperative complications of clinical importance with the two anesthetic management regimens

is necessary before one anesthetic approach can be favored over another.

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