Influence of Inotropy and Chronotropy on the Mitral Valve Sphincter Mechanism

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Background. **This study was designed to isolate and quantify the effects of ventricular inotropic and chronotropic state on the normal mitral valve annular sphincter mechanism.**

Methods. **Sonomicrometry tansducers were placed around the mitral annulus in six sheep; atrial pacing wires were also placed. One week later, esmolol was titrated to produce a baseline hemodynamic state with a heart rate of 90 bpm; hemodynamic and sonomicrometry data were recorded. Then animals were paced at 120 bpm and 150 bpm; data were recorded at each heart rate. Isoproterenol infusion was titrated to achieve a heart rate, without pacing, of 120 and 150 bpm; again, data were recorded. Annular area was calculated at end diastole (ED) and end systole (ES) for all experiments using sonomicrometry array localization. Analysis of variance was used to assess the independent effects of heart rate and inotropic state on annular area.**

Results. **Atrial pacing at 120 bpm produced ES and ED annular areas of 777 ± 150 mm^2 and 748.8 ± 140.1 mm^2, respectively. At the same heart rate, isoproterenol-treatment resulted in significantly smaller ES and ED areas: 699 ± 160 mm^2 and 641.9 ± 156.5 mm^2, respectively. Atrial pacing at 150 bpm produced ES and ED annular areas of 745.2 ± 131.3 mm^2 and 723.7 ± 141.3 mm^2, respectively. At the same heart rate, isoproterenol-treatment resulted in significantly smaller ES and ED areas: 652.8 ± 146.4 mm^2 and 569.7 ± 155.9 mm^2, respectively.**

Conclusions. **The inotropic state of the left ventricle directly affects the mitral valve annular orifice area, independent of heart rate. This inotropic effect on valve size is more pronounced at ED than at ES in the sheep.**

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The mitral valve is a complex structure whose proper function is dependent on the integrated performance of six individual elements: leaflets, annulus, chordae tendineae, papillary muscles, left ventricle, and left atrium. The annulus is a vital component of the mitral valve, and through its well-coordinated sphincteric mechanism contributes to timely, efficient, and competent valve closure [1]. The sphincteric action of the annulus can be affected by hemodynamic conditions [2–4], lack of atrial contraction [5], ischemia [6–8], atrial fibrillation [1, 9], and end-stage heart failure [10]. The dynamics of annular motion and contraction have been an area of active investigation because mitral annular size and the sphincteric mechanism likely have important effects on valve performance under normal and pathologic conditions.

It has been observed in clinical studies [11–13] and experimental studies [6–8, 14, 15] that both regional and global left ventricular function can play an important role in the development of mitral regurgitation (MR). Ischemic mitral regurgitation (IMR) and cardiomyopathies are associated with ventricular distortions that lead to annular dilatation and "functional" valvular incompetence [12, 13]. The administration of catecholamines in patients with cardiomyopathy has been reported to reduce functional MR but the mechanism of this phenomenon remains poorly elucidated [16, 17]. It has been speculated that this salutary effect on MR can be attributed to a reduction in annular size secondary to increased ventricular performance and heart rate (HR) [18]. However, the direct effect of inotropic and chronotropic stimulation on the size of the mitral valve annulus has not been assessed.

This study was designed to isolate the effect of left ventricular inotropic and chronotropic state on the size of the normal ovine mitral valve annulus. Sonomicrometry array localization (SAL) was used to measure the changes in ovine mitral annular area in response to alterations in HR and ventricular contractility under constant loading conditions.

Material and Methods

Sonomicrometry array localization accurately determines the three-dimensional spatial relationships of an array of cardiac sonomicrometry transducers every 5 ms [19]. We used this imaging modality to measure mitral valve area throughout the cardiac cycle, as previously described [20].

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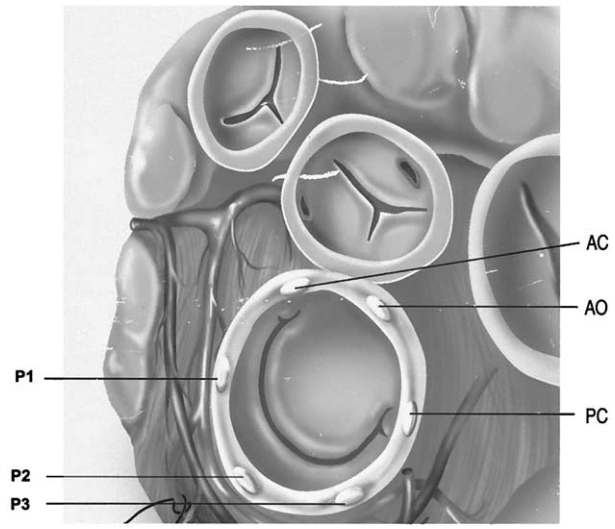

Fig 1. The relationship of the sonomicrometry transducers to mitral annular and leaflet anatomy. Note that AC and Ao are closely related to the anterior and posterior trigones of the heart's fibrous skeleton, respectively. (AC = *anterior commissure;* Ao = *aortic;* PC = *posterior commissure;* P1 = *anterior portion of posterior annulus;* P2 = *midportion of posterior annulus;* P3 = *posterior portion of posterior annulus.)*

Surgical Protocol

In compliance with guidelines for humane care (National Institutes of Health Publication No. 85-23, revised 1985) six male Dorsett sheep (35 to 45 kg) were induced with sodium thiopental (10 to 15 mg/kg iv), intubated, and anesthetized and ventilated with isofluorane (1.5% to 2%) and oxygen. The surface electrocardiogram and arterial blood pressure were continuously monitored.

Through a sterile left lateral thoracotomy, six 2-mm hemispherical PZT-5A piezoelectric transducers (Sonometrics Corp, London, Ontario, Canada) were implanted in each sheep during cardiopulmonary bypass, as described previously [7, 8]. Figure 1 illustrates the relationship of the annular transducers to leaflet and annular anatomy. The posterior commissure (PC) and the anterior commissure (AC) transducers were placed at the cleft between the anterior and posterior leaflets. The AC transducer was, in all animals, adjacent to the central fibrous body. The aortic crystal (Ao) was placed on the aortic-mitral continuity very near the posterior trigone. The annular transducers marked P1, P2, and P3 were centered over the anterior, middle, and posterior scallops of the posterior leaflet. An aortic flow probe was implanted to measure cardiac output (CO). The chest was closed and the animal recovered.

Data Acquisition

Seven days later sheep were again sedated with thiopental, placed supine, intubated, anesthetized with isofluorane, and mechanically ventilated. A high fidelity double pressure transducer (SPC-350; Millar Instruments Inc, Houston, TX) for simultaneous measurements of left ventricular and aortic root pressures was passed percutaneously into the left ventricle (LV) through a femoral artery. A pulmonary artery catheter (7 Fr; Baxter Healthcare Corp, Deerfield, IL) was also placed. Surface electrocardiogram (ECG), left ventricular pressure (LVP), aortic root pressures (AP), left ventricular end-diastolic pressure (LVEDP), central venous pressure (CVP), and CO were monitored continuously (HP 78534C monitor; Hewlett-Packard, Inc., Palo Alto, CA).

Subdiaphragmatic color-flow Doppler echocardiography (model 77020A; Hewlett-Packard Inc) was performed through a midline laparotomy after each pharmacologic or pacing intervention to assess valve competency [7]. Transducer wires were connected to a Sonometrics Series 5001 Digital Sonomicrometer (Sonometrics Corp).

Animals were β-blocked with esmolol (mean infusion rate 6.7 $\pm$ 3.5 mg/min) to a HR of 90 beats per minute (bpm), and SAL data were recorded. Subsequently, SAL data were recorded during atrial pacing at 120 and 150 bpm. Esmolol was discontinued, and the animals were allowed to return to the steady state. An isoproterenol infusion was then titrated to produce rates of 120 bpm (mean infusion rate 4.6 $\pm$ 2.9 μg/min) and 150 bpm (5.5 $\pm$ 2.1 μg/min); SAL data were recorded at both rates. Ventilation was suspended during sonomicrometry measurements. Hemodynamic data were always recorded simultaneously with the sonomicrometry data.

Data Analysis

Sonomicrometry distance data were used to determine the three-dimensional coordinates of each transducer every 5 ms throughout the cardiac cycle. From these data, annular area throughout the cardiac cycle was calculated as previously described. End diastole (ED), end isovolemic contraction, end systole (ES) and end isovolemic relaxation (EIVR) were also defined as previously described [19, 20].

To allow comparison, every data set was then normalized in time by means of linear interpolation such that the time of the cardiac cycle was equal to 400 ms, isovolemic contraction (from ED to EIVC) was equal to 100 ms, ejection (EIVC to ES) was equal to 100 ms, isovolemic relaxation (ES to EIVR) was equal to 100 ms, and diastolic filling (EIVR to ED) was equal to 100 ms.

The statistical significance of the independent effects of HR and inotropic state on annular area and hemodynamic variables was assessed using a two-way multivariate analysis of variance method. If the effect of a particular factor (HR or inotropic state) was found to be significant overall, within group comparisons were carried out using Students paired t test with Boneferroni correction. All results are presented as means $\pm$ standard deviations.

Results

Hemodynamics and Echocardiography

Placement of the sonomicrometry transducers did not affect valve competency. There was no more than trace

Table 1. Summary of the Independent Effects of Inotropy and Choronotropy on Hemodynamics

Inotropic State	HR	LVEDP (mm Hg)	MAP (mm Hg)	CVP (cmH_2O)	CO (L/min)
Baseline	91.8 ± 1.5	10.2 ± 6.2	71.7 ± 11.5	16.6 ± 3.6	2.6 ± 0.3
Isoproteronol	120.7 ± 3.0	6.2 ± 4.2*	78.3 ± 13.1	14.0 ± 5.1	4.5 ± 1.0*
Paced	120.2 ± 2.8	11.8 ± 5.7	76.7 ± 20.0	15.5 ± 5.1	2.8 ± 0.5†
Isoproteronol	148.8 ± 2.1	6.2 ± 5.3*	92.5 ± 20.8	13.5 ± 5.7	5.8 ± 1.5*
Paced	149.1 ± 1.7	10.3 ± 5.7	78.8 ± 18.8	13.7 ± 4.9	3.2 ± 0.5†

Isoproteronol infusion effected left ventricular end diastolic pressure (LVEDP) and cardiac output (CO) significantly (*), while heart rate only had an effect on CO (†).

CVP = central venous pressure; HR = heart rate; MAP = mean arterial pressure.

MR after any of the pharmacologic or pacing interventions.

The hemodynamic data are summarized in Table 1. Both HR and inotropic state had a significant effect on cardiac output. Baseline CO (HR = 90 bpm) was 2.6 ± 0.3 L/min. Atrial pacing at 120 bpm and 150 bpm produced COs of 2.80 ± 0.47 L/min and 3.2 ± 0.5 L/min, respectively ($p < 0.05$). Isoproterenol infusion to achieve heart rates of 120 bpm and 150 bpm resulted in COs of 4.8 ± 1.0 L/min and 5.8 ± 1.5 L/min, respectively ($p < 0.05$). Cardiac outputs with isoproterenol were significantly higher than with atrial pacing, at each target heart rate.

Heart rate had no significant effect on any of the other measured hemodynamic factors. Increased inotropy caused a significant decrease in LVEDP, but in none of the other variables.

Effects on Mitral Annular Area

Inotropic state had a significant effect on mitral valve annular area (f = 6.4, $p < 0.02$), throughout the cardia cycle, while heart rate did not (Fig 2). The baseline annular areas (HR = 90 bpm) at ED and ES were 735.8 ± 132.4 mm^3 and 756.4 ± 147.9 mm^3, respectively. A target HR of 120 bpm with isoproterenol infusion produced an ED annular area of 641.9 ± 156.5 mm^3; with atrial pacing the same HR resulted in an ED area of 748.8 ± 140.1 mm^3 ($p < 0.05$ between pacing and isoproterenol, see Table 2 for more details). When compared with baseline, pacing at 120 bpm did not affect annular area significantly but isoproterenol infusion titrated to HR = 120 did produce a statistically significant reduction in annular area (Fig 3). At a target heart rate of 150 bpm, ED annular area for the isoproterenol infusion and atrial pacing groups were 569.7 ± 155.9 mm^3 and 723.7 ± 141.3 mm^3, respectively ($p < 0.05$ between pacing and isoproterenol). Figure 4 illustrates these results graphically.

At a target heart rate of 120 bpm, ES annular area for the isoproterenol infusion and atrial pacing groups were 699.6 ± 160.4 mm^3 and 777.5 ± 150.1 mm^3, respectively ($p < 0.05$ between isoproterenol and pacing). At a target heart rate of 150 bpm, ES annular area was 652.8 ± 146.4 mm^3 for the isoproterenol infusion group and 745.2 ± 131.3 mm^3 for the atrial pacing group ($p < 0.05$ between isoproterenol and pacing). Figure 5 demonstrates these effects graphically.

Using a separate one-way ANOVA, the effect of inot-

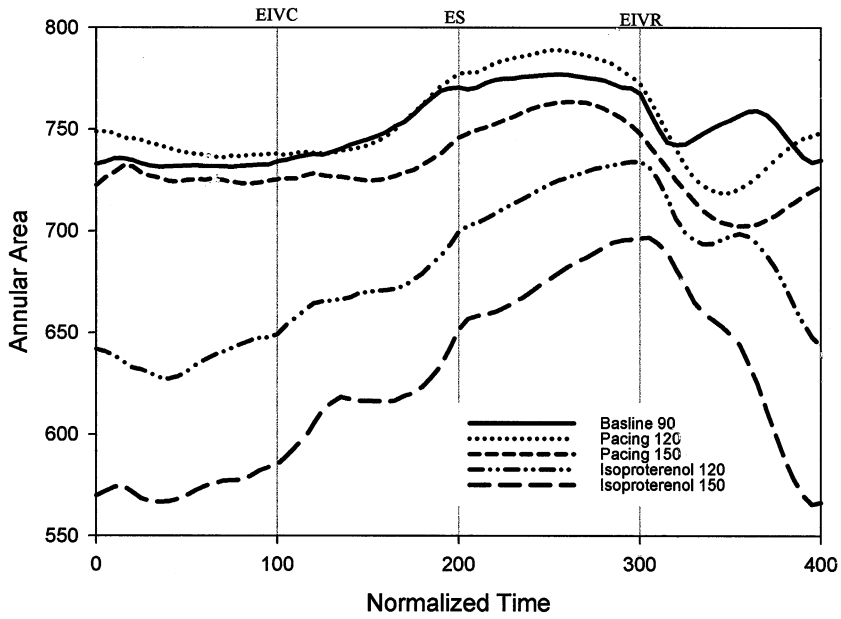

Fig 2. Curves *represent annular area for a composite animal (n = 6) throughout a normalized cardiac cycle at each hemodynamic condition studied. ANOVA (considering all normalized time points together) revealed that the pacing 120 and pacing 150 conditions were not significantly different from each other or from baseline. ANOVA also demonstrated that the isoproterenol 150 condition was significantly smaller than all other hemodynamic conditions and that the isoproteronol 120 group was significantly smaller than baseline and both of the pacing groups* (p ≤ *0.001).* (EIVC = *end isovolemic contraction;* EIVR = *end isovolemic relaxation;* ES = *end systole.)*

Table 2. Summary of Independent Effects of Inotropy and Choronotropy on Mitral Valve Annular Area (mm^3)

	Heart Rate			
	120 bpm		150 bpm	
Inotropic State	End Diastole	End Systole	End Diastole	End Systole
No inotropic stimulation (atrial pacing)	748.8 ± 140.1*	777.5 ± 150.1†	723.7 ± 141.3‡	745.2 ± 131.3§
Inotropic stimulation (isoproteronol)	641.9 ± 156.5*	699.6 ± 160.4†	569.7 ± 155.9‡	652.8 ± 146.4§

Two way ANOVA revealed that inotropic state significantly effected annular area ($f = 6.4$, $p < 0.02$) while heart rate had no significant effect. Subsequent within group comparisons were carried out using paired Student's t test with Bonferroni correction (*, †, ‡, §, $p < 0.05$).
bpm = beats per minute.

ropy on reducing annular area was more pronounced at ED than at ES ($f = 4.6$, $p < 0.04$). These results are summarized in Table 3.

Comment

Our group and others have demonstrated that the mitral valve annulus is a very complex and dynamic structure [21–23]. Its size and shape may vary with the cardiac cycle, with hemodynamic conditions, and with various pathologic states. Because of its diaphanous nature, a complete understanding of the dynamic function of the mitral valve annulus has been elusive, despite significant interest and much study. The effect of inotropic stimulation on annular physiology is also poorly understood. Marker angiography and the SAL technique used in this experiment are likely the best tools for examining the dynamic anatomy and physiology of the mitral annulus. Both techniques require direct operative visualization of the annulus and, therefore, reduce the uncertainty associated with identifying this structure using less invasive imaging techniques such as echocardiography. Timek and Miller [1] have presented an in-depth analysis of these important issues regarding mitral annular imaging in a recent meticulous review. Given the ever-increasing incidence of functional and ischemic mitral regurgitation, a thorough understanding of normal and pathologic annular physiology are of more than academic interest. This study demonstrates that mitral annular area can be directly manipulated by pharmacologically controlling the inotropic state of the left ventricle, and that this effect is independent of HR to a great degree. These inotropic effects are also independent of hemodynamic loading, and indicates that the contractile state of the left ventricle can directly affect mitral valve geometry and function. These results provide an explanation for the clinical observations made by others that dobutamine infusion reduces the degree of MR in patients with dilated cardiomyopathies [24].

This ovine study likely underestimates the effect of LV inotropic state on mitral orifice size in humans. The human mitral annulus is directly anchored to the deep sinospiral muscle and the deep bulbospiral muscle of the left ventricle. These muscles act as a powerful sphincter encircling the left ventricular base and enclose both the aortic and mitral orifices [25]. In the sheep the mitral annulus is more directly attached to the atrium [20]. These anatomic considerations indicate that ventricular

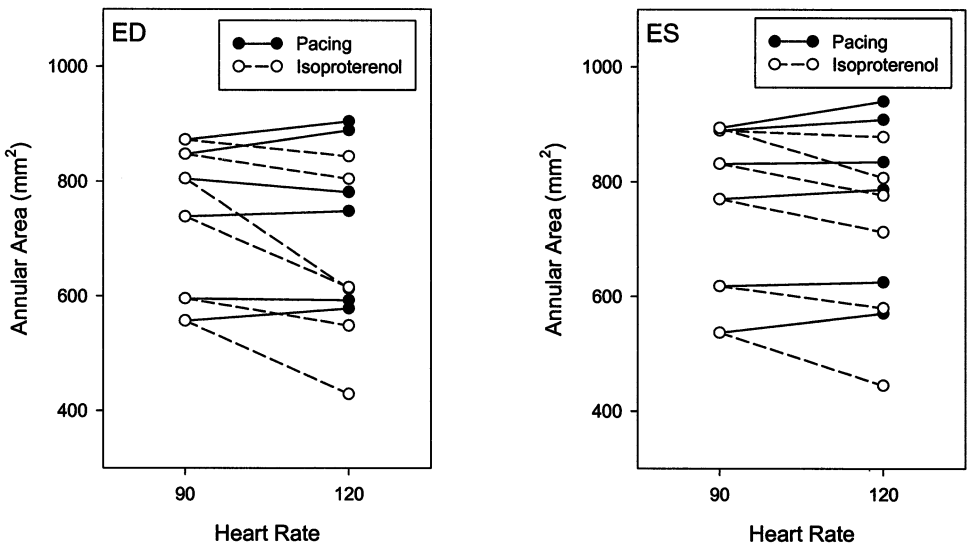

*Fig 3. The ED and ES effect of chronotropy and inotropy (baseline to 120 bpm) on mitral annular area. All six animals are illustrated. For all animals, inotropy decreased annular area while pure chronotropy had little if any effect on annular area. This figure also demonstrates that the effect of inotropy is more pronounced at ED than at ES. (*ED = *end diastole;* ES = *end systole.)*

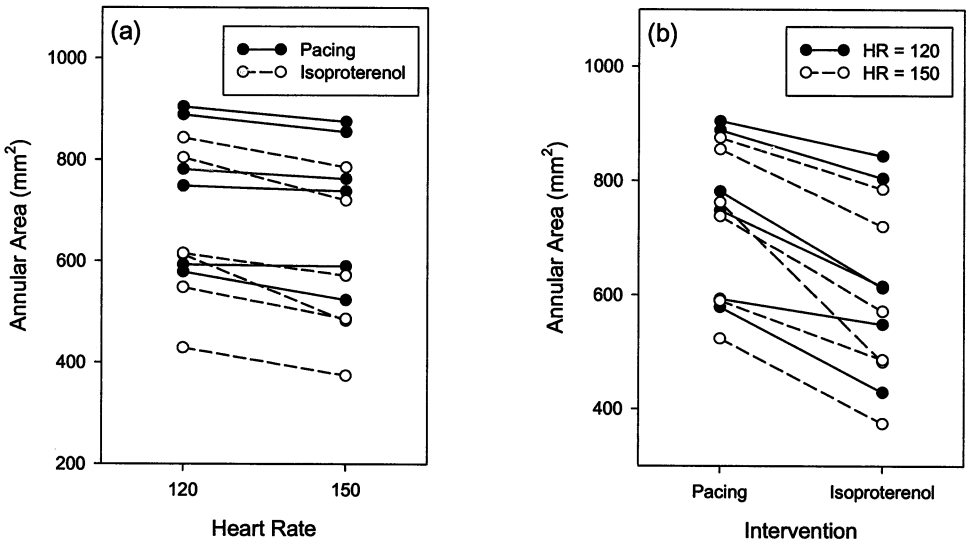

Fig 4. The independent effect of chronotropy and inotropy on mitral annular area at ED in six sheep at heart rates of 120 and 150 bpm. Note, in particular, the greater negative slope of the lines in (b), demonstrating that inotropy has a more pronounced effect on mitral annular area than does chronotropy. (ED = *end diastole;* HR = *heart rate.)*

contractility may have an even greater influence on mitral valve sphincter mechanism in humans. Correlation of SAL data with 3-day echocardiography in sheep (or other animals) may allow the clinical extrapolation of these findings to patients.

Clinical Implications

These findings clearly demonstrate that increased ventricular contractility changes mitral valve geometry in sheep, leading to a decrease in mitral valve area. Clinically, the decrease in mitral valve area caused by inotropy may be beneficial in patients with hypokinetic or remodeled ventricles and concomitant ischemic or functional mitral regurgitation. Therefore, cardiac surgery patients who demonstrate moderate mitral regurgitation not warranting surgical therapy may benefit from inotropic support during and after separation from cardiopulmonary bypass. The temporary use of inotropic support may ameliorate the degree of mitral regurgitation and allow ventricular function to return to baseline.

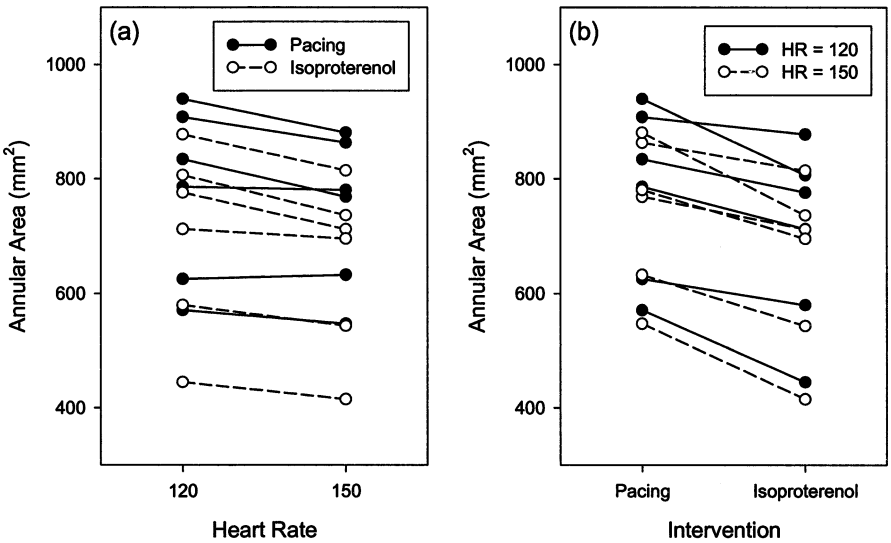

Fig 5. The independent effect of chronotropy and inotropy on mitral annular area at ES in six sheep at heart rates of 120 and 150 bpm. Note the greater negative slope of the lines in (b), demonstrating that inotropy has a more pronounced effect on mitral annular area than does chronotropy. Also note the greater negative slope of the lines in Figure 4b compared with Figure 5b, demonstrating that inotropy has a greater effect on annular area at ED than at ES in the sheep. (ED = end diastole; ES = end systole; HR = *heart rate.)*

Table 3. Effects of Inotropy on Annular Area at ED and ES

Annular Area Reduction as a Result of Increased Inotropy		
	120 bpm	150 bpm
ED	106.8 ± 50.5 mm^3	153.9 ± 67.7 mm^3
ES	77.9 ± 42.6 mm^3	92.7 ± 38.7 mm^3

Numbers represent differences in annular area between isoproteronol and pacing experiments at the specified heart rates and specified points in the cardiac cycle. ED and ES were significantly different by ANOVA ($f = 4.6$, $p < 0.04$): the effect of inotropy on decreasing annular area was greater at ED than at ES.

bpm = beat per minute; ED = end diastole; ES = end systole.

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INVITED COMMENTARY

The mitral annulus is a discontinuous fibromuscular ring circumscribing the valve orifice, which has a poorly defined anatomical boundary and incompletely understood physiology. Since the pioneering canine experiments of Tsakiris et al in the 1960's, the sphincteric action of the mitral annulus has been thought to have important effects on valve performance by aiding both mitral valve closure and ventricular filling by virtue of its dynamic area change during the cardiac cycle. The current ovine data reported by Gorman and colleagues further elucidate the sphincteric action of the mitral annulus and emphasize its dynamic physiology.

In this elegantly designed sheep experiment, these investigators showed that the inotropic state of the myocardium directly affects the size of the mitral orifice, an effect beyond that exerted by faster heart rate alone. These experimental findings have important clinical implications, especially since the reduction in mitral annular area was found to be greatest at end-diastole, ie during the end of mitral valve closure when minimal

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