Comparison of Effects of Dobutamine and Ouabain on Left Ventricular Contraction and Relaxation in Closed-Chest Dogs

William C. Little, Anis Rassi, Jr., and Gregory L. Freeman*
*Cardiology Section, Department of Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27103; and *Division of Cardiology, University of Texas Health Science Center, San Antonio, Texas 78284*

Abstract

Because catecholamines and digitalis have different effects on the time course of myocardial intracellular calcium concentration, their effects on the time course of left ventricular contraction and relaxation may also be different. To study this question, dogs were instrumented to measure left ventricular pressure and determine left ventricular volume from three ultrasonic dimensions. After full recovery from the instrumentation, the effects of dobutamine (2–10 μg/kg), ouabain (0.5 mg i.v.) alone, and ouabain given after propanolol (2 mg/kg i.v.), or phentolamine (5 mg i.v.) and incremental doses of ouabain (0.25–0.75 mg i.v.) were assessed on different days. Left ventricular pressure and volume were varied by caval occlusions. Dobutamine significantly increased the slope of the left ventricular end-systolic pressure-volume relation (E_{max}) and the slope of the dP/dt_{max}–end-diastolic volume relation (dE/dt_{max}), while significantly decreasing the time from end-diastole to end-systole (t_{max}) and the time constant (T) of the isovolumic fall in left ventricular pressure. Ouabain also increased E_{max} and dE/dt_{max} but did not alter t_{max} or T. Dobutamine produced a greater increase in dE/dt_{max} than in E_{max}, whereas ouabain produced similar increases in both. These effects of ouabain were not altered by pretreatment with propanolol or phentolamine.

We conclude that although dobutamine and ouabain are both positive inotropes that increase E_{max}, dobutamine speeds the rate of left ventricular contraction (t_{max}) and relaxation (T), whereas ouabain does not. These effects of ouabain and dobutamine on global parameters of left ventricular chamber performance mirror their influence on intracellular calcium availability. Furthermore, these observations are consistent with the predictions of the time-varying elastance model of the left ventricle and support its usefulness as a conceptual framework to understand and link events occurring during isovolumic contraction, end-systole, and isovolumic relaxation.

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Address reprint requests to William C. Little, M.D., Department of Medicine (Cardiology), Bowman Gray School of Medicine, Wake Forest University, 300 S. Hawthorne Road, Winston-Salem, NC 27103.

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Introduction

Left ventricular (LV)[1] systole can be divided into phases: isovolumic contraction, ejection, end-systole, and isovolumic relaxation (1). Indices have been developed that describe LV performance during each of these four phases. However, it has been difficult to provide a description of the LV that spans all four phases, unifying and relating the various measures of LV performance. One possibility is to consider that LV systolic pumping function can be described as a time-varying elastance (2–5). In this concept, the LV is considered to behave as an elastic structure that stiffens in a predictable manner during systole. The LV pressure, $P(t)$, at any time after the onset of contraction, t, is described by: $P(t) = E(t)\,[V(t) - V_0]$, where $E(t)$ is LV elastance at t, $V(t)$ the LV volume at t, and V_0 the minimum volume required for the LV to generate super-atmospheric pressure. LV elastance, $E(t)$, reaches a maximum value, E_{max}, at time t_{max}, which has been termed end-systole. E_{max}, which is the slope of the end-systolic pressure (P_{ES})–volume (V_{ES}) relation, is a measure of the global inotropic state of the LV and is relatively insensitive to changes in loading conditions in isolated canine hearts (2, 3, 5–10), conscious dogs (11), and man (12, 13). Inotropic stimulation with catecholamines increases E_{max} and decreases t_{max}, the time from end-diastole to end-systole (2–4).

In addition to the P_{ES}-V_{ES} relation, the time-varying elastance model has other implications that suggest links between the four phases of systole. For example, the model suggests that the maximum rate of rise of LV pressure (dP/dt_{max}), normally occurring during isovolumic contraction, is linearly related to the LV end-diastolic volume (V_{ED}) (3, 4). The slope of this relation, dE/dt_{max}, is also predicted to be sensitive to inotropic state and proportional to E_{max}/t_{max}, providing a link between events occurring during isovolumic contraction and at end-systole. Further consideration of the time-varying elastance hypothesis (Appendix) also suggests that the rate of LV pressure fall during isovolumic relaxation should be inversely proportional to t_{max}. These predictions of the time-varying elastance model linking events occurring during isovolumic contraction (dP/dt_{max}-V_{ED} relation), at end-systole (the P_{ES}-V_{ES} relation and t_{max}), and during isovolumic relaxation (T) suggest that this model may provide a unified description of LV performance throughout systole.

1. *Abbreviations used in this paper:* dE/dt_{max}, slope of dP/dt_{max}–end-diastolic volume relation; dP/dt_{max}, maximum rate of rise of $P(t)$; ED, end-diastolic; E_{max}, slope of end-systolic pressure-volume relation; ES, end-systolic; LV, left ventricular; $P(t)$, LV pressure; t_{max}, time from end-diastole to end-systole.

The increase in LV elastance after electrical stimulation is a manifestation of the tension generated by the sarcomeres reflected through the complex geometry of the LV chamber (14, 15). Because the force of sarcomere contraction is directly related to amount of calcium available to the contractile proteins, the time course of LV systolic elastance should follow the time course of calcium availability, though lagging behind in time. Studies using the bioluminescent indicator aequorin suggest that catecholamines increase the peak amount of calcium available after electrical stimulation and also decrease the time required to achieve this peak (13, 16). The time course of calcium availability after catecholamine stimulation is qualitatively very similar to the effect of catecholamines on LV elastance (i.e., increasing E_{max} and decreasing t_{max}). Digitalis, however, has a different effect on calcium availability. While the peak of calcium is increased, the time to reach this peak is unchanged. If the time course of LV elastance reflects calcium availability then digitalis glycosides should increase E_{max} but not alter t_{max}. If this is correct, then the time-varying elastance hypothesis predicts that digitalis compounds should produce similar increases in E_{max} and dE/dt_{max} and should not alter the time course of the fall of LV pressure during isovolumic relaxation.

This study was undertaken to test these predictions by comparing the effects of dobutamine and ouabain (a digitalis glycoside) on the P_{ES}-V_{ES} and dP/dt_{max}-V_{ED} relations, t_{max}, and the time constant of LV relaxation.

Methods

Instrumentation. 16 healthy, adult mongrel dogs weighing 23±3 kg (mean±SD) were instrumented by a slight modification of a previously described technique (4, 17, 18). A sterile left lateral thoracotomy was performed under anesthesia with halothane (1–2%) after induction with xylene (1 mg/kg) and sodium thiopental (6 mg/kg). The pericardium was opened widely. A micromanometer pressure transducer (Konigsberg Instruments, Inc., Pasadena, CA) and a polyvinyl catheter for transducer calibration (inside diameter, 1.1 mm) were inserted through the LV apex. Three pairs of ultrasonic crystals (5 MHz) were implanted in the endocardium of the LV to measure the anterior-posterior, septal-lateral, and base-apex (long-axis) dimensions. Bipolar pacing leads were sutured to the left atrial appendage. Hydraulic occluder cuffs were placed around the inferior and superior venae cavae.

Data collection. All studies were performed after full recovery from the thoracotomy (10–14 d) with the dogs lying on their right sides in a sling. The LV catheter was connected to a pressure transducer (Statham P23DB) calibrated with a mercury manometer. The signal from the micromanometer was adjusted to match that of the catheter. The transit time of 5 MHz sound between the crystal pairs was determined and converted to distance assuming a constant velocity of sound in blood of 1.55 m/ms. The first derivative of LV pressure (dP/dt) was obtained by electronically differentiating the micromanometer signal using an analogue circuit with a linear frequency response to > 70 Hz. The analog signals were recorded on an eight-channel oscilligraph (Beckman Instruments Inc., Fullerton, CA), digitized with an on-line analog-to-digital converter (Data Translation Devices, Marlboro, MA) at 200 Hz, and stored on a floppy disk memory system utilizing a computer system (PDP 11/23, Digital Equipment Corp., Marlboro, MA).

Experimental protocol. To avoid the confounding influences of respiratory changes in intrathoracic pressure and variations in the level of autonomic tone, the dogs were sedated with fentanyl (0.03–0.06 mg/kg i.v.) in combination with droperidol (1.5–3.0 mg/kg i.v.), given 0.5 h after pretreatment with xylene (1 mg/kg i.m.), and intubated. All data were recorded during 12-s periods while the dogs were apneic, with the glottis held open by the endotracheal tube (17). During each experiment the heart rate was kept constant by pacing from the atrium. Small amounts of atropine (0.2–1 mg i.v.) were administered as needed to prevent atrio-ventricular block in the animals that received ouabain.

In six dogs, the effect of dobutamine (10 μg/kg per min i.v.), ouabain (0.5 mg i.v.), ouabain (0.5 mg i.v.) after propanolol (2 mg/kg i.v.), and ouabain (0.5 mg i.v.) after phentolamine (5 mg i.v.) were assessed on different days. During each study, data were recorded during a steady-state, nonintervention period to obtain baseline values. The P_{ES}-V_{ES} and dP/dt_{max}-V_{ED} relations were then generated by sudden occlusion of the cavae. This caused a progressive fall in LV end-systolic pressure, volume, and dP/dt_{max} over a 12-s recording period. Immediately after the recording period, the caval occlusion was released. After all parameters had returned to their baseline level, the caval occlusion was repeated. Then dobutamine was infused or ouabain given. The animal was allowed to equilibriate for 5 min (dobutamine infusion) or 10 min (ouabain), and then the measurements were repeated.

In four animals pretreated with atropine (2 mg i.v.), the effects of incremental infusions of dobutamine (0, 2, 4, 6, 8 g/kg per min) were assessed in a similar manner. Finally, in a separate group of six animals, the effects of ouabain (0.25 mg) given every 5 min to produce total doses of 0.25, 0.50, and 0.75 mg were assessed in a similar manner. Higher doses of ouabain could not be used because they produced junctional and ventricular dysrhythmias.

Data analysis. The stored digitized data were analyzed by computer algorithm (11, 17). Baseline hemodynamic values in each dog were obtained by averaging the data obtained during the 12-s steady-state, nonintervention recording periods. End-systole was defined as the time when the ratio of LV pressure to volume reached its maximum (19). End-diastole was defined as the peak of the R wave of the electrocardiogram. The time from end-diastole to end-systole was defined as t_{max}. End-ejection was defined as peak negative dP/dt. The LV volume (V_{LV}) was calculated as a modified general ellipsoid using the equation $V_{LV} = (\pi/6)D_{AP}D_{SL}D_{LA}$, where D_{AP} = the anterior-posterior LV dimension, D_{SL} = the septal-lateral LV dimension, and D_{LA} = the long-axis LV dimension. Because this method of volume determination depends on dimensional measurements, it is important to assess its accuracy under the conditions used in this study (19). This method of volume calculation has been validated in our laboratory (11, 17, 19, 20, 21) and is similar to that used by others (22), except that we determined endocardial dimensions directly. Thus, the subtraction of LV wall thickness or volume was not necessary. We (11, 17, 18, 20) and Olsen et al. (22) have found that this method gives a consistent measure of LV volume ($r > 0.97$, standard error of estimate < 2 ml) despite changes in LV loading conditions and configuration produced by caval occlusions.

The time constant (T) of the isovolumic fall in LV pressure was determined by fitting the steady-state data from end-ejection to the time that LV pressure had fallen to 10 mmHg above the end-diastolic pressure to the equation: $P_{LV} = P_0e^{-t/T} + P_B$, using BMDP program PAR (23), where t is the time from end-ejection, and P_0 and P_B are constants determined by the data.

Only caval occlusions that produced a fall in LV systolic pressure of at least 30 mmHg, and that produced no extra systoles, were analyzed. The LV end-systolic pressure-volume data during the fall of LV pressure produced by the caval occlusions were fit to: $P_{ES} = E_{max}(V_{ES}-V_0)$, using the linear least squares technique. The LV V_{ED} and dP/dt_{max} were fit to $dP/dt_{max} = (dE/dt_{max})(V_{ED}-V_0)$, where dE/dt_{max} is the slope of the relation and V_0 is the volume intercept. In animal 2, the ultrasonic dimension crystals malfunctioned before administration of ouabain, thus the effect of this intervention on the P_{ES}-V_{ES} and dP/dt_{max}-V_{ED} relations could not be determined in this animal.

Statistical methods. All results were summarized as the mean±SD, and the level of significance was $P < 0.05$. Dose-response curves were analyzed using a split-plot, repeated-measures analysis of variance. Multiple comparisons were performed by analysis of variance. Single

intergroup comparisons were performed using paired t tests or the Wilcoxon signed rank test (24).

Postmortem studies. At the conclusion of the experiments, the animals were sacrificed and the hearts were examined to confirm the proper positioning of the instrumentation.

Results

Typical analog recordings before and after the infusion of dobutamine and ouabain are shown in Fig. 1. An analog recording after the occlusion of the vena cava is shown in Fig. 2.

Effect of dobutamine. The infusion of dobutamine (10 μg/kg per min) significantly increased dP/dt_{max}, while decreasing t_{max}, end-diastolic and end-systolic LV volumes, LV end-diastolic pressure, and T. Heart rate was kept constant during dobutamine infusion by atrial pacing at 138±24 beats/min. The LV end-systolic pressure as well as P_0 and P_B were unchanged (Table I). E_{max} increased from 7.24±4.40 to 13.61±5.80 mmHg/ml ($P < 0.05$) in response to the infusion of 10 μg/kg per min of dobutamine, whereas the volume axis intercept of the P_{ES}-V_{ES} relation was unchanged (Table II). Dobutamine also shifted the dP/dt_{max}-V_{ED} relation to the left, increasing its slope, dE/dt_{max} from 63.0±20.4 to 177.1±83.6 mmHg/ml per s ($P < 0.05$) without changing its volume intercept (Table III). The increase in dE/dt_{max} to 282±170% of control was greater than the increase in E_{max} to 184±57% of control ($P < 0.05$). These effects of dobutamine (10 μg/kg per min) on the dP/dt_{max}-V_{ED} and P_{ES}-V_{ES} relations are similar to previous observations reported from our laboratory (4, 11). Similar dose-related effects on E_{max}, dE/dt_{max}, t_{max}, and T ($P < 0.05$) were seen with the incremental infusion of lower doses of dobutamine (Fig. 3). Of special note is the progressive fall in t_{max} and T with incremental doses of dobutamine (Fig. 4).

Effect of ouabain. The administration of 0.5 mg of ouabain increased P_{ES} from 100±14 to 123±26 mmHg ($P < 0.05$) (Table I). A similar effect was seen after beta blockade but was attenuated after pretreatment with phentolamine. Ouabain significantly increased dP/dt_{max} from 2,098±87 to 2,775±362 mmHg/s ($P < 0.05$) but had no effect on t_{max} (178±22 vs. 175±26 ms) or T (28.7±6.6 vs. 29.9±6.4 ms). Pretreatment with propanolol or phentolamine did not alter this effect. Ouabain shifted the P_{ES}-V_{ES} relation to the left (Fig. 5) increasing the slope, E_{max} from 8.87±4.35 to 9.99±4.81 mmHg/ml ($P < 0.05$) and decreasing V_0 from 13.30±6.43 to 10.61±7.85 ml. This leftward shift results in a higher P_{ES} being associated with each V_{ES}. Ouabain had a similar effect on E_{max}, V_0 after pretreatment with propanolol, but after the administration of phentolamine, E_{max} increased from 8.19±2.71 to 11.71±4.11 mmHg/ml ($P < 0.05$) without a change in V_0 (11.23±5.45 vs. 11.75±5.40 ml). Ouabain also shifted the dP/dt_{max}-V_{ED} relation to the left so that each V_{ED} was associated with a higher dP/dt_{max} (Fig. 4). The increases in the slope of this relation, dE/dt_{max}, with ouabain (unblocked, beta-blocked, and after phentolamine) were similar to the increases in E_{max} (113±9, 130±18, 142±11% vs. 131±20, 144±48, 145±12% of control). Incremental doses of ouabain produced similar significant dose-related increases ($P < 0.05$) of E_{max} and dE/dt_{max}, but did not alter t_{max} or T (Fig. 6).

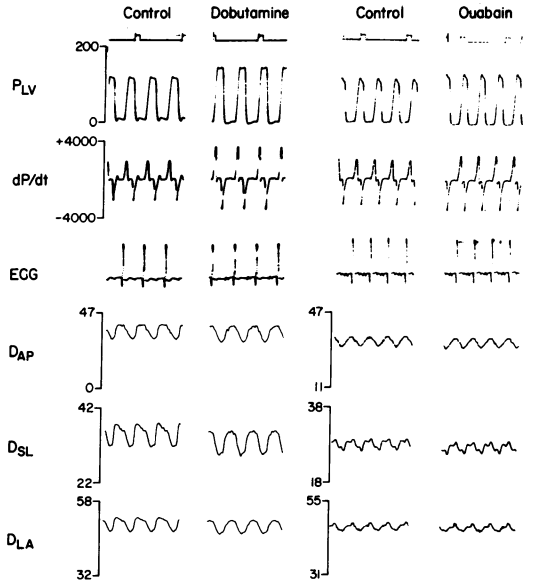


Figure 1. Analog recordings of left ventricular pressure (P_{LV}), the time derivative of left ventricular pressure (dP/dt), and the three left ventricular dimensions (anterior-posterior [D_{AP}], septal-lateral [D_{SL}], and long-axis [D_{LA}]) during control and dobutamine infusion (10 μg/kg per min) and after ouabain (0.5 mg).

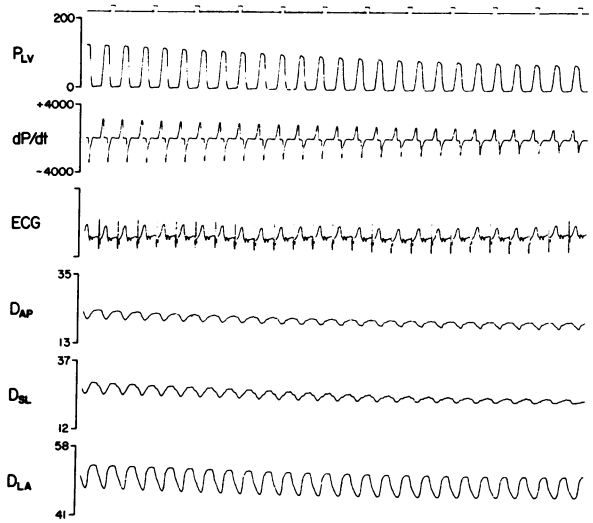


Figure 2. Analog recording after vena cava occlusion. Abbreviations are same as Fig. 1.

Comparison of dobutamine and ouabain. Both ouabain and dobutamine increased E_{max} and dE/dt_{max}. dE/dt_{max} increased by 120±109% more than E_{max} in response to dobutamine, but dE/dt_{max} increased by only 18±21% more than E_{max} in response to ouabain ($P < 0.05$). Dobutamine produced a 25±17-ms greater decrease in t_{max} ($P < 0.05$) than occurred with ouabain (i.e., t_{max} decreased 28.3±15.1 ms with dobutamine and only changed by 3.3±4.1 ms with ouabain). Similarly, dobutamine produced an 11.8±8.1-ms greater decrease ($P < 0.05$) in T than occurred with ouabain (i.e., T decreased by 10.7±7.6 ms with dobutamine, and increased by 1.1±4.1 ms in response to ouabain).

Discussion

This study demonstrates that although dobutamine and the digitalis glycoside, ouabain, are both positive inotropes that

Table I. Effect of Dobutamine and Ouabain on Hemodynamic Parameters

	Control	Dobutamine	Control	Ouabain	Beta-blocked control	Ouabain after beta blockade	Phentolamine control	Ouabain after phentolamine
HR	138±24	138±24	130±18	130±18	124±18	124±18	133±23	133±23
dP/dt_{max}	2,155±477	3,200±902*	2,098±87	2,775±362*	1,723±408*	2,382±530*	2,292±736	2,876±953*
dP/dt_{min}	−2,231±562	−2,487±799	−2,039±363	−2,450±578	−1,733±265	−2,509±481*	−2,093±546	−2,514±684*
V_{ED}	38.8±14.4	29.4±12.5*	33.3±11.9	32.3±10.4	34.9±11.1	35.5±11.8	29.9±12.3	28.7±10.9
V_{ES}	29.7±10.8	21.2±8.9	24.1±9.4	23.8±8.6	26.8±9.0	26.6±9.6	20.7±9.2	19.5±7.3
P_{ED}	5.8±5.4	1.06±3.5*	2.9±2.6	2.7±1.2	5.8±2.5	7.3±4.3	4.8±4.0	4.8±4.3
P_{ES}	128±26	115±28	100±14	123±26*	100±7.9	139±8.3*	94±16	107±17
t_{max}	188±17	160±23*	178±22	175±26	189±7	188±15	168±15	163±19
T	37.4±11.0	26.6±6.6*	28.7±66	29.9±6.4	34.9±8.6	37.2±6.6	27.0±7.3	24.1±8.6
P_0	85.8±18.2	68.6±13.3	62.9±4.5	82.4±28*	62.5±12.4	93.3±3.5*	56.6±17.7	66.2±15.4
P_B	−15.0±4.4	−11.1±5.6	−11.9±13.7	−15.6±15.3	−7.5±9.6	−17.9±1.43*	−9.4±1.43	−4.4±10.2

* $P < 0.05$ vs. control. HR, heart rate (min); dP/dt_{max}, maximum rate of use of LV pressure (mmHg/s); dP/dt_{min}, maximum rate of fall of LV pressure; V_{ED}, LV end-diastolic volume (ml); V_{ES}, LV end-systolic volume (ml); P_{ED}, LV end-diastolic pressure (mmHg); P_{ES}, LV end-systolic pressure (mmHg); t_{max}, time from end-diastole to end-systole (ms); T, time constant of the fall in LV pressure (ms); P_0 and P_B, constants in the exponential model of fall of LV pressure (ms).

increase E_{max}, they have different effects on t_{max}, T, and the dP/dt_{max}-V_{ED} relation. Dobutamine decreases t_{max}, and T and produces a greater increase in dE/dt_{max} (slope of dP/dt_{max}-V_{ED} relation) than in E_{max}. In contrast, ouabain does not alter t_{max} or T and produces an equivalent increase in dE/dt_{max} and E_{max}.

The effects of dobutamine and ouabain on peak elastance (E_{max}) and time from stimulation to occurrence of peak elastance (t_{max}) mirror their effects on the time-course of intracellular myocardial Ca^{2+} availability assessed using aequorin (13, 16). Dobutamine increases peak Ca^{2+} availability and E_{max} and decreases the time to achieve peak Ca^{2+} and t_{max}. Ouabain increases peak Ca^{2+} and E_{max} without altering the time to peak Ca^{2+} and t_{max}. These similarities between the time-course of LV elastance and intracellular Ca^{2+} suggest that despite the complex geometry, LV chamber properties reflect the subcellular events underlying contraction (14, 15).

Both dobutamine and ouabain are positive inotropes that increase E_{max}, thus shifting the P_{ES}-V_{ES} relation to the left. Dobutamine produces no significant change in V_0, the volume intercept of the P_{ES}-V_{ES} relation, while with ouabain, V_0 is decreased somewhat. This decrease in V_0 with ouabain is similar to the change in V_0 that has been observed in responses to vasoconstriction (4, 11, 21, 25). When the acute vasoconstrictive effect of ouabain is blunted by pretreatment with phentolamine, no decrease in V_0 was seen. Both ouabain and dobut-

Table II. Effect of Dobutamine and Ouabain on the P_{ES}-V_{ES} Relation

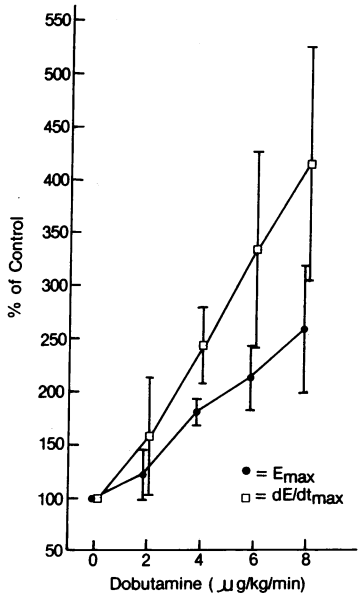
	Control					Dobutamine or ouabain				
	No.	R	SEE	E_{max}	PVR VO	No.	R	SEE	E_{max}	PVR VO
Effect of dobutamine										
Mean	29	0.986	1.99	7.24	12.42	22	0.978	3.11	13.61*	13.75
SD	25	0.010	1.84	1.02	4.40	12	0.015	2.01	5.80	5.47
Effect of ouabain										
Mean	32	0.983	2.04	8.87	13.03	23	0.990	2.13	9.99*	10.61*
SD	22	0.011	0.83	4.35	6.56	12	0.004	1.34	4.81	8.01
Effect of ouabain after beta-blockade										
Mean	33	0.985	1.51	6.65	12.51	30	0.971	2.70	8.61*	10.73*
SD	17	0.008	0.52	1.47	5.60	13	0.019	1.02	2.19	6.07
Effect of ouabain after phentolamine										
Mean	56	0.986	2.01	8.19	11.23	41	0.976	2.67	11.71*	11.75
SD	31	0.010	1.06	2.71	5.45	16	0.018	0.74	4.11	5.40

* Different from control, $P < 0.05$. No., number of points used in the regression of P_{ES} and V_{ES}; R, correlation coefficient; SEE, standard error of the estimate (mmHg); E_{max}, slope of the P_{ES}-V_{ES} relation (mmHg/ml); PVR VO, volume axis intercept of P_{ES}-V_{ES} relation (ml).

Table III. Effect of Ouabain and Dobutamine on the dP/dt_{max}-V_{ED} Relation

	R	SEE	dE/dt_{max}	VO	dE_N/dt_N	R	SEE	dE/dt_{max}	VO	dE_N/dt_N
Effect of Dobutamine										
	Control					Dobutamine				
Mean	0.985	25	63.02	8.22	1.34	0.956	58.08	177.13*	10.90	2.38
SD	0.013	10	20.38	2.63	0.65	0.045	48.87	83.60	5.55	0.94
Effect of ouabain										
	Control					Ouabain				
Mean	0.983	40	73.08	11.47	1.50	0.992	70.20	98.60*	11.31	1.68
SD	0.019	29	30.68	3.04	0.33	0.005	75.95	47.88	6.10	0.34
Effect of ouabain after beta-blockade										
	Beta-blocked					Control				
Mean	0.968	35	60.11	7.50	1.71	0.954	54.86	93.84*	9.45	1.86
SD	0.037	18	20.77	6.27	0.39	0.042	22.03	71.03	5.92	0.65
Effect of ouabain after phentolamine										
	Phentolamine					Ouabain				
Mean	0.987	41.12	119.08	9.09	2.19	0.983	56.88	177.05*	9.92	2.18
SD	0.010	31.28	98.15	6.23	0.76	0.010	22.04	159.98	5.34	0.86

* Different from control, $P < 0.05$. dE/dt_{max}, slope of the dP/dt_{max}-V_{ED} relation (mmHg/s per ml); VO, volume axis intercept of the dP/dt_{max}-V_{ED} relation (ml); dE_N/dt_N, $(dE/dt_{max})(t_{max})/E_{max}$. Other abbreviations as in Table II.



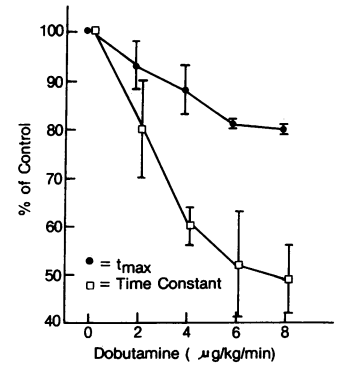


Figure 3. Responses of E_{max}, dE/dt_{max} (*A*), t_{max}, and T (*B*) to incremental infusions of dobutamine. E_{max} and dE/dt_{max} increase ($P < 0.05$), while t_{max} and T decrease ($P < 0.05$) in response to dobutamine. Data are represented by mean±SD.

amine increase the slope (dE/dt_{max}) of the dP/dt_{max}-V_{ED} relation. The time-varying elastance model predicts that dE/dt_{max} is proportional to E_{max}/t_{max} (3, 4). Consistent with this prediction, dobutamine, which decreased t_{max}, caused a greater increase in dE/dt_{max} than in E_{max}, whereas ouabain, which did not change t_{max}, produced an equivalent increase in E_{max} and dE/dt_{max}. Our previous study, which demonstrated that catecholamine administration produced a greater increase in dE/dt_{max} than in E_{max}, suggested that the dP/dt_{max}-V_{ED} relation may be more sensitive to inotropic state than the P_{ES}-V_{ES} relation (4). However, this present study indicates, consistent with the prediction of the time-varying elastance model, that this is true only for inotropic interventions that decrease t_{max}, and not for interventions such as digitalis administration that do not alter t_{max}.

We found that dobutamine and ouabain have different effects on isovolumic relaxation. Because relaxation is an active process, isovolumic relaxation can be considered part of systole (1). During this period LV pressure declines exponentially (1, 15, 26–28). Thus, the rate of fall of LV pressure can be

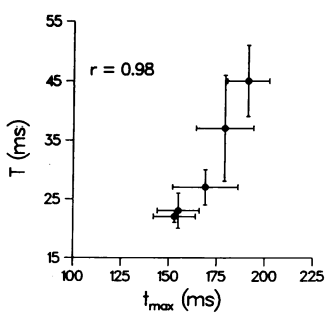


Figure 4. Both T and t_{max} increase during the incremental infusion of dobutamine. The mean values are linearly related ($r = 0.98$).

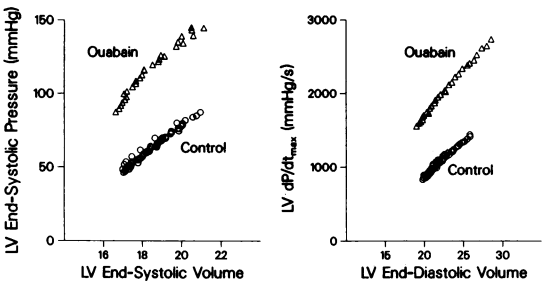


Figure 5. Ouabain shifts both the left ventricular end-systolic pressure-volume and dP/dt_{max}–end-diastolic volume relations to the left with comparable increases in the slope of both relations.

quantified using the time constant (T) of the pressure fall. We assessed the rate of pressure fall using an exponential model including a pressure asymptote. It has been shown that T can be substantially altered by changes in loading conditions, most markedly the afterload (28, 29). In addition, T is also influenced by the rate of contractile inactivation (1). Most positive inotropic interventions such as catecholamine administration decrease T, whereas negative inotropic interventions such as ischemia increase T. This has led to the concept that inotropic state is a determinant of the rate of isovolumic relaxation (30, 31). The current study and observations in isolated cardiac muscle (32) are not consistent with this hypothesis. We found that ouabain, a positive inotrope, increased E_{max} and dE/dt_{max}, but did not alter t_{max} or T. Ouabain's lack of effect on T was not altered by pretreatment with propanolol or phentolamine given to blunt the hypertensive response to acute ouabain administration. Thus, ouabain's lack of influence on T, does not appear to result from changes in afterload. These results are consistent with the observations of Weiss et al. (26) that another digitalis compound, acetylstrophanthidin, did not alter T in isovolumic, isolated canine hearts. We found that dobutamine, which also increases E_{max} and dE/dt_{max}, decreases t_{max} and T. The decrease in T with incremental infusions of dobutamine parallels the decrease in t_{max}. These findings suggest that the positive inotropic response that increases E_{max} and dE/dt_{max} can be separated from the response that speeds the rate of activation (t_{max}) and relaxation (T). These observations of the possible relation between changes in t_{max} and T are consistent with a prediction of the time-varying elastance hypothesis as derived in Appendix.

The differences in the effects of inotropic agents on isovolumic relaxation may have clinical importance. Catecholamines, such as dobutamine, that speed relaxation may help improve early diastolic filling of the LV, whereas digitalis would not.

Since our results are consistent with the predictions of the time-varying elastance model concerning the P_{ES}-V_{ES} relation and its links to the dP/dt_{max}-V_{ED} relation and to T, our study supports the use of time-varying elastance as a conceptual framework to understand and link events occurring during isovolumic systole (dP/dt_{max}-V_{ED} relation), at end-systole (P_{ES}-V_{ES} relation) and isovolumic relaxation (T). During these parts of systole there is little or no change in LV volume. It is important to recognize that the simple time-varying elastance model may not provide an accurate description of the LV during ejection when LV volume is rapidly changing (21, 33).

In conclusion, this study shows that although dobutamine and ouabain are both positive inotropes that increase E_{max}, dobutamine speeds the rate of LV contraction (t_{max}) and isovolumic relaxation (T), whereas ouabain does not. These effects of ouabain and dobutamine on global parameters of LV chamber performance mirror their influences on intracellular calcium availability. Furthermore, our observations are consistent with the predictions of the time-varying elastance model of the LV and support its usefulness as a conceptual framework to understand and link the events occurring during isovolumic contraction, at end-systole, and during isovolumic relaxation.

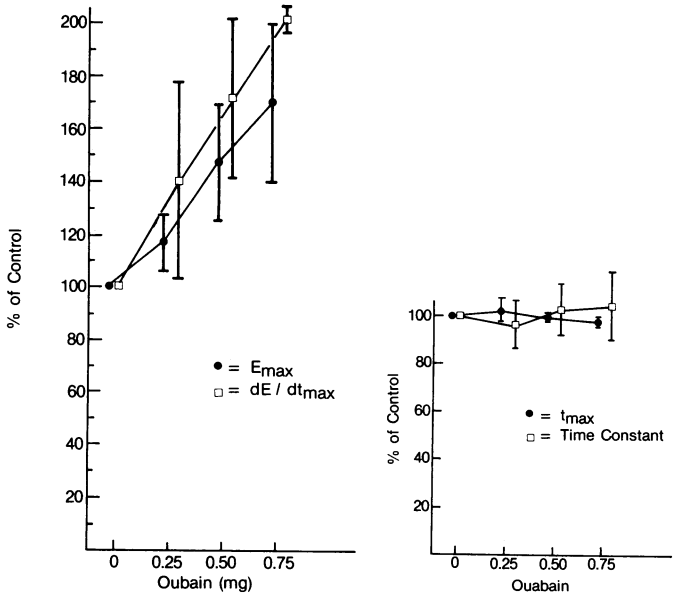


Figure 6. Response of E_{max}, dE/dt_{max} (*A*), t_{max}, and T (*B*) to a range of doses of ouabain. E_{max} and dE/dt_{max} increase ($P < 0.05$) while t_{max} and T are unchanged in response to ouabain. Data are represented by mean±SD.

Appendix

The time-varying elastance model holds that:

$$P(t) = E(t)[V(t) - V_0]. \quad (1)$$

Furthermore, $E(t)$ can be characterized by E_{max}, t_{max}, and $E_N(t/t_{max})$, as:

$$E(t) = E_{max}E_N(t/t_{max}). \quad (2)$$

$E_N(t/t_{max})$ is a normalized elastance function independent of loading and inotropic state from end-diastole to end-systole, but during isovolumic relaxation there is some variation in E_N that is probably due to changes in loading conditions and the history of the preceding contraction (2). During isovolumic relaxation $V(t) = V_{EE}$, the end-ejection volume; thus Eq. 1 reduces to:

$$P(t) = E(t)[V_{EE} - V_0]. \quad (3)$$

Because $P(t)$ falls exponentially during isovolumic systole it can be described as:

$$P(t) = P_0e^{-t/T} + P_B, \quad (4)$$

where T is the time constant of LV pressure decline, P_B is the residual pressure after complete relaxation and $(P_0 + P_B)$ is the initial pressure at which the exponential decline begins. Using Eqs. 3 and 4, this results in the following relation during isovolumic relaxation:

$$E(t) = E_0e^{-t/T} + E_B, \quad (5)$$

where $E_0 = P_0/(V_{EE}\text{-}V_0)$ and $E_B = P_B/(V_{EE}\text{-}V_0)$. Combining Eqs. 2 and 5 and rearranging results in:

$$E_N(t_N) = (E_0/E_{max})e^{-(t_Nt_{max}/T)} + (E_B/E_{max}),$$

where t_N is t/t_{max}. Thus, T_N, the time constant of the decline in normalized elastance, is given by:

$$T_N = T/t_{max}.$$

Rearranging gives:

$$T = t_{max}T_N.$$

Thus, the time-varying elastance hypothesis predicts that the time constant of the fall in LV pressure during isovolumic relaxation (T) is proportional to t_{max}, the time from end-diastole to end-systole, and T_N, the time constant of the decline of normalized elastance.

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