The effects of acute ischemia on the isovolumic index

The isovolumic index is the ratio of the duration of isovolumic contraction (IVC) and relaxation (IVR) divided by ejection time (ET), and has been proposed as a more sensitive descriptor of ventricular performance than the systolic time index, which ignores the period of isovolumic relaxation. To determine the effects of acute ischemia on these indices, IVC, IVR, and ET were measured in seven open-chest dogs instrumented with high-fidelity micromanometers and ultrasonic crystals and subjected to a 10-second period of coronary occlusion. Fractional shortening was significantly impaired (18.4 ± 6.9% vs 1.9 ± 7.3%, $p < 0.001$) during coronary occlusion. ET was unaffected by the brief ischemia, whereas IVC time showed directional shortening that attained statistical significance (55 ± 7 msec control vs 50 ± 6 msec, $p < 0.01$) at 8 to 10 seconds. IVR time was prolonged by occlusion, significantly so at 6 to 8 seconds (72 ± 26 msec control vs 88 ± 22 msec, $p < 0.01$) and at 8 to 10 seconds (81 ± 19 msec, $p < 0.05$). The systolic time index showed no deterioration during ischemia, whereas the isovolumic index did show directional prolongation. Assessment of IVC, IVR, and ET at the time of the maximal change in the isovolumic index revealed significant changes of IVC and IVR (each $p < 0.05$ vs control), though ET and the systolic time index were unchanged. Through incorporation of IVR, the isovolumic index was more sensitive to acute brief ischemia than the systolic time index. (AM HEART J 1988;115:978.)

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The isovolumic index, defined as the sum of the total time of isovolumic contraction and relaxation divided by ejection time, was formulated to take into account abnormalities of relaxation known to occur in patients with left ventricular myocardial disease.[1-9] The isovolumic index has been demonstrated to be a sensitive measure of left ventricular dysfunction in patients with cardiomyopathy and coronary artery disease.[10] Recent animal studies[10-12] have compared it to the traditional systolic time index, and have quantified its hemodynamic determinants and its response to various cardioactive drugs. The purpose of this investigation was to examine, in a canine model, the effect of a period of brief coronary occlusion on the systolic and diastolic time parameters involved in calculation of both the isovolumic index and the systolic time index.

METHODS

Seven mongrel dogs of either sex (mean weight 25 ± 3.6 kg) were anesthetized with sodium pentobarbitol (35 mg/kg), intubated, and ventilated (15 ml/kg) with a Harvard respirator. A left carotid arteriotomy and jugular venotomy were performed and sheaths were inserted for vascular access. A left thoracotomy was performed in the fifth intercostal space and the heart was suspended in a pericardial cradle. High-fidelity micromanometers (No. 5F, Millar Instruments Inc., Houston, Texas) were inserted via the left carotid sheath into the ascending aorta, via a left ventricular apical stab wound into the left ventricle, and via a left atriotomy into the left atrium and then advanced through the mitral valve into the left ventricle. The catheters were made equisensitive by matching the systolic blood pressure readings of the left ventricular and aortic manometers and by matching the high-gain left ventricular diastolic pressures of the left atrial and left ventricular catheters. Once this was achieved, the left atrial catheter was withdrawn through the mitral valve into the left atrium. Frequent checks for zero drift were made throughout the experiments.

The left anterior descending artery was dissected free for 2 to 3 cm and was surrounded with an appropriately sized and calibrated electromagnetic flow probe and an elastic vessel loop. The vessel loop was used to occlude the artery for a 10-second period, and measurements of coronary flow were used to determine when postocclusion, steady-state conditions were reattained.

Table I. The effects of acute ischemia on hemodynamics, regional function, and time intervals

	Control	Duration of ischemia (sec)				Recovery
		2-4	4-6	6-8	8-10	
Heart rate (beats/min)	155 ± 22	154 ± 19	155 ± 19	156 ± 20	157 ± 20	151 ± 16
Left ventricular end-diastolic pressure (mm Hg)	10 ± 5	11 ± 6	12 ± 7	13 ± 7†	13 ± 7‡	10 ± 5
Systolic blood pressure (mm Hg)	130 ± 15	129 ± 15	128 ± 15	128 ± 16	129 ± 17	132 ± 14
Peak positive dP/dt (mm Hg/sec)	2044 ± 695	1973 ± 620	1940 ± 612	1941 ± 629	1971 ± 662	2073 ± 683
Peak negative dP/dt (mm Hg/sec)	2155 ± 556	2005 ± 505	1730 ± 498†	1595 ± 414‡	1548 ± 381‡	2088 ± 482
Isovolumic relaxation half-time (msec)	25 ± 7	27 ± 6	30 ± 6*	31 ± 9‡	31 ± 3†	26 ± 8
Fractional shortening (%)	18.4 ± 6.9	10.9 ± 7.8*	5.6 ± 7.5‡	2.8 ± 7.7‡	1.9 ± 7.3†	20.9 ± 7.5
Ejection time (msec)	169 ± 17	170 ± 19	164 ± 17	165 ± 20	167 ± 22	171 ± 14
Isovolumic contraction time (msec)	55 ± 7	53 ± 5	53 ± 7	52 ± 7	50 ± 6†	54 ± 5
Isovolumic relaxation time (msec)	72 ± 26	73 ± 23	80 ± 24	82 ± 22†	81 ± 19*	75 ± 24
Systolic time index	0.33 ± 0.03	0.31 ± 0.03	0.32 ± 0.05	0.31 ± 0.03	0.30 ± 0.03	0.32 ± 0.03
Isovolumic index	0.75 ± 0.13	0.74 ± 0.09	0.80 ± 0.13	0.81 ± 0.12	0.78 ± 0.11	0.75 ± 0.12

Values are mean ± standard deviation.
dP/dt = rate of change of pressure with time.
* = $p < 0.05$, † = $p < 0.01$, ‡ = $p < 0.001$, each vs control.

A pair of subendocardial ultrasonic crystals were placed in the distribution of the left anterior descending coronary artery in the mid-equatorial plane of the ventricle. The crystal transducers were attached to a sonomicrometer (Model 120, Triton Technology, San Diego, Calif.) interfaced to a wide-band oscilliscope (Model 2213A, Tektronix, Beaverton, Or.) for confirmation of crystal alignment. Subendocardial positioning of the crystals was confirmed by observation of prompt dyskinesis during brief coronary occlusion and by postmortem inspection.

Continuous recordings of left ventricular pressure, first derivative of left ventricular pressure (dP/dt), aortic and atrial pressures, segment lengths, and ECG were made on a Gould recorder (Model 2800S, Gould Electronics, Cleveland, Ohio). Reported values were averaged from four to six normally conducted beats recorded at 200 mm/sec paper speed during control, from two to three beats occurring in five, 2-second periods during the total 10 seconds of coronary occlusion, and from four to six beats at 0.5, 1, 5, and 10 minutes postocclusion.

These animals were part of a cohort of dogs that were also studied to determine the effects of intravenous verapamil infusion on the isovolumic index.[12] The present ischemic intervention was performed prior to cardioactive drug administration.

Data analysis. Measurements of left ventricular end-diastolic pressures were taken at the time when dP/dt became positive and this was considered the onset of isovolumic contraction. End systole was taken at peak negative dP/dt and this was considered the beginning of isovolumic relaxation.[13]

The isovolumic contraction time was determined as the time from end-diastolic pressure to peak positive dP/dt.[14] The ejection time was determined as the time from peak positive to peak negative dP/dt.[13, 14] The isovolumic relaxation time was taken from peak negative dP/dt to the point where left atrial and left ventricular pressures crossed over.[15-19]

The isovolumic index was defined as [(IVC + IVR)/ ET)] where IVC = isovolumic contraction time, IVR = isovolumic relaxation time, and ET = left ventricular ejection time. The systolic time index was defined as IVC/ET. Segment shortening was defined as segment excursion between end diastole and end systole divided by end-diastolic length and multiplied by 100. To determine directional changes in relaxation, an estimate of the isovolumic relaxation half-time was determined by calculating the time required for the left ventricular pressure at peak negative dP/dt to decrease by half.[20, 21]

Data averaged from beats recorded during ischemia were divided into five groups of 2 seconds' duration. There were no significant differences from control in any parameter for the 0 to 2 second observations, and these data are not reported. Likewise, there were no significant differences between any of the four recovery period groups, and only the 30-second recovery values are reported below.

Statistical analysis. All results are reported as mean ± one standard deviation, and were analyzed by repeated measures analysis of variance. When overall significance was detected, a Bonferroni test was utilized to determine which stages were significantly different from control.[22] A p value of less than 0.05 was considered significant.

Table II. Measurements of hemodynamics, regional function, and time intervals at control and at time of maximal isovolumic index value during ischemia

	Control	*During maximal isovolumic index*	*Significance*
Heart rate (beats/min)	155 ± 22	156 ± 18	NS
Left ventricular end-diastolic pressure (mm Hg/sec)	10 ± 5	12 ± 7	$p < 0.05$
Systolic blood pressure	130 ± 15	130 ± 17	NS
Peak positive dP/dt (mm Hg/sec)	2044 ± 695	1954 ± 646	NS
Peak negative dP/dt (mm Hg/sec)	2155 ± 557	1577 ± 447	$p < 0.05$
Isovolumic relaxation half-time (msec)	25.1 ± 7.2	32.4 ± 4.5	$p < 0.01$
Fractional shortening (%)	18.4 ± 6.9	3.5 ± 5.8	$p < 0.001$
Ejection time (msec)	168.6 ± 17.3	163.1 ± 18.2	NS
Isovolumic contraction time (msec)	54.6 ± 7.3	52.0 ± 6.6	$p < 0.05$
Isovolumic relaxation time (msec)	72.1 ± 26.4	84.7 ± 22.1	$p < 0.05$
Systolic time index	0.33 ± 0.03	0.32 ± 0.03	NS
Isovolumic index	0.75 ± 0.13	0.84 ± 0.13	$p < 0.05$

Values are mean ± standard deviation.
dP/dt = rate of change of pressure with time; NS = nonsignificant.

To further assess the impact of hemodynamic, functional, and time interval measurements on the isovolumic index, the value of each of these parameters was assessed at the point of the maximal isovolumic index value for each animal during ischemia. These data were averaged and compared to control by a paired t test.

RESULTS

Hemodynamic consequences of the brief occlusion period included significant elevations of left ventricular end-diastolic pressure at 6 to 8 seconds ($p < 0.01$) and at 8 to 10 seconds ($p < 0.001$) (Table I). Peak negative dP/dt was significantly depressed at 4 to 6 seconds ($p < 0.01$), 6 to 8 seconds, and 8 to 10 seconds (each $p < 0.001$). Heart rate, systolic blood pressure, and peak positive dP/dt were not significantly affected by the brief coronary occlusion, and all hemodynamic variables returned to basal levels upon recovery.

Regional function was significantly altered throughout the occlusion period; the nadir was reached at 8 to 10 seconds, when fractional shortening fell to 1.9 ± 7.3% from the control value of 18.4 ± 6.9% ($p < 0.001$). Time intervals showed disparate changes in response to brief myocardial ischemia. ET revealed no differences in any portion of the intervention. IVC time showed directional shortening that became significant ($p < 0.01$) by 8 to 10 seconds. IVR time showed a directional lengthening that became significant at 6 to 8 seconds ($p < 0.01$) and at 8 to 10 seconds ($p < 0.05$). The IVR half-time increased with the duration of ischemia, and was significantly elevated at 4 to 6 seconds ($p < 0.05$), at 6 to 8 seconds ($p < 0.001$), and at 8 to 10 seconds ($p < 0.01$). Each of these parameters returned to basal levels upon recovery.

The systolic time index was not significantly different from control at any point during the ischemic intervention. Directionally, this index showed a very slight shortening. Conversely, the isovolumic index, though also not significantly different from control, showed a directional increase that paralleled the functional deterioration revealed by fractional shortening.

The analysis of data at the point of the maximal deterioration of the isovolumic index is shown in Table II. Left ventricular end-diastolic pressure was significantly increased ($p < 0.05$) and peak negative dP/dt was likewise decreased ($p < 0.05$). The fall in fractional shortening was highly significant ($p < 0.001$). The IVR half-time was significantly increased ($p < 0.01$), as was the IVR time ($p < 0.05$) (Fig. 1, A), while IVC time decreased ($p < 0.05$) (Fig. 1, B). ET showed a directional decrease in this analysis, but this was not significant (Fig. 1, C). Derivation of the isovolumic and systolic time indices from these data revealed a significant increase in the isovolumic index from control, but no change in the systolic time index (Fig. 2, A and B).

DISCUSSION

This study assessed the comparative sensitivity of the isovolumic index and of the systolic time index during episodes of acute myocardial ischemia. A brief period of coronary occlusion resulted in prolongation of the IVR time, a decrease in IVC time, and no significant change in ET. These disparate responses, and particularly the preferential change in IVR time, potentiated the ability of the isovolumic index to discern the presence of ischemic myocardial dysfunction. In contrast, the traditional systolic
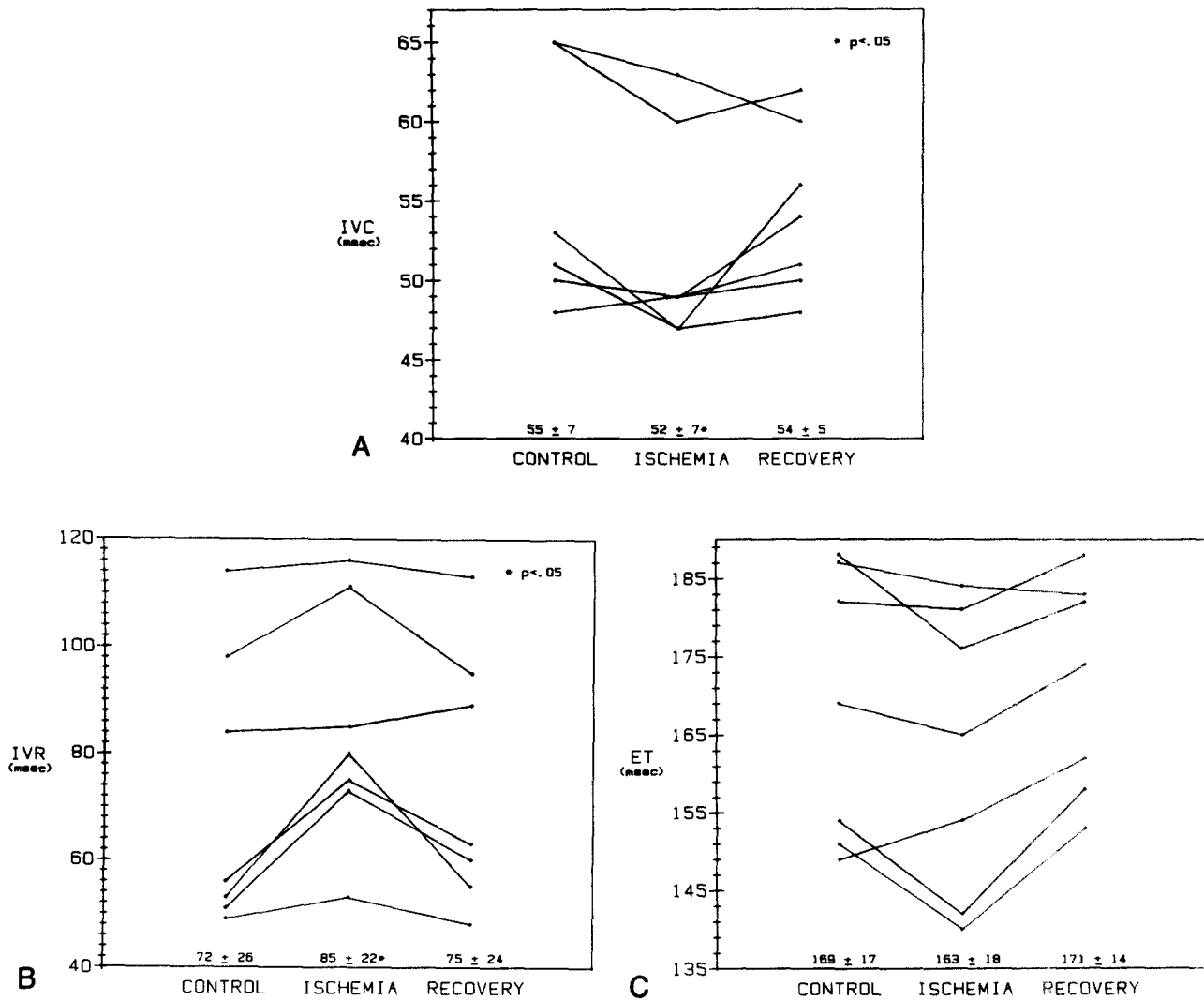
Fig. 1. Isovolumic contraction time, isovolumic relaxation time, and ejection time intervals, in milliseconds, assessed at the time of the maximal change in the isovolumic index. Data from each of seven dogs is represented graphically. Numerals = mean ± standard deviation. *Panel A*, Isovolumic contraction time was significantly shortened ($p < 0.05$ vs control) during ischemia. *Panel B*, Isovolumic relaxation time was significantly prolonged ($p < 0.05$ vs control) during ischemia. *Panel C*, Ejection time during ischemia was not significantly different from control. IVC = isovolumic contraction time; IVR = isovolumic relaxation time; ET = ejection time.

time index, defined as IVC time divided by ET, showed neither directional nor statistical change in response to ischemic dysfunction.

Ejection time. Changes in ET may be variable during ischemia. While prolongation of ET during acute ischemia can occur as a consequence of increased peripheral resistance[23] and has been reported to occur postexercise in patients with angina pectoris,[24] concomitant reductions in cardiac output and ejection fraction may offset this prolongation.[25, 26] The present study showed no significant changes in this interval during ischemia. A decrease in ET would have improved the ability of both the

systolic time index and the isovolumic index to increase in response to ischemia. The somewhat greater effect of ET changes in the calculation of the systolic time index impaired the ability of this index to reflect ongoing dysfunction.

Isovolumic contraction time. As with measurements of ET, the response of IVC to acute ischemia is variable. Its duration is dependent upon left ventricular end-diastolic pressure, arterial diastolic pressure, and rate of change of pressure throughout the isovolumic period.[27] Unfortunately, the response of this interval to these parameters is not consistently reproduced in the presence of ischemia: patients
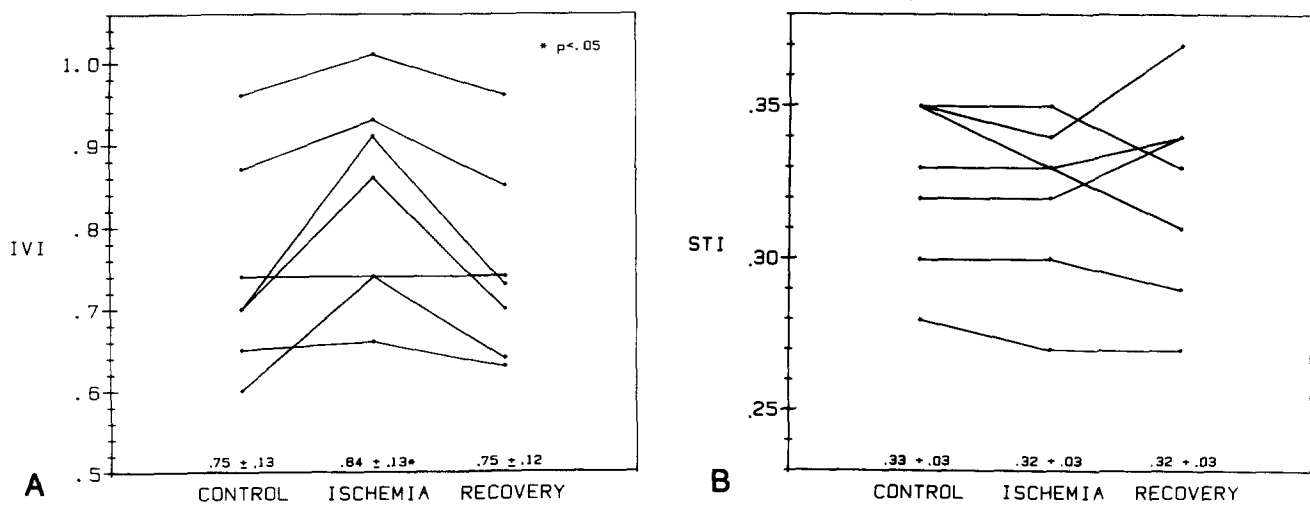
Fig. 2. *Panel A,* Maximal increase (deterioration) of the isovolumic index is significantly different from control ($p < 0.05$) during ischemia. *Panel B,* The systolic time index, assessed at the time of maximal change in isovolumic index, showed no significant change during ischemia. Data from each of seven dogs is represented graphically. Numerals = mean ± standard deviation; *IVI* = isovolumic index; *STI* = systolic time index.

with induced angina have been reported to display either shortened IVC time[25] or no change in this interval.[26] Brief coronary occlusion in the present study resulted in directional shortening of IVC. This relatively mild response further hindered the ability of the systolic time index to reflect acute deterioration in myocardial function.

Isovolumic relaxation time. Myocardial relaxation has been shown to be a dynamic and energy-requiring phase of the cardiac cycle.[28, 29] Thus while modulated by the potential effects of left atrial pressure, aortic closing pressure, and rate of left ventricular pressure fall on IVR time,[6, 30, 31] ischemia secondary to coronary occlusion is expected to prolong this interval.[32] The present study did show lengthening of IVR that paralleled a prolonged IVR half-time and preferentially influenced the directional deterioration of the isovolumic index.

Assessment of time intervals at the time of maximal change of the isovolumic index further emphasized the effect of incorporating a measurement of myocardial relaxation (Table II). By this analysis, maximal deterioration of the isovolumic index was associated with significant depression of IVC time and significant prolongation of IVR. Importantly, even at this point of maximal change, the systolic time index failed to reveal deterioration of function.

The isovolumic index was developed to incorporate abnormalities of relaxation known to accompany myocardial dysfunction. The systolic time index, while useful in the diagnosis of chronic left ventric-

ular disease,[33, 34] appears to be less sensitive when responses of ET and IVC time are mild or variable, as in brief ischemia. The nonsignificant and inconsistent response of the ET interval, and to a lesser extent the IVC time, appears to be a limitation, however, to implementation of even the isovolumic index in the noninvasive evaluation of acute ischemic episodes.

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