EFFECTS OF DOBUTAMINE ON LEFT VENTRICULAR RESTORING FORCES

STEVEN P. BELL, JUDIT FABIAN, AND MARTIN M. LEWIN
Cardiology Unit, University of Vermont College of Medicine, Burlington, Vermont 05405

Eleven adult mongrel dogs [weight, 23.7 ± 1.9 (SD) kg] of either sex were anesthetized with thiopental sodium (15–30 mg/kg iv), intubated, and mechanically ventilated with O2 and 0.5–1.5% halothane. The dogs were positioned in right lateral recumbency on a heating pad to maintain body temperature, and blood gases were maintained in the physiological range. A surgical plane of anesthesia was confirmed, and succinylcholine (0.5 mg/kg iv) was administered. A left thoracotomy and pericardiotomy were performed to expose the heart. Vascular constrictors were placed around the pre- and postcava and the ascending aorta. After heparin sodium (300 U/kg iv) was administered, the carotid artery was dissected and a 7-Fr catheter-tip micromanometer with fluid port (SPC 471A, Millar Instrument, Houston, TX) was inserted and advanced into the LV. A dual-excitation volume conductance catheter (Leycom, Sigma 5, CardioDynamics) was inserted through the apex of the LV and its tip positioned just below the aortic valve. We did not calibrate the conductance catheter by estimating the parallel conductance because we did not require knowledge of the absolute LV volume to assess shifts in the relation between FRP and ESV. A large-bore (8-mm ID) rigid cannula was placed in the LA via the appendage, positioned just above and at the midpoint of the mitral valve, and attached to the servomotor. A 5-Fr high-fidelity pressure transducer (MPC 500, Millar) inserted into a rigid sheath with multiple side holes and a fluid-filled catheter attached to the large-bore cannula were used to measure LAP. Pacing electrodes were attached to the LA and connected to a stimulator (SD-9, Grass Instruments, Quincy, MA) that was controlled by a computer (486/33 MHz, Gateway 2000, North Sioux City, SD). A 26-gauge angiocath was then inserted retrograde in the left anterior descending (LAD) coronary artery with the tip proximal to the first diagonal branch and secured in place while allowing flow to be maintained. In two additional dogs, in addition to the instrumentation previously described, we...
implanted epicardial and subendocardial ultrasonic crystals to measure anterior wall thickness in the perfusion zone of the LAD artery. The LAD catheter was inserted in only one of these dogs.

Protocol. After instrumentation was completed, the calcium channel blocker zatebradine (UL-FS 49, 1 mg/kg iv, Boehringer Ingelheim, Ridgefield, CT) was administered to reduce native heart rate. Atrial pacing was then initiated at a rate as close to 90 beats/min as possible and maintained constant. Average heart rate was 91 ± 5 (SD) beats/min. We then applied brief partial caval constrictions and aortic constrictions to generate a range of steady-state ESVs. At each ESV, data were recorded during filling and nonfilling diastoles with respiration suspended at end expiration. To produce nonfilling diastoles, the servomotor system was used to rapidly clamp the LAP below the LV diastolic pressure during ventricular systole, as described previously (3). The LV was allowed to fully relax at its ESV, and the FRP was measured. To ensure that no LV filling occurred during LAP clamp beats, we required that there be no change in the conductance catheter volume signal after the time of the LV-LA crossover pressure determined from the normal filling beat preceding the LAP clamp beat and that the LV pressure (LVP) decline monotonically to a plateau value during the LAP clamp. After return to baseline conditions, dobutamine, the slope of the relation between FRP and ESV by measuring the smallest LV volume preceding peak negative LV dP/dt. As indicated earlier, conductance catheter volumes were not corrected for parallel conductance.

An intrinsic difficulty in detecting changes in the relation between FRP and ESV after an intervention using our preparation and this protocol is that FRP usually varied over a small range of pressure, typically no more than 2–3 mmHg above and 2–3 mmHg below zero. As a result, even modest amounts of noise in these data resulted in large confidence intervals regardless of how they were fitted and difficulty in detecting changes. To overcome this problem, for the dogs without wall thickness crystals we fit all positive and negative FRP-ESV data points by least-squares linear regression. We then excluded all experiments in which the regression line was <0.85. Six experiments met this criterion for control and intravenous dobutamine, and four of the six for intracoronary dobutamine. For these experiments, we used the confidence intervals of the control FRP-ESV relation to determine whether dobutamine caused a change. The slopes of the control and intravenous dobutamine FRP-ESV relations were compared using a paired t-test. The magnitude of shifts in the relation was quantified by using the regression statistics of the control relation to calculate Veq (i.e., volume with FRP at 0 mmHg) and the intravenous dobutamine regression statistics to calculate the FRP at the same LV volume. We then compared the dobutamine FRP at this LV volume to the control value (0 mmHg) using a paired t-test. All data are reported as means ± SD. Because the experiments with wall thickness crystals were performed for the specific purpose of determining whether dobutamine alters the relation between ESV and wall thickness during nonfilling diastoles, we did not require that the control FRP-ESV data meet any specific goodness-of-fit criteria in these two dogs.

RESULTS

Figure 1 shows representative tracings of LVP and LV volume during nonfilling diastoles under control and intravenous dobutamine conditions. In five of six experiments, we observed a downward and rightward shift of the FRP-ESV relation after intravenous dobutamine (Fig. 2A), such that the confidence intervals of control and dobutamine data sets did not overlap. In one experiment, no shift was apparent (Fig. 2B). Using linear fits of the data, we found that after intravenous dobutamine, the slope of the relation between FRP and ESV was not significantly changed (0.17 ± 0.03 vs. 0.14 ± 0.03 mmHg/ml, P = 0.18). FRP averaged 2.6 ± 1.6 mmHg at the same LV volume as the control Veq.
(P < 0.05). Thus, even though there was no shift in one experiment based on the confidence intervals of the FRP-ESV relations, there was a statistically significant downward shift for the group. In three of four experiments, intracoronary dobutamine also resulted in a downward shift of the FRP-ESV relation (Fig. 2A), which was not as great as that caused by intravenous dobutamine. It did not cause a shift in the one experiment in which a shift was also not observed with intravenous dobutamine (Fig. 2B). An example of wall thickness signals during a nonfilling diastole is shown in Fig. 3. During nonfilling diastoles, we observed gradual wall thinning. Therefore, to assess the relation between ESV and wall thickness after completion of LVP fall, we arbitrarily measured wall thickness 600 ms after the QRS complex. Figure 4 is a graph of the relation between wall thickness after completion of LVP fall during nonfilling diastoles and ESV for control, intravenous, and intracoronary dobutamine conditions for one of these experiments. As expected, wall thickness decreased as ESV increased. With both intravenous and intracoronary dobutamine, there were consistent but modest increases in wall thickness at overlapping ranges of ESV compared with control conditions. The increase was on the order of 8–10% with both intravenous and intracoronary administration. In the other wall thickness experiment, the increase with intravenous dobutamine was similar in magnitude.

**DISCUSSION**

Ventricular restoring forces, when present, are inversely related to the ESV. This study demonstrates that administration of systemic dobutamine induces a downward shift of the relation between FRP and ESV, indicating that this intervention increased restoring forces independent of changes in ESV. Regional dobutamine administered via the LAD coronary artery produced a similar effect. Previously, in preparations in which the mitral valve was replaced by a prosthesis used to prevent filling, Nikolic et al. (13) reported increased stiffness of this relation below Veq during dobutamine administration, whereas Hori et al. (7) reported a more negative FRP at ESV less than Veq during calcium administration. Thus, in both of these studies, increased contractility appeared to augment restoring forces. However, replacement of the mitral valve appears to increase the magnitude of restoring forces assessed as the FRP during a nonfilling diastole (3, 14). In the present study, we confirmed that dobuta-
mine augments restoring forces in a preparation in which nonfilling diastoles were produced with an intact mitral valve.

At the level of the ventricle, restoring forces are thought to be generated in part as a result of transmu
tral and three-dimensional deformations during contraction that allow storage of potential energy that is con
tverted to suction during the succeeding diastole (8, 9, 15, 16). These contraction-related deformations in
dude differences in subepicardial and subendocardial fiber orientation, shear, and timing of relen
gthening, and twist, or counterclockwise rotation of the LV about its long axis (9, 15). However, because our measure of restoring forces was a negative pressure after completion of LV fall during a nonfilling diastole, these deformations in theory should not have influenced the FRP. Another factor related to whether a restoring force is present at any ESV is the wall thickness. After full
development during a nonfilling diastole at ESV less than $V_{eq}$, elastic elements in the wall, for example, titin (6), are below their rest length, accounting for a restoring force. Because, by conservation of mass, wall thickness
is inversely related to ESV, the presence and magni
tude of a restoring force should parallel the wall thickness. Our results in the two animals in which wall thickness was measured indicate that there is a detectable increase in wall thickness independent of ESV during dobutamine. Thus a component of the mecha
nism of increased restoring forces during dobutamine may be related to the drug’s influence on wall thick
ness. Moreover, the increased wall thickness was also demonstrable in the anterior wall after intracoronary administration of dobutamine. Evidently, a regional increase in wall thickness can be associated with the same effects on the FRP. It is also logical that the shift in the FRP-ESV relation produced by intracoronary dobutamine did not appear to be as large as that produced by systemic dobutamine.

The only plausible explanation for the acute increase in wall thickness caused by dobutamine under these conditions is an increase in coronary blood volume. Thus it is highly likely that dobutamine increases coronary blood volume independent of ESV. We are unaware of any previous studies in which wall thickness was measured at common ranges of ESV before and after administration of dobutamine or other catecholamines. This observation suggests that there may be a dynamic relationship between coronary perfusion and the FRP-ESV relation. The effects of turgor on diastolic compliance at LV volumes greater than $V_{eq}$ are well known (2), but the possibility that coronary perfusion influences $V_{eq}$ and the FRP-ESV relation at volumes less than $V_{eq}$ has not previously been considered. We question, however, whether the increase in wall thickness is sufficient to explain the shift in the FRP-ESV relation observed. The increase was quite modest. Moreover, an increase in wall thickness at a given ESV due to increased coronary blood volume would, if anything, be expected to shift the FRP-ESV relation downward at ESV values less than $V_{eq}$ but have the reverse effect at ESV values greater than $V_{eq}$ (2). Instead, we observed a rightward and downward shift of the relation both above and below $V_{eq}$. Finally, during the course of a nonfilling diastole, we observed gradual wall thinning, which must have been related to a net decrease in coronary blood volume. The thinning was not dissimilar in magnitude to that observed during dobutamine (see Fig. 3). Despite this, the FRP remained constant. Thus this magnitude of change in blood volume did not measurably affect the LVP. These considerations led us to suspect that the mechanism of the shift in the FRP-ESV relation may be more compli
cated than that related to an increase in coronary blood volume. We have assumed that contraction-related deformations other than increased wall thickness do not contribute to the relation between FRP and ESV after completion of relaxation. However, it is possible that the process of constraining volume at the end-
systolic level by preventing filling could alter the normal reversal of these deformations, for instance, by
tethering effects. Alternatively, we previously reported evidence of “creep” during changes in loading condi
tions (10), i.e., deformable elements in the myocardium that return slowly to the undeformed state. If dobuta
mine influences these elements, it is conceivable that the time period of a nonfilling diastole is too short for them to return to the undeformed state. Thus, despite the presence of complete relaxation by conventional criteria, an alteration in contractile performance could possibly continue to influence wall forces.

A potential limitation of our study is the fact that we did not measure absolute LV volumes. Although it would have been ideal to do so, nonlinearities in the relation between true volume and conductance catheter volume because of volume-dependent variation in the parallel conductance, especially at small ESVs, indicate that this method of measuring LV volume may be most reliable for detection of relative changes (1, 4). In this regard, it is important to consider whether such differences in the parallel conductance could have invalidated our conclusions, which were based on the “raw” conductance catheter volumes uncorrected for parallel conductance. We believe this is unlikely for two reasons. First, the curvilinear relation between true volume and conductance volume is convex toward the conductance volume axis (4). As a result, the conduc
tance catheter overestimate of true volume increases progressively as volume decreases. Because we ob
served a rightward shift in the relation between FRP and ESV (a larger volume at any pressure), this feature of the conductance catheter actually biases against the result we observed. Second, we used a dual-excitation conductance catheter system (17) that substantially reduces volume-dependent nonlinearity compared with single excitation systems (1, 4, 17). We also assumed that the parallel conductance did not change as a function of time during the course of our studies. Although there is no a priori reason to believe it should change, the assumption is supported by the work of Boltwood et al. (4), who made repeated parallel conduc
tance measurements during a similar protocol in open-
chest dogs and did not observe any time-dependent variation.

In addition to increasing relaxation rate, dobutamine decreases ESV in the intact heart and circulation. A smaller ESV enhances early diastolic filling by virtue of increased passive chamber compliance if ESV is greater than $V_{eq}$ or increased restoring forces if ESV is less than $V_{eq}$, with consequent augmentation of the early diastolic gradient across the mitral valve. The present study identifies an additional mechanism, greater restoring forces at any level of ESV in association with an increase in $V_{eq}$, which contributes to the effects of dobutamine on diastolic filling patterns. Future research directed at more precisely delineating global and regional deformation patterns will be helpful in better understanding the mechanism of this phenomenon.

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Address for reprint requests: M. M. LeWinter, Cardiology Unit, Fletcher Allen Health Care, MCHV Campus, 111 Colchester Ave., Burlington, VT 05401.

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