Title: THE EFFECT OF AMRINONE ON INDICES OF LEFT VENTRICULAR DIASTOLIC FUNCTION ASSESSED BY VOLUME (CONDUCTANCE) CATHETER

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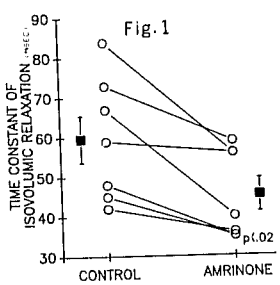
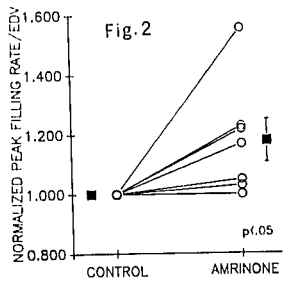
Introduction Depression of left ventricular function can occur during general anesthesia and cardiac surgery necessitating the use of positive inotropic agents. Interest in the bipyridine inotrope amrinone has centered mostly on its systolic phase actions. Studies of ventricular performance are typically done without regard for possible simultaneous effects on diastolic function. It is clear, however, that preserved systolic function does not automatically mean normal diastolic function.[1] We, therefore, examined the effects of amrinone on three commonly used indices of diastolic activity: 1) the time constant of isovolumic relaxation (T), 2) the peak left ventricular filling rate (PFR)/end diastolic volume (EDV), and 3) the diastolic pressure - volume relationship chamber stiffness coefficient (B). Furthermore, we used a relatively new technology, the volume (conductance) catheter for pressure-volume loop data acquisition.[2] This enabled the determination of the peak filling rate and chamber stiffness coefficient which are volume derived.

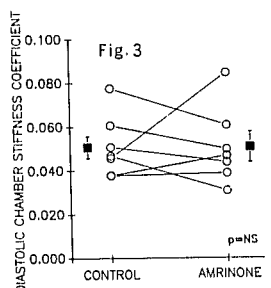
Methods Seven open chest, anesthetized (pentobarbital/chloralose) dogs were studied. Autonomic blockade was produced by IV hexamethonium chloride (35 mg/kg) and bilateral vagotomy. A high fidelity micromanometer catheter (Millar Instruments) was positioned in the LV to measure pressure (P) and a multi-electrode volume catheter (Webster Labs) was passed retrograde across the aortic valve along the ventricular long axis to the apex to measure LV volume. An IVC balloon occlusion catheter was placed just below the right atrial-inferior vena cava (IVC) junction. Data before and 5 minutes after a 2 mg/kg bolus of amrinone were compared. The heart rate was constant due to autonomic blockade and end diastolic volume was maintained near control levels with Hetastarch. T was calculated from the slope (A) of the dP/dt vs. P relationship starting at peak negative dP/dt where $T = -(1/A)$.[3] The peak filling rate (dV/dt_{max})/EDV following amrinone was normalized to its pre-drug baseline. The diastolic stiffness coefficient (B) was determined from pressure-volume data obtained during rapid preload reduction by IVC balloon occlusion. B was determined by non linear regression in the form $P = Po + A(1-e^{BV})$. (Fig. 4) Comparisons were made by paired Students t-test with $P < 0.05$ considered significant.

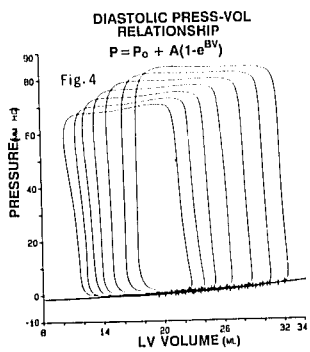
Results Amrinone significantly shortened T from 59.5 ± 5.9 to 45.4 ± 4.1 msec with all dogs experiencing improved relaxation ($p < 0.02$) (Fig. 1). The normalized PFR/EDV also showed significant improvement (18%) from baseline 1.0 to 1.18 after amrinone ($p < 0.05$) (Fig. 2). In contrast, amrinone had no effect on the diastolic pressure-volume relationship mono-exponential chamber stiffness coefficient (3.0 ± 1.4 vs. 3.5 ± 1.8) (Fig. 3).

Discussion A recent study of the effect of amrinone on relaxation of isolated cardiac muscle yielded inconclusive results.[4] The present study on the intact ventricle demonstrated that amrinone significantly shortens the time course of early relaxation and speeds early ventricular filling, but does not alter the chamber stiffness through the filling phase. Amrinone's mechanism of action (phosphodiesterase inhibition) may explain these different effects on the phases of diastole. By causing vascular smooth muscle dilation as well as increased inotropy, the heart is "unloaded" and ejection is enhanced. The subsequent relaxation and early filling phase can then occur faster. The actual stiffness of the cardiac muscle in diastole, however, need not be improved by afterload reduction. Hence amrinone exerts beneficial effects on diastolic as well as systolic ventricular function which can contribute to improved cardiac performance. Finally, additional uses to which the volume catheter can be put to assess ventricular function are demonstrated.









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