Load Independence of Early Diastolic Filling Parameters in the Anesthetized Canine Model

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To evaluate radionuclide diastolic filling indices during acute pharmacologic changes in ventricular loading, 11 atrially paced dogs underwent simultaneous micromanometer left atrial and left ventricular pressure measurements. During phenylephrine infusion, systolic blood pressure increased from 110 ± 16 (s.d.) to 147 ± 19 mmHg ($p < 0.01$), causing the atrioventricular gradient to increase from 5 ± 2 to 8 ± 5 mmHg ($p < 0.03$) with no change in the time constant of isovolumic relaxation (Tau). Absolute peak filling rate increased from 40 ± 21 to 59 ± 44 kcts/sec ($p < 0.05$), but there was no change in first-half filling fraction. During dobutamine infusion, Tau shortened from 43 ± 13 msec to 33 ± 5 msec ($p < 0.01$) and first-half filling fraction increased from 39% ± 19% to 56% ± 18% ($p < 0.05$), with no change in atrioventricular gradient or absolute peak filling rate. Absolute changes from baseline for the first-half filling fraction were inversely proportional to absolute changes in Tau ($r = -0.76$, $p < 0.05$). We conclude that the left ventricular absolute peak filling rate is a load dependent index of diastolic function. In contrast, the radionuclide first-half filling fraction is independent of loading conditions, but is sensitive to substantial alterations in the rate of left ventricular isovolumic myocardial relaxation.

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As many as one-third of all patients hospitalized with congestive heart failure have normal left ventricular systolic function (*1,2*). These patients may have left ventricular diastolic dysfunction due to hypertensive heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, ischemic heart disease or valvular heart disease. Institution of appropriate therapy may be facilitated by prompt and accurate diagnosis of diastolic impairment.

Many investigators have studied the determinants of left ventricular diastolic function in animal preparations (*3–7*). Results of these studies have differed, in part, as a consequence of the analytic framework employed to examine diastolic ventricular function and, in part, due to differences in experimental design. The majority of these studies have focused on hemodynamic alterations measured during the period of left ventricular isovolumic relaxation. Although this portion of the cardiac cycle is unaffected by changes in either the ability of the left atrium to empty or the diastolic left atrioventricular pressure gradient, it may be affected by changes in loading conditions, rate of inactivation and nonuniformity of ventricular relaxation (*8*). This kind of analysis of isovolumic relaxation is not routinely performed clinically as it requires the use of invasive instrumentation (*9*).

Invasive studies in the anesthetized dog have shown parallel directional responses of the left ventricular rapid filling phase and the isovolumic relaxation phase in response to changes in both loading conditions and inotropic state (*10*). Noninvasive analysis of ventricular filling may improve the diagnosis of diastolic dysfunction. Radionuclide angiography provides a convenient and reproducible tool to define serial changes in the rapid filling phase. Several factors have been shown to affect the measurement of global radionuclide diastolic indices. These factors include heart rate (*11*), aging (*12*), physiological hypertrophy (*13*), hypertensive heart disease (*14*), hypertrophic cardiomyopathy (*15*), coronary artery disease (*16*) and sympathomimetic amines (*17*). Previous investigators have studied the effect of left ventricular end-diastolic pressure, afterload and volume infusions on the peak filling rate (*18,19*). However, there has never been an attempt to critically assess how radionuclide rapid filling phase variables are affected by changes in the left atrial to left ventricular pressure gradient or how the ability of these parameters to detect changes in the rate of left ventricular filling is affected by alterations in loading conditions or contractile state. In addition, many previous noninvasive studies of left ventricular filling failed to hold constant the critical variable heart rate before and during interventions.

The present investigation was designed to test the hypothesis that one or more of the available radionuclide indices of early diastolic filling is unaffected by altered ventricular loading conditions at a constant heart rate. To address this issue, left ventricular radionuclide diastolic filling indices were measured during atrial pacing and simultaneously with accepted invasive measures of left ventricular relaxation during acute pharmacologically altered loading and inotropic states in a canine preparation.

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TABLE 1
Effect of Phenylephrine on Hemodynamics and Radionuclide Indices

	n	Baseline	Phenylephrine	p value
Heart rate (beats/min)	11	134 ± 27	132 ± 24	N.S.
Left ventricular systolic pressure (mmHg)	11	110 ± 16	147 ± 19	<0.01
Left atrial pressure (mmHg)	10	14.12 ± 5.00	22.51 ± 10.04	<0.01
Atrioventricular gradient (mmHg)	10	5.07 ± 2.18	7.77 ± 4.71	<0.03
Tau (msec)	11	41.43 ± 11.43	42.09 ± 9.83	N.S.
dP/dt max (mmHg/sec)	11	1464 ± 392	1633 ± 266	N.S.
dP/dt min (mmHg/sec)	11	−1462 ± 337	−1763 ± 341	<0.01
End-diastolic counts (kcts)	11	7.05 ± 3.46	10.62 ± 5.66	<0.05
End-systolic counts (kcts)	10	4.48 ± 2.97	6.54 ± 4.58	N.S.
Ejection fraction	10	0.46 ± 0.11	0.39 ± 0.23	N.S.
Normalized peak filling rate (E.D.V./Sec)	10	5.78 ± 1.03	5.44 ± 1.73	N.S.
Absolute peak filling rate (kcts/sec)	10	40.48 ± 20.76	58.66 ± 43.94	<0.05
Time to peak filling rate (sec)	10	0.102 ± 0.027	0.107 ± 0.020	N.S.
First-half filling fraction (% of stroke volume)	10	45.5 ± 20.7	47.4 ± 21.8	N.S.

METHODS

Eleven healthy adult mongrel dogs (23.0 ± 1.9 kg) were surgically instrumented for physiological monitoring by methods previously described (*20*). After premedication with morphine sulfate (1.0 mg/kg intravenously), endotracheal intubation was accomplished and anesthesia was maintained throughout the entire experiment with alpha-chloralose (80 mg/kg intravenously). Supplemental anesthesia was given before baseline hemodynamic measurements if possible. The chest was opened in the left fifth intercostal space. The pericardium was opened, the heart was exposed and suspended on a pericardial cradle. Pacing wires were placed on the right atrium. Polyvinyl 16-gauge catheters were implanted in the left atrium and left ventricle, through the left thoracotomy. A solid-state micromanometer pressure transducer (Millar Instruments, Houston, TX) was implanted in the left atrium via the appendange. A solid-state micromanometer pressure transducer with an additional fluid-filled lumen (Millar Instruments, Houston, TX) was inserted into the left ventricular cavity via the apex of the left ventricle.

The solid-state micromanometers were calibrated with a standard mercury manometer prior to implantation. Zero drift of the system was corrected by matching the left atrial and the high-gain left ventricular pressure obtained during a postextrasystolic diastasis to that of the fluid-filled lumen of the left ventricular catheter. The rate of change of the left ventricular pressure with respect to time, dP/dt, was obtained electronically from the micromanometer signal using a resistance capacitance circuit with a linear frequency response to 70 Hz and 3 dB down at 100 Hz. The isovolumic relaxation period was defined as the interval beginning at peak (−)dP/dt and ending 10 mmHg above left ventricular end-diastolic pressure of the following beat. This was done to ensure that mitral valve opening had not occurred. The fall in left ventricular pressure with respect to time allowed the derivation of the isovolumic relaxation constant, Tau, using a monoexponential model for pressure decay (*3*).

The time constant of left ventricular isovolumic relaxation was calculated by the method proposed by Weiss et al. which assumes that the left ventricular pressure declines monoexponentially during the isovolumic relaxation period to zero. Therefore:

$$P(t) = P_0 e^{-t/\tau},$$

where P(t) is the left ventricular pressure at any time t; τ equals the isovolumic relaxation constant Tau; P_0 is the left ventricular pressure at the onset of the relaxation period; and e is the base of the natural logarithm. The natural logarithmic transformation of both sides of the equation yields:

$$\ln P(t) = -1/\tau(t) + \ln P_0.$$

Tau is derived by obtaining the negative of the reciprocal of the slope of ln P(t) versus time (t). This approach to quantification of left ventricular pressure decay has been shown to behave in a directionally similar manner to multiple alternative approaches measuring the time constant (*9*).

The high-fidelity and fluid left ventricular pressures, the high-fidelity left atrial pressure, the first derivative of high-fidelity left ventricular pressure (dP/dt), the aortic pressure and an electrocardiogram were recorded continuously with an eight-channel, forced-ink pen physiological recorder (Gould Instruments, Cleveland, OH). Hemodynamic data were collected at 25 mm/sec paper speed during 5-sec apneic periods that were induced by disconnecting the respirator. Analog signals were digitized with an on-line analog to digital converter (Dual Control Systems, Data Translation, Marlboro, MA) at 5-msec intervals and stored on floppy disks utilizing a microcomputer system (IBM PC AT, Armonk, NY) and software previously developed in our laboratory. The diastolic atrioventricular pressure gradient was defined as the difference between the peak height of the left atrial V-wave and the nadir of the left ventricular pressure (*21*) as obtained from visual inspection of the digitized data from the high-gain left atrial and left ventricular channels. The dogs were paced at a constant atrial rate approximately 20% faster than their baseline heart rate throughout the experiment. There was no statistically significant difference in heart rate before and during each drug intervention (Tables 1, 2, 3).

Radionuclide Angiography

Data Acquisition. Radionuclide angiography was performed by standard methods as previously reported (*22*). The animal's red blood cells were labeled in vivo with 25–30 mCi of ^{99m}Tc. Imaging was performed with a Siemen's LEM portable gamma camera equipped with a general purpose technetium collimator (Siemens Medical Systems, Hoffman Estates, IL). Scintigraphic events were recorded on a Medical Data Systems A^2 or A^3 computer (MEDASYS, Inc., Ann Arbor, MI). The animal's electrocardiogram R-wave, as detected by a Physiocontrol or an American Optical gating device (Reicher-Jung, Buffalo, NY), was employed to sort the scintigraphic data into 28–32 equal usable frames with a mean time per frame of less than 15 msec. Image frames con-

TABLE 2
Effect of Nitroprusside on Hemodynamics and Radionuclide Indices

	n	Baseline	Nitroprusside	p value
Heart rate (beats/min)	11	143 ± 9	152 ± 15	N.S.
Left ventricular systolic pressure (mmHg)	11	116 ± 16	104 ± 12	<0.01
Left atrial pressure (mmHg)	10	14.71 ± 4.18	10.39 ± 2.57	<0.01
Atrioventricular gradient (mmHg)	10	5.39 ± 3.22	5.69 ± 4.46	N.S.
Tau (msec)	11	37.21 ± 9.12	32.65 ± 7.26	<0.02
dP/dt max (mmHg/sec)	11	1641 ± 489	1949 ± 743	<0.03
dP/dt min (mmHg/sec)	11	−1610 ± 397	−1418 ± 408	<0.02
End-diastolic counts (kcts)	11	7.92 ± 3.46	5.65 ± 3.54	<0.01
End-systolic counts (kcts)	10	5.64 ± 2.74	3.59 ± 2.80	<0.01
Ejection fraction	10	0.41 ± 0.15	0.51 ± 0.20	<0.01
Normalized peak filling rate (E.D.V./sec)	10	5.76 ± 0.95	5.79 ± 0.89	N.S.
Absolute peak filling rate (kcts/sec)	10	48.39 ± 15.14	33.24 ± 15.83	<0.01
Time to peak filling rate (sec)	8	0.119 ± 0.023	0.126 ± 0.033	N.S.
First-half filling fraction (% of stroke volume)	10	34.6 ± 17.0	30.7 ± 11.1	N.S.

tained 250,000 scintigraphic events. Diastolic filling data were acquired from a "best septal" left anterior oblique view. The "best septal" image angle was identified from 15-sec to 30-sec images in the computer terminal and was selected to provide optimal separation of the right and left ventricular blood pools. Craniocaudal angulation was added to insure optimal separation of the left atrium and left ventricle.

Data Processing. All data were run through a "last usable frame" program designed to exclude frames that do not contain at least 95% of the mean number of counts present in scintigraphic frames from the initial one-third of the cardiac cycle. However, frame rate variability was minimal as the dogs were electronically paced. A left ventricular time-activity curve (background corrected and normalized to total end-diastolic counts) and left ventricular ejection fraction were calculated by an automatic program (MEDASYS). The left ventricular ejection fraction consists of background-corrected left ventricular stroke counts divided by background-corrected left ventricular end-diastolic counts. In order to eliminate random statistical variation in the individual points on the time-volume curve, the raw data curve was Fourier transformed and a low-pass filter was applied to the resulting coefficients (*22,23*). The filter coefficients were 1.0, 0.853, 0.50 and 0.146 for the first through fourth harmonics, respectively. After filtering, the Fourier coefficients were used to determine the inflection point. Newton's method was used for determination of the peak filling rate (PFR) and the iteration was carried on until the error was ±1/360 times the R-R interval. The inverse Fourier transformation was performed to regenerate the data curve with 64 points on the curve.

The end-systolic and end-diastolic points were identified as the least and greatest values in the curve, respectively. Since this curve was reconstructed from filtered Fourier coefficients, these points were always unambiguous, and noise in the curve did not make it difficult to define them. The time-to-peak filling rate was defined as the time from end-systole to the time of peak diastolic filling. The absolute peak filling rate was derived by multiplying the number of end-diastolic scintigraphic counts by their respective peak filling rates; the normalized peak filling rate was defined in terms of end-diastolic scintigraphic counts per second (*24*). The first-half filling fraction consisted of the percentage of diastolic filling occurring during the first one-half of diastole. Five uninterpretable time activity curves resulting from excessive noise were eliminated from the final analysis.

Experimental Protocol

Hemodynamic recordings were averaged for 10–15 beats at three different times separated by approximately 3 min (once a hemodynamic steady state was established during the control

TABLE 3
Effect of Dobutamine on Hemodynamics and Radionuclide Indices

	n	Baseline	Dobutamine	p value
Heart rate (beats/min)	11	149 ± 14	150 ± 15	N.S.
Left ventricular systolic pressure (mmHg)	11	114 ± 21	146 ± 30	<0.01
Left atrial pressure (mmHg)	8	14.77 ± 4.14	15.24 ± 6.91	N.S.
Atrioventricular gradient (mmHg)	8	5.80 ± 1.59	8.24 ± 4.61	N.S.
Tau (msec)	11	43.07 ± 13.42	33.32 ± 4.93	<0.01
dP/dt max (mmHg/sec)	11	1482 ± 474	2529 ± 627	<0.01
dP/dt min (mmHg/sec)	11	−1509 ± 438	−2205 ± 701	<0.01
End-diastolic counts (kcts)	11	9.85 ± 6.07	8.33 ± 5.12	N.S.
End-systolic counts (kcts)	11	6.88 ± 5.23	3.77 ± 3.25	<0.04
Ejection fraction	8	0.42 ± 0.17	0.59 ± 0.14	<0.01
Normalized peak filling rate (E.D.V./sec)	8	6.37 ± 1.09	6.59 ± 0.62	N.S.
Absolute peak filling rate (kcts/sec)	8	49.83 ± 24.23	47.73 ± 27.83	N.S.
Time to peak filling rate (sec)	8	0.123 ± 0.026	0.103 ± 0.013	N.S.
First-half filling fraction (% of stroke volume)	9	39.3 ± 19.4	56.4 ± 17.6	0.05

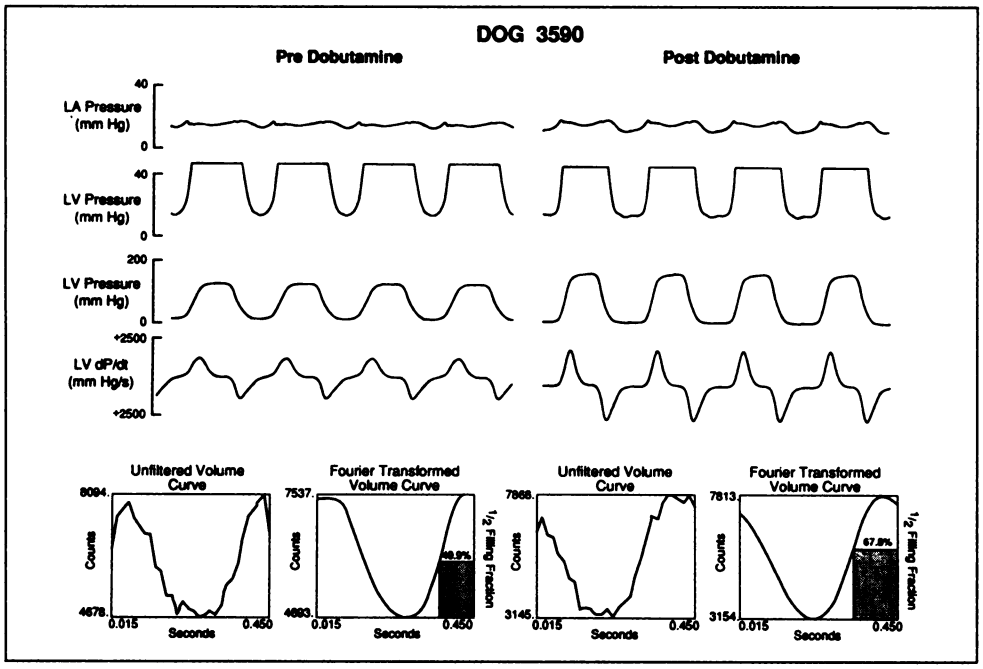

FIGURE 1. Hemodynamic and scintigraphic data from dog 3590 illustrate the effect of dobutamine hydrochloride on left atrial pressure, left ventricular pressure, rate of change of left ventricular pressure with respect to time and the first-half filling fraction (1/2 filling fraction).

interval and after infusion of each pharmacological agent). Each of these stages was followed immediately by a set of radionuclide measurements. Each dog received an infusion of sodium nitroprusside (50 mg/250 ml infused at a rate between 80 and 120 μg/min) until a 10%–20% decrease in left ventricular systolic pressure below baseline values was achieved. After allowing time for hemodynamics to return to baseline, each dog received an infusion of the beta adrenergic inotropic agent dobutamine hydrochloride (5–10 μg/kg/min). Recordings were made when dP/dt reached a new steady state. After dobutamine infusion, time was again allowed to permit all hemodynamic variables to return to baseline. Each dog then received an infusion of the alpha adrenergic vasoconstrictor phenylephrine hydrochloride (20–40 μg/min) until the left ventricular systolic pressure increased by 30%–40% above baseline values. A hemodynamic steady state was defined for each pharmacologic intervention as less than a 10 mmHg variation in left ventricular peak pressures. During the first four experiments, the order of drug administration was varied randomly. After observing that phenylephrine had persistent hemodynamic effects, it was assigned as the last drug intervention but the order of nitroprusside and dobutamine infusion was selected randomly.

Typical hemodynamic and radionuclide data acquired before and again during pharmacologic intervention are shown in Figure 1.

Analysis of Data

All data are presented as the mean ± 1 s.d. Baseline values for each of the hemodynamic variables studied during the three drug interventions were subjected to a one-way repeated measures analysis of variance. If no significant difference among the three baselines was noted, baseline results were compared to those of the respective drug intervention with a two-tailed paired t-test. Least squares linear regression analyses were used to determine how variables relate to each other. A probability of 0.05 or less was required to establish statistical significance.

RESULTS

Phenylephrine Infusion

Table 1 summarizes the effect of systemic arterial vasoconstriction with the alpha agonist phenylephrine on both hemodynamic and radionuclide variables. In response to phenylephrine infusion, an increase of 34% in the left ventricular peak systolic pressure ($p < 0.01$) was accompanied by a 59% increase in left atrial pressure and a 53% increase in the atrioventricular pressure gradient ($p < 0.01$ and $p < 0.03$, respectively). Left ventricular and left atrial size during diastole increased visibly (Fig. 2). Scintigraphic left ventricular end-diastolic counts increased by 51% ($p < 0.05$) and mean absolute peak filling rate increased by 45% ($p < 0.01$) with phenylephrine infusion. End-systolic counts, the time constant of left ventricular relaxation, the normalized peak filling rate, the time to peak filling rate and the first-half filling fraction were not significantly affected by this intervention.

Nitroprusside Infusion

Table 2 summarizes the effect of systemic vasodilation with nitroprusside on both hemodynamic and radionuclide variables. In response to the nitroprusside infusion, a decrease of 10% in left ventricular pressure ($p < 0.01$) was accompanied by a 29% decrease in left atrial pressure ($p < 0.01$), but no significant change in the atrioventricular pressure gradient. Left ventricular diastolic size decreased visibly. The time constant of isovolumic relaxation decreased by 12% ($p < 0.02$); yet, the time to peak filling rate, the normalized peak filling rate and the first-half filling fraction were not affected by nitroprusside. Absolute peak filling rate, end-diastolic and end-systolic scintigraphic counts all

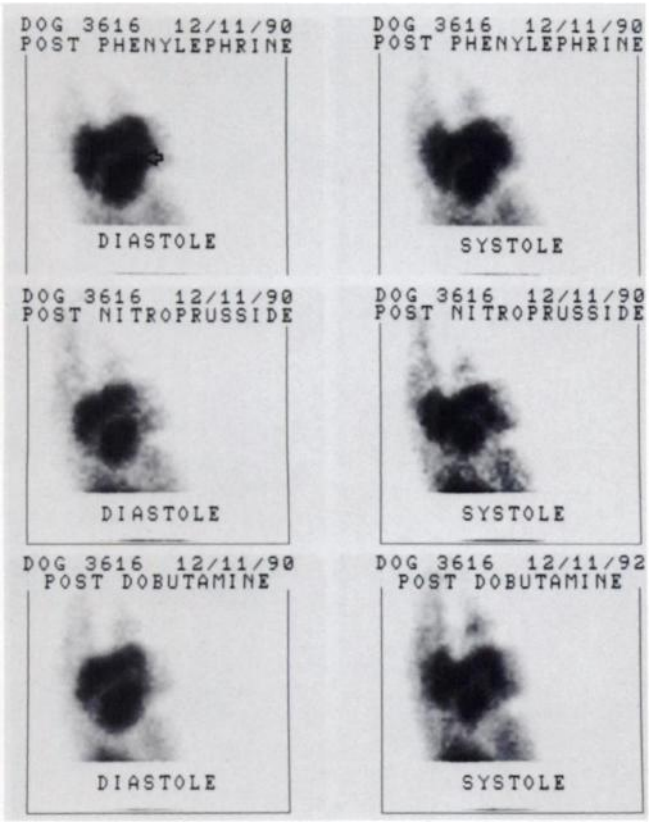

FIGURE 2. "Best septal" radionuclide ventriculographic images in diastole and systole from a single dog are shown with infusion of phenylephrine (top), nitroprusside (middle), and dobutamine (bottom). With phenylephrine, the left ventricle and left atrium (arrow) are relatively dilated in response to elevated left ventricular afterload and preload. Absolute peak filling rate rose by 34% from baseline in response to a 65% increase in atrioventricular gradient. The first-half filling fraction was unchanged from baseline in response to phenylephrine. With nitroprusside infusion, the left ventricular size in diastole is visibly smaller than with phenylephrine and the left atrium is much less prominent. The left atrioventricular gradient fell by 58% with nitroprusside infusion resulting in a 24% decline in absolute peak filling rate. With dobutamine infusion there is a visible increase in left ventricular ejection fraction compared to the phenylephrine images. The atrioventricular gradient remained constant as did the absolute peak filling rate. However, Tau shortened by 11% reflecting improved active relaxation with dobutamine infusion and the first-half filling fraction increased by 15%.

decreased significantly (31%, $p < 0.01$; 29%, $p < 0.001$; and 36%, $p < 0.01$, respectively).

Dobutamine Infusion

Table 3 summarizes the effect of positive inotropic stimulation with the beta adrenergic agonist dobutamine on both hemodynamic and radionuclide variables. An average infusion rate of 10 μg/kg/min produced a 28% increase in left ventricular systolic pressure unaccompanied by a significant change in either left atrial pressure or the atrioventricular pressure gradient. The time constant of left ventricular relaxation decreased by 23% ($p < 0.01$) and left ventricular end-systolic counts decreased by 45% ($p < 0.04$). Importantly, the first-half filling fraction increased by 44% ($p < 0.05$). The time to peak filling rate, the absolute peak filling rate, the normalized peak filling rate and the number of end-diastolic scintigraphic counts did not change significantly.

Effect of the Atrioventricular Pressure Gradient on the Absolute Peak Filling Rate and the Normalized Peak Filling Rate

In the control state and during phenylephrine infusion, the atrioventricular pressure gradient was unrelated to the absolute peak filling rate ($r = 0.43$; p = NS), but was weakly related to the normalized peak filling rate ($r = 0.49$; $p < 0.05$). In response to phenylephrine infusion, there was no relationship between the change from baseline for the atrioventricular pressure gradient and the change from baseline for either absolute peak filling rate or the normalized peak filling rate ($r = 0.46$; p = NS and $r = 0.52$; p = NS, respectively).

Effect of Left Atrial Pressure on the Absolute Peak Filling Rate and Normalized Peak Filling Rate

In the control state and during phenylephrine infusion, the left atrial pressure was linearly related to the absolute peak filling rate ($r = 0.57$; $p < 0.01$, Fig. 3A) but not to the normalized peak filling rate ($r = 0.31$; p = NS). In response to phenylephrine infusion, there was no relationship between the change from baseline for the left atrial pressure and the change from baseline for either the absolute peak filling rate or the normalized peak filling rate ($r = 0.47$; p = NS and $r = 0.15$; p = NS, respectively). Thus, the absolute peak filling rate of the left ventricle was related to single measurements of the left atrial pressure but was not influenced significantly by changes in left atrial pressure induced by phenylephrine infusion.

Relationship Between the Time Constant of Left Ventricular Isovolumic Relaxation and the Absolute and Normalized Peak Filling Rates

During dobutamine infusion, there was no significant relationship between the time constant of left ventricular isovolumic relaxation and either the absolute or the normalized peak filling rate ($r = 0.20$; p = NS and $r = 0.24$, p = NS, respectively). Following dobutamine infusion, there was no correlation between the change from baseline for the time constant of isovolumic relaxation and the change from baseline for either absolute or the normalized peak filling rate ($r = 0.18$; p = NS and $r = 0.37$; p = NS, respectively).

Relation Between the Time Constant of Left Ventricular Isovolumic Relaxation and the First-Half Filling Fraction

In the control state and during dobutamine infusion, there was no linear correlation between the time constant of isovolumic relaxation and the first-half filling fraction ($r = -0.43$; p = NS). Nevertheless, the change in Tau from its baseline value, in response to dobutamine infusion, was inversely proportional to the change in first-half filling fraction ($r = -0.76$; $p < 0.05$, Fig. 3B). The change from

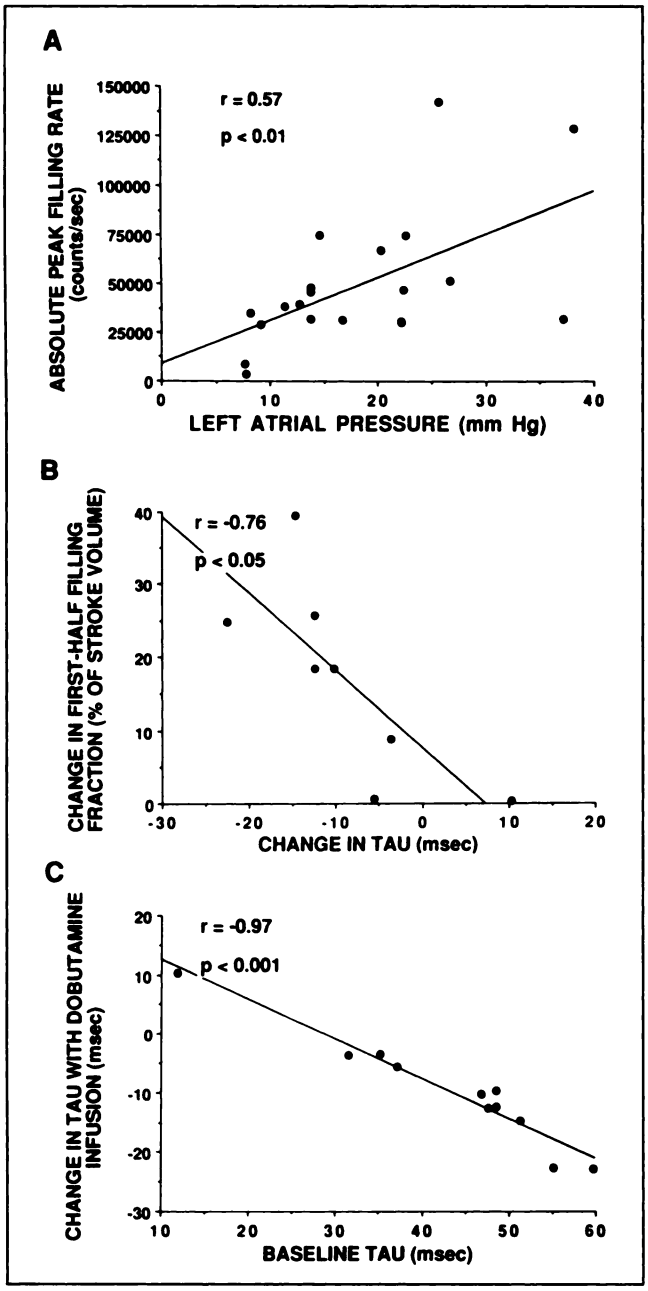

FIGURE 3. (A) Plot of left atrial pressure versus absolute left ventricular peak filling rate demonstrating a direct correlation of individual measurements of the two variables. (B) Plot of the change in Tau from baseline levels to levels observed during dobutamine infusion versus corresponding change in radionuclide first-half filling fraction. A strong inverse relationship was observed between the two variables. (C) Plot of the time constant Tau versus change in Tau from baseline in response to dobutamine infusion. Prolonged baseline values of Tau predicted more extensive shortening of Tau with dobutamine infusion. This shortening of Tau corresponds to augmented first-half filling fraction with dobutamine infusion shown in 3B.

baseline for the time constant of isovolumic relaxation was also inversely proportional to its baseline value ($r = -0.97$; $p < 0.001$, Fig. 3C). During phenylephrine infusion, there was no correlation between the time constant of isovolumic relaxation and the first-half filling fraction nor between the changes from baseline for these two variables ($r = 0.09$, p = NS and $r = 0.16$, p = NS, respectively). During the nitroprusside infusion, there was no correlation between the time constant of isovolumic relaxation and the first-half filling fraction nor between the changes from baseline for these two variables ($r = 0.12$; p = NS, $r = 0.38$; p = NS, respectively).

DISCUSSION

In the present study, left ventricular first-half filling fraction, as measured by radionuclide ventriculography, was unaffected by acute alterations in left ventricular loading conditions but was sensitive to isolated changes in ventricular active relaxation. Thus, in response to the beta adrenergic positive inotropic agent, dobutamine, shortening of the time constant of isovolumic relaxation was significantly related to increased filling of the left ventricle during the first half of diastole as detected by radionuclide imaging. In contrast, the radionuclide first-half filling fraction was not changed by pharmacologic manipulation of left ventricular loading conditions with either the alpha adrenergic vasoconstrictor, phenylephrine or the direct-acting vasodilator, nitroprusside.

Strengths of the Present Study

This study differs importantly from all previous studies of radionuclide assessment of left ventricular diastolic filling because the left atrioventricular pressure gradient was directly measured using micromanometer-tipped catheters in the left atrium and left ventricle. This approach permits separate analysis of the effects of altered left ventricular load and altered left ventricular active relaxation on radionuclide indices of ventricular filling. The present study also differs from most previous radionuclide studies of left ventricular filling because the relative contributions of early and late left ventricular filling were considered by measuring filling fractions. The first-half filling fraction provided a ratio of early to global left ventricular filling which was sensitive to changes in active relaxation of the left ventricle. The absolute peak filling rate of the left ventricle was noted, under baseline conditions and conditions of drug intervention, to be significantly related to left ventricular loading conditions (*23*). Similarly, the radionuclide time to peak filling rate may be altered by factors affecting early diastolic filling but does not encompass changes in early relative to global left ventricular filling. In addition, important confounders of radionuclide left ventricular filling indices were eliminated in the present study by using atrial pacing to maintain a constant heart rate before and during each pharmacologic intervention, and by using each animal as its own control. The anesthetized canine model used in the present study provides the best opportunity for correlative measurement of Tau and the left atrioventricular gradient with radionuclide diastolic filling variables, as the former measurements are highly invasive and both require stable catheter position.

Relevant Aspects of Diastolic Ventricular Filling

The rate of isovolumic active relaxation is primarily determined by the intrinsic rate of detachment of actin-myosin crossbridges and reuptake of calcium into the sarcoplasmic reticulum of the myocyte (*25*). In most studies, augmentation of ventricular preload by volume loading (*3,4,6,7*) or reduction in ventricular preload by inferior vena cava occlusion (*26*) or nitroprusside infusion (*9*) have resulted in no change in active relaxation as measured by the time constant of isovolumic relaxation. In differing experimental models, augmentation of left ventricular afterload by volume loading (*5*) or vasoconstricting drugs has variably affected the time constant of isovolumic relaxation (*9,27*). Early rapid filling of the left ventricle is determined by the rate and segmental sequence of active ventricular relaxation, left atrioventricular gradient, preload, end-systolic dimension and ventricular suction (*28,29*). Subsequent ventricular filling is largely determined by the passive properties of the left ventricular chamber (*30*). The atrial contribution to left ventricular filling represents an interplay between the force, volume and timing of left atrial contraction and the passive properties of the left ventricle. Positive inotropic interventions would be expected to primarily augment early diastolic filling by enhancing active ventricular relaxation and, perhaps, ventricular suction (*28*). This would enhance early relative to global left ventricular filling. Augmented left atrioventricular gradient (*31,32*) frequently increases both early left ventricular filling and late filling related to atrial contraction so that no consistent redistribution of global left ventricular filling to early diastole can be expected. Consequently, although an increase in the left atrioventricular gradient increases left ventricular peak filling rate (*31*), the atrial contribution to filling is also frequently increased so that no net change in first-half filling fraction may be observed.

Comparison to Previous Canine Models

Magorien et al. (*18*) provided the only previous study comparing the relationship of radionuclide diastolic filling measurements and invasive measurement of the time constant of isovolumic relaxation (Tau). Weak correlation ($r = -0.49$) was observed between the radionuclide peak filling rate and Tau. The left atrioventricular gradient, reflecting the net forward driving force from the left atrium, was not measured in that study, but is one of the principal determinants of left ventricular filling (*27,31*).

No previous studies have systematically examined the effects of drug interventions on radionuclide measurements of left ventricular filling in the anesthetized but anatomically normal canine heart. However, previous studies in animals using invasive techniques (*27,31*) and/or Doppler ultrasound have contributed substantially in clarifying the effects of altered ventricular load and inotropic state to left ventricular filling. Cheng et al. (*27*) instrumented 10 normal, conscious dogs with left atrial and left ventricular micromanometer pressure catheters. In response to dobutamine infusion, the time constant of isovolumic relaxation shortened significantly without changing left atrial pressure. Choong et al. (*21*) used Doppler echocardiography and micromanometer catheters in the left atrium and left ventricle to study the influence of altered loading conditions on left ventricular filling in dogs. Doppler peak filling velocity of the left ventricle was related to left atrial pressure and, to a lesser extent, to left ventricular active relaxation and systolic left ventricular pressure. In comparison, Doppler proportions (e.g., first-third velocity-time integral to total diastolic velocity-time integral), which are analogous to radionuclide filling fractions (*33*), correlated with the time constant of isovolumic relaxation and were relatively independent of left atrial pressure. These observations are confirmed in the present study with the measurement of relative left ventricular volumes (instead of Doppler velocities) by radionuclide ventriculography.

Previous Noninvasive Studies of Pharmacologic Effects on Diastole

A few previous studies have examined the response of radionuclide ventriculographic indices of left ventricular filling to pharmacologic intervention in normal human subjects. In normal subjects, pharmacologic alteration of left ventricular preload has led to variable responses of peak filling rate (*34,35*). Numerous studies have documented reduced radionuclide left ventricular filling rate in hypertensive patients compared to normal subjects (*36,37*), however, the effect of pharmacologic elevation of left ventricular afterload in normal human subjects has not been extensively investigated by radionuclide ventriculography. Human radionuclide studies of the response of left ventricular filling to positive inotropic drugs are largely limited to patients with advanced congestive heart failure (*38*) or hypertrophic cardiomyopathy (*17*).

Left ventricular diastolic filling has also been noninvasively characterized in man by Doppler echocardiography. The Doppler approach differs from radionuclide ventriculography in that filling velocity is assessed rather than filling volumes. The Doppler velocity measurements are altered by positioning of the Doppler gate and effects of respiration as well as by the many variables that alter filling rates measured by the volumetric radionuclide method. In human Doppler echocardiographic studies, left ventricular filling indices have varied by relationship to left ventricular end-diastolic pressure (*39,40*), left atrial pressure (*39,41,42*), left ventricular systolic pressure (*39*), the time constant of isovolumic relaxation (*39,41*), heart rate (*42–44*), age (*45,46*) and autonomic blockade (*44,47*). A Doppler index that measures active relaxation of the left ventricle without the influence of these other variables has not been reported.

Study Limitations

In the present study, altered afterload in response to phenylephrine infusion was accomplished without change in inotropic state as measured by peak rate of change of left ventricular pressure (dP/dt max). Conversely, altered inotropic response with dobutamine infusion occurred without

change in the left atrioventricular gradient. Nevertheless, an observation from this study that is not immediately explained is the lack of a statistically significant increase in the radionuclide first-half filling fraction accompanying a 12% shortening of Tau with nitroprusside infusion. Nitroprusside has no direct inotropic effect but likely resulted in reflex sympathetic nerve stimulation. This is suggested by the increase in dP/dt max and ejection fraction which were produced by nitroprusside-induced systemic hypotension. It may be that the first-half filling fraction can detect a 23% shortening of Tau with dobutamine infusion but is not sufficiently sensitive to noninvasively detect the smaller change in Tau noted with nitroprusside.

CONCLUSIONS

In dogs paced at constant heart rate, the radionuclide first-half filling fraction can detect hemodynamically important changes in active relaxation of the left ventricle and this index is independent of acute pharmacologically induced changes in loading conditions. Whether radionuclide ventriculographic indices of diastolic left ventricular filling can detect serial changes in active relaxation in response to inotropic drug treatment in patients maintained at constant heart rate must be determined by future studies.

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