Effects of Alterations in Systolic Pressure on Radionuclide Measurements of Left Ventricular Filling Dynamics

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To determine the effects of steady-state left ventricular systolic pressure alterations on radionuclide measures of left ventricular filling dynamics, we studied 15 normal patients and 17 patients with nonischemic heart disease. Micromanometer left ventricular pressures and computer assisted forward gated radionuclide angiograms were acquired simultaneously. Right atrial pacing maintained heart rates constant during the baseline condition and methoxamine and nitroprusside infusions. Diastolic filling dynamics, peak filling rate and time to peak filling rate were calculated using a three harmonic Fourier analysis of the left ventricular time-activity curves. Left ventricular systolic pressure increased to 165 \pm 25 mmHg with methoxamine (p < 0.001) and decreased to 106 ± 18 mmHg with nitroprusside (p < 0.001) from a baseline value of 133 ± 16 mmHg. Radionuclide left ventricular filling dynamics did not change significantly. Thus, we conclude that radionuclide measurements of left ventricular filling dynamics are not affected by modest, steady-state alterations in left ventricular systolic pressure and can therefore be useful for the assessment of left ventricular diastolic function during interventions which may also affect left ventricular systolic pressure.

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Left ventricular systolic dysfunction has been shown to be an important factor in many disease states (1-6). Radionuclide angiography (7-10) and two-dimensional echocardiography (11, 12) have gained acceptance as clinically useful noninvasive techniques for the evaluation of left ventricular systolic and diastolic function. Indices obtained from the radionuclide time-activity curve during left ventricular filling have been used to identify patients with cardiac pathology, who have abnormal left ventricular diastolic function but preserved systolic function (10, 13-17) and to assess the effects of pharmacologic interventions on diastolic filling events (18-20). However, these indices have demonstrated an inverse relationship with age (21) and systolic arterial pressure (22, 23) and a direct relationship with left ventricular ejection fraction (14, 19, 23), which may limit their clinical utility.

Following pharmacologic interventions, these radionuclide measures of left ventricular diastolic filling may also be affected by concurrent alterations in left ventricular systolic pressure rather than detecting true improvements in left ventricular filling dynamics. Whether the beneficial effects of pharmacologic alterations on radionuclide measures of left ventricular filling dynamics are due to concomitant alterations in left ventricular systolic pressure or improvements in left ventricular diastolic function per se remain unknown. Accordingly, this investigation was undertaken to establish whether pharmacologic alterations in left ventricular systolic pressure at a constant heart rate alters the characterization of left ventricular filling dynamics by radionuclide angiography.

METHODS

Patients

The patient population consisted of 15 patients aged 53 \pm 8 (1 s.d.) yr who underwent cardiac catheterization for evaluation of an atypical chest pain syndrome (normal group) and 17 patients (cardiac pathology group) aged 55 ± 16 yr who underwent cardiac catheterization for evaluation of the severity of their aortic regurgitation (n = 9), mitral regurgitation (n = 2), mixed aortic and mitral regurgitation (n = 2) or cardiomyopathy (n = 2)4). No patient had a prior history of an ischemic event or significant hypertension; and, at cardiac catheterization, all patients were in normal sinus rhythm and had normal coronary arteriograms. These kinds of patients were selected because alterations in left ventricular systolic pressure may have caused regional myocardial ischemia in patients with coronary artery disease and therefore would have introduced an additional variable that would preclude fulfilling the objective of this investigation.

All patients had their medications discontinued for 24 to 48 hr prior to cardiac catheterization.

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Protocol

All patients provided written, informed consent and had been evaluated by right heart catheterization, coronary arteriography and biplane contrast cineventriculography (with or without aortography) prior to commencing the protocol. A right atrial bipolar pacing catheter was placed to maintain heart rate constant (14,24). A micromanometer catheter (SPC-784, Millar instruments, Houston, TX) was positioned, after zero calibration, to measure left ventricular pressure. Following in vivo red blood cell labeling with 30 mCi of 99mTc, gated equilibrium radionuclide angiograms were first obtained under baseline conditions and then during steady-state infusions of methoxamine and nitroprusside, respectively. Steady-state hemodynamics were acquired sequentially after 10-20 min of methoxamine or nitroprusside continuous infusion when left ventricular systolic pressure varied by less than 10 mmHg without intervening baseline hemodynamic measurements. Methoxamine increased left ventricular systolic pressure by approximately 30-40 mmHg, while nitroprusside decreased left ventricular systolic pressure by approximately 20-30 mmHg (see Table 2).

Radionuclide Angiograms

ECG-gated equilibrium radionuclide angiograms were obtained following in vivo labeling of red blood cells with 30 mCi of [^{99m}Tc]pertechnetate (25). Data were acquired using a gamma camera oriented in such a position as to best isolate the left ventricle (typically 45° left anterior oblique). A 10° caudal tilt was used to minimize overlap of the atrium and left ventricle. Acquisition was performed during atrial pacing and encompassed 250-500 cardiac cycles. Data were formatted into consecutive corresponding frames of 30 msec duration. During the midpoint of each acquisition, a 2-ml blood sample was drawn. The blood samples were later counted for 2 min and the time delay between acquisition and counting of the blood samples were recorded. At the end of the protocol, distance measurements were made for attenuation correction. Attenuation-corrected radionuclide left ventricular volumes were calculated frame-by-frame from background-subtracted hand-drawn region of interest left ventricular count data, decay-corrected blood sample counts and attenuation correction as previously validated in this laboratory (26).

Image data were formatted using forward gating (27, 28), and left ventricular time-activity curves were generated using a semi-automated commercial program (Medical Data Systems, Ann Arbor, MI). Left ventricular ejection fraction was calculated using this program. To obtain filling parameters, the left ventricular time-activity curve was filtered and reconstructed from a three harmonic Fourier fit (29) followed by numerical differentiation to determine the peak filling rate (PFR) and the time from end-systole to peak filling rate (TTPFR). Peak filling rate was normalized to units of end-diastolic volumes per second (EDV/sec) (13).

Statistics

All data are presented as the mean ± 1 s.d. Radionuclide left ventricular volumes were indexed to body surface area (BSA). Differences in hemodynamic variables between the normal patients and cardiac pathology patients were determined by nonpaired t-tests. To determine whether differences occurred in hemodynamic variables between the three loading conditions for the total population, normal patients or cardiac pathology patients, an analysis of variance was performed. When a signif-

 TABLE 1

 Baseline Hemodynamic Data

	Normal patients $(n = 15)^*$	Cardiac pathology patients $(n = 17)^*$	р
Heart rate (bpm)	78 ± 9	82 ± 15	ns
LV peak pressure (mmHg)	132 ± 16	133 ± 17	ns
LV end-diastolic pressure (mmHg)	14 ± 5	18 ± 8	ns
LVEDV index (ml/m ²)	55 ± 19	134 ± 126	<0.05
LVESV index (ml/m ²)	21 ± 9	73 ± 85	<0.05
LVEF (%)	63 ± 9	50 ± 17	< 0.05
(+)dP/dt _{max}	1294 ± 273	1212 ± 257	ns
(-)dP/dt _{min}	1789 ± 331	1481 ± 343	<0.05
LV PFR (EDV/sec)	2.57 ± 0.68	1.97 ± 0.60	<0.05
LV PFR index (EDV/sec/m ²)	1.42 ± 0.44	1.05 ± 0.34	<0.05
LV TTPFR (msec)	180 ± 59	171 ± 102	ns

*Mean ± 1 s.d.

LV = left ventricular; EDV = end-diastolic volume; ESV = end-systolic volume.

icant F-statistic was obtained, multiple range tests were used to identify differences. To establish whether there were relationships between PFR and other hemodynamic variables, linear and nonlinear regression analyses were performed. A significant difference or relationship was established by a probability value (p) of 0.05 or less.

RESULTS

Baseline Hemodynamics

The baseline hemodynamic data for normal patients and cardiac pathology patients are shown in Table 1. There was no significant difference in their mean heart rates and left ventricular systolic or end-diastolic pressures. Left ventricular end-diastolic and end-systolic volume indices were, however, larger in the patients with cardiac pathology (p < 0.05 for both). In contrast, the average left ventricular ejection fraction in normal patients was $63\% \pm 9\%$, while it was only $50\% \pm 17\%$ (range 15%-59%) in the patients with cardiac pathology (p < 0.05). To illustrate these differences, left ventricular pressure-volume loops for a representative normal patient and patients with cardiac pathology are shown in Figure 1. Although (+)dP/dt_{max} did not differ between the two patient groups, peak $(-)dP/dt_{min}$ was less in the patients with cardiac pathology than in the normal patients (p < 0.05).

A similar observation was made for the left ventricular PFR (2.57 \pm 0.68 versus 1.97 \pm 0.60 EDV/sec, p < 0.05, Fig. 2), while the TTPFR was not significantly different between the two groups (180 \pm 59 versus 171 \pm 102 msec, Fig. 2). The values reported in the literature as lower



FIGURE 1. Pressure-volume loops for representative patients with and without cardiac pathology.

limits of PFR, defined as 2 s.d.s below the mean value in normal patients, have ranged from 1.3 to 2.2 EDV/sec (9-10, 13, 16-18, 21, 23, 32). For example, our range of normal PFR values was from 1.38 to 3.80 EDV/sec, which, considering our older aged patients (21), is well within an acceptable range of normal.

Relationship Between PFR and Hemodynamic Variables

The PFR correlated with the left ventricular ejection fraction (r = 0.65, p < 0.001, Fig. 3). This relationship was present in both normal patients (r = 0.47, p < 0.05, Fig. 3) and cardiac pathology patients (r = 0.69, p < 0.01, Fig. 3). In addition, there were inverse curvilinear relationships between PFR and both left ventricular end-



FIGURE 2. Baseline radionuclide diastolic filling measurements. The individual and mean ± 1 s.d. for radionuclide PFR (left) and TTPFR (right) are illustrated for normal and cardiac pathology patients. A significant difference in the PFR is noted between these patient groups (p < 0.05).

diastolic and end-systolic volume indices in all patients studied (p < 0.0001 for both), as well as in the cardiac pathology patients (p < 0.0001 for both, Fig. 3). No significant relationship could be demonstrated between PFR and left ventricular volume indices in the normal patients (p > 0.10 for both, Fig. 3). There was also no definable relationship found between PFR and peak (+)dP/dt_{max} (r = 0.10, p > 0.10) or (-)dP/dt_{min} (r = 0.07, p > 0.10).

Effects of Alterations in Left Ventricular Systolic Pressure on Radionuciide Diastolic Filling Parameters

The effects of alterations in left ventricular systolic pressure on radionuclide filling parameters are shown in Table 2. Due to right atrial pacing, heart rate remained unchanged. In contrast, left ventricular systolic and enddiastolic pressures increased during methoxamine infusion and decreased during nitroprusside infusion when compared to baseline conditions (p < 0.01 to p < 0.001). Left ventricular volume indices increased with the methoxamine infusion and decreased with the nitroprusside infusion, particularly end-systolic volume index (p < 0.001), in comparison to baseline conditions. Left ventricular ejection fraction was unchanged by methoxamine infusion, but it was increased by nitroprusside infusion when compared to baseline (p < 0.05). The methoxamine infusion increased $(+)dP/dt_{max}$ (p < 0.01), and the nitroprusside infusion decreased $(-)dP/dt_{min}$ (p < 0.001) when compared to baseline conditions.

Despite these significant changes in left ventricular systolic pressure, there was no significant effect of these alterations in left ventricular systolic pressure on radionuclide left ventricular filling dynamics (Table 2). The lack of effect of altered left ventricular systolic pressure on PFR, either in end-diastolic or stroke volumes per seconds (PFR indexed to BSA) and TTPFR was valid for both normal patients and cardiac pathology patients. This is shown for each individual patient over the full range of loading conditions (Fig. 4). Individual variation in PFR of more than 1 s.d. was seen in only 4 of 30 control patient studies and in two studies of patients with cardiac pathology, suggesting a lack of effect of left ventricular systolic pressure alterations on radionuclide indices of diastolic filling in the majority (>90%) of patients in this investigation.

DISCUSSION

Indices obtained from the radionuclide time-activity curve have been used to assess left ventricular diastoic filling dynamics in normal patients and patients with cardiac pathology at both rest and during exercise (13, 16, 17, 19, 30). The PFR and TTPFR have been shown to be useful measurements to suggest a diagnosis of coronary artery disease in patients who have normal left ventricular ejection fractions and wall motion (15) and to identify abnormal diastolic filling dynamics in patients



FIGURE 3. Relationships between PFR and left ventricular diastolic filling measurements. Individual data points, regression lines, correlation coefficients and probability values are illustrated for baseline, methoxamine and nitroprusside conditions in normal and cardiac pathology patients. (A) The relationship between radionuclide PFR on the ordinate and left ventricular ejection fraction (LVEF) on the abscissa is shown. (B) The relationship between radionuclide PFR on the ordinate and left ventricular end-systolic volume indexed to body surface area (ESVi) on the abscissa is shown. (C) The relationship between radionuclide PFR on the ordinate and left ventricular end-diastolic volume indexed to body surface area (EDVi) on the abscissa is shown.

TABLE 2					
Effects of Alterations in Left Ventricular Pressures on					
Radionuclide Diastolic Filling Parameters*					

	All patients $(n = 32)^{\dagger}$		
	Baseline	Methoxamine	Nitroprusside
Heart rate (bpm)	81 ± 13	80 ± 14	84 ± 13
LV systolic pressure (mmHg)	133 ± 16	165 ± 25 ^{\$}	106 ± 18 [¶]
LV end-diastolic pressure (mmHg)	16 ± 7	23 ± 13 [‡]	10 ± 6 ^{\$}
LVEDV index (ml/m ²)	98 ± 101	111 ± 120 ^{\$}	83 ± 88
LVESV index (ml/m ²)	50 ± 68	59 ± 90 ^{\$}	38 ± 62¶
LVEF (%)	56 ± 15	55 ± 12	63 ± 16 [‡]
(+)dP/dt _{max}	1260 ± 266	1515 ± 402 ^{\$}	1344 ± 295
(-)dP/dt _{min}	1626 ± 367	1793 ± 431	1258 ± 289 [¶]
LV PFR (EDV/sec)	2.26 ± 0.70	2.37 ± 0.69	2.38 ± 0.71
LV PFR index (EDV/sec/m ²)	1.22 ± 0.43	1.27 ± 0.41	1.26 ± 0.38
TTPFR (msec)	176 ± 82	214 ± 93	196 ± 82

LV = left ventricular; EDV = end-diastolic volume; ESV = endsystolic volume.

*Mean \pm standard deviation.

*Normal and cardiac pathology patients.

 $p^{*} < 0.05$; $p^{*} < 0.01$; $p^{*} < 0.00$ as compared to the baseline conditions. All others were not statistically significant.

who have hypertensive heart disease (9) and hypertrophic obstructive cardiomyopathy (18). The PFR has been shown, however, to be inversely related to age (21) and systolic arterial pressure (22, 23) and directly related to left ventricular ejection fraction (14, 19, 23), which may limit its clinical applicability when comparisons are made between different patients.

In contrast, these radionuclide measurements of left ventricular filling dynamics may be particularly useful in assessing the efficacy of medical or interventional therapy in patients with cardiac pathology (18-20,31). For example, Bonow et al. (19) reported that treatment of coronary heart disease with verapamil decreased heart rate, left ventricular pressure and ejection fraction, while the left ventricular PFR increased and the TTPFR decreased. Similarly, in patients with hypertrophic obstructive cardiomyopathy, verapamil improved PFR (18). These authors suggested that verapamil had a primary effect on calcium transients which improved diastolic performance in these patients. Bonow et al. (31) further demonstrated in patients with coronary artery disease and normal left ventricular ejection fraction that the PFR improved after angioplasty. These data all suggest that radionuclide measurements of left ventricular filling dynamics may be useful to assess the efficacy of various treatment modalities on left ventricular diastolic function in patients with cardiac pathology.

Despite these observations, all of these interventions have variable effects on left ventricular loading condition and alterations in left ventricular and arterial systolic pressures may have an effect on radionuclide PFRs as they do on left ventricular ejection fraction. However, no data have been previously presented to document the impact of steady-state left ventricular systolic pressure alterations on radionuclide measurements of left ventricular diastolic filling dynamics.

In order to eliminate the potential confounding effects of ischemia on left ventricular filling dynamics, which may result from changes in systolic arterial load and myocardial perfusion, our study excluded any patient with evidence of coronary artery disease manifest either as a prior myocardial infarction, angina or angiographic coronary artery disease. Therefore, the cardiac pathology population in this investigation, consisted of either aortic regurgitation, mitral regurgitation or nonvalvular cardiomyopathy patients with normal coronary angiograms. However, by limiting our study population to valvular regurgitation and cardiomyopathy patients, a potential confounding feature may have been introduced. For instance, one might assume that the presence of valvular regurgitation would affect the measurement of diastolic filling dynamics by radionuclide angiography, since changes in regurgitant volume would be expected by afterload alterations. This assumption was, surprisingly, not demonstrated (Fig. 4). This may be explained by the significant, but modest, alterations in left ventricular systolic pressure with nitroprusside and methoxamine infusions during our study. Even with these alterations in left ventricular afterload in valvular regurgitation, an effect on PFR, which was standardized to either end-diastolic volume or stroke volume, was not significantly affected, probably because the amount of regurgitant volume increase and decrease, respectively, with the increase and decrease in left ventricular systolic pressure was small, as reflected in the minor changes in left ventricular enddiastolic volume indices. In addition, the average change in end-diastolic volumes between loading conditions, which would be reflective of changes in regurgitant indices in the cardiac pathology patients, did not differ substantially between the control patients and patients with cardiac pathology.

Another surprising and somewhat unexpected finding was the lack of any relationship between PFR and (+)dP/ dt_{max} or $(-)dP/dt_{min}$ in our study population. This lack of relationship may be explained by the fact that our patients had paced heart rates and no ischemia or significant hypertension. It may also represent the following: first, $(-)dP/dt_{min}$ is very sensitive to pressure changes, while PFR may be relatively insensitive to comparable pressure changes; and second, $(+)dP/dt_{max}$ is sensitive to volume changes, while PFR is standardized to volumes. Thus, the strong load dependence of dP/dt measurements could account for these observations.

Regardless of these observations, the data presented in



FIGURE 4. Effects of pressure alterations on radionuclide diastolic filling parameters. The individual radionuclide PFR and TTPFR during the baseline (B) condition and during the methoxamine (M) and nitroprusside (N) infusions are shown for normal patients and cardiac pathology patients. No significant differences are evident.

this investigation clearly demonstrate that modest alterations in left ventricular systolic pressure do not affect radionuclide PFR or TTPFR (Fig. 4). This was apparent for individual patients over the modest range of systolic pressure alterations used in this study. Thus, the absence of an effect of modest alterations in systolic pressures on radionuclide parameters of left ventricular filling dynamics further emphasizes the ability of radionuclide imaging to document clinically useful therapeutic benefits of pharmacologic agents or interventions on left ventricular diastolic function in patients with cardiac pathology. One provision that should be considered is that we had only a few patients with low (<30%) left ventricular ejection fractions in whom modest changes in left ventricular systolic pressure might produce greater changes in PFR. Thus, the data in this study should be interpreted with caution in such patients.

The specific mechanism for an abnormal radionuclide PFR is unclear, but it is most likely multifactorial. Several authors have suggested that the isovolumic relaxation rate and duration may be responsible for abnormal radionuclide filling rates (13, 16-20). Betocchi et al. (30) reported that the radionuclide PFR was related to a prolongation of isovolumic relaxation in patients with hypertrophic obstructive cardiomyopathy, and Yamagichi et al. (32) demonstrated that an abnormal radionuclide PFR

in patients with coronary artery disease was related to asynchronous left ventricular filling.

There are also other possibilities. An inverse relationship between radionuclide PFR and left ventricular enddiastolic pressure suggests that variability in left atrial and left ventricular filling pressures may have a significant impact on PFR. This has been further elucidated by Ishida et al. (33) who demonstrated a correlation between radionuclide PFR and the left atrial:left ventricular pressure difference (r = 0.899, p < 0.001). Although they also found a weaker relationship with isovolumic relaxation rate, the left atrial:left ventricular pressure difference was the major determinant of the radionuclide PFR. Thus, with the radionuclide PFR being related inversely to age, left ventricular ejection fraction and left atrial:left ventricular pressure differences, the utility of this index for detecting abnormal left ventricular filling dynamics between patients may be somewhat limited. In contrast, the absence of any relationship between alterations in left ventricular systolic and end-diastolic pressures and radionuclide PFR in this study suggests that radionuclide measurements of left ventricular filling dynamics in the same patient following an intervention may be useful for identifying beneficial therapeutic effects on left ventricular diastolic function.

In conclusion, modest steady-state alterations in left

ventricular systolic pressure do not affect radionuclide measurements of left ventricular diastolic filling dynamics. Specifically, PFR and TTPFR are unchanged in the majority of patients with or without cardiac pathology. Therefore, these indices may be useful to assess the therapeutic effects of interventions on left ventricular diastolic function in an individual patient, but they may have limited ability to detect differences in left ventricular filling dynamics between patients.

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REFERENCES

- 1. Carroll JD, Hess OM, Hirzel HO, et al. Dynamics of left ventricular filling at rest and during exercise. *Circulation* 1983;68:59-67.
- Hammermeister KE, Walbasse JR. The rate of change of left ventricular volume in man. I. Validation and peak systolic ejection rate in health and disease. *Circulation* 1974;49:729-738.
- Hammermeister KE, Warbasse JR. The rate of change of left ventricular volume in man. II. Diastolic events in health and disease. *Circulation* 1974;49:739-747.
- Ludbrook PA, Byrne JD, Mcknight RC. Influence of right ventricular hemodynamics on left ventricular diastolic pressure-volume relations in man. *Circulation* 1979;59:21-31.
- Shepard RFJ, Zachariah PK, Shub C. Hypertension and left ventricular diastolic function. Mayo Clin Proc 1989;64:1521-1532.
- Weisfeldt ML, Scully HE, Frederiksen J, et al. Hemodynamic determinants of maximum negative dP/dt and periods of diastole. *Am J Physiol* 1974;227:613-621.
- Bianco JA, Makey DG, Laskey WK, et al. Radionuclide left ventricular dV/dt for the assessment of cardiac function in patients with coronary disease. J Nucl Med 1979;20:1-6.
- Bonow RO. Noninvasive evaluation of left ventricular diastolic function by radionuclide angiography: limitations and applications. *Int J Cardiol* 1984;5:659-663.
- Inouye I, Massie B, Loge D, et al. Abnormal left ventricular filling: an early finding in mild to moderate systemic hypertension. Am J Cardiol 1984;53:120-126.
- Lee KJ, Southee AE, Bautovich GJ, et al. Normalised radionuclide measures of left ventricular diastolic function. J Nucl Med 1989;15:123– 127.
- Nishimura RA, Housmans PR, Hatle LK, et al. Assessment of diastolic function of the heart: background and current applications of doppler echocardiography. Part I. Physiologic and pathophysiologic features. *Mayo Clin Proc* 1989;64:71-81.
- Nishimura RA, Abel MD, Hatle LK, et al. Assessment of diastolic function of the heart: background and current applications of doppler echocardiography. Part II. Clinical studies. *Mayo Clin Proc* 1989;64:181-204.
- Bonow RO, Bacharach SL, Green MV, et al. Impaired left ventricular diastolic filling in patients with coronary artery disease: assessment with radionuclide angiography. *Circulation* 1981;64:315-323.
- 14. Mancini GBJ, Slutsky RA, Norris SL, et al. Radionuclide analysis of peak filling rate, filling fraction, and time to peak filling rate: response to supine

bicycle exercise in normal subjects and patients with coronary disease. Am Heart J 1983;51:43-51.

- Miller TR, Goldman KJ, Sampathkuaran KS, et al. Analysis of cardiac diastolic function: application in coronary artery disease. J Nucl Med 1983;24:2-7.
- Polak JF, Kemper AJ, Bianco JA, et al. Resting early peak diastolic filling rate: a sensitive index of myocardial dysfunction in patients with coronary artery disease. J Nucl Med 1982;23:471–478.
- Reduto LA, Wickemeyer WJ, Young JB, et al. Left ventricular diastolic performance at rest and during exercise in patients with coronary artery disease: assessment with first-pass radionuclide angiography. *Circulation* 1981;63:1228-1237.
- Bonow RO, Rosing DR, Bacharach SL, et al. Effects of verapamil on left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy. *Circulation* 1981;64:787–796.
- Bonow RO, Leon MB, Rosing DR, et al. Effects of verapamil and propranolol on left ventricular systolic and diastolic filling in patients with coronary artery disease: radionuclide angiographic studies at rest and during exercise. *Circulation* 1982;65:1337–1350.
- Inouye IK, Massie BM, Loge D, et al. Failure of antihypertensive therapy with diuretic, beta-blocking and calcium channel-blocking drugs to consistently reverse left ventricular diastolic filling abnormalities. Am J Cardiol 1984;53:1583-1587.
- Iskandrian AS, Hakki AH. Age-related changes in left ventricular diastolic performance. Am Heart J 1986;112:75-78.
- Magorien DJ, Shaffer P, Bush C, et al. Hemodynamic correlates for timing intervals, ejection rate and filling rate derived from the radionuclide angiographic volume curve. Am J Cardiol 1984;53:567-571.
- Slutsky RA, Mancini GBJ, Gerber KH, et al. Analysis of ventricular emptying and filling indexes during acute increases in arterial pressure. *Am J Cardiol* 1983;51:468-475.
- 24. Iskandrian AS, Bemis CE, Hakki AH, et al. Ventricular systolic and diastolic impairment during pacing-induced myocardial ischemia in coronary artery disease: simultaneous hemodynamic, electrocardiographic, and radionuclide angiographic evaluation. Am Heart J 1986;112:382-391.
- Thrall JH, Freitas JE, Swanson D, et al. Clinical comparison of cardiac blood pool visualization with technetium-99m red blood cells labeled in vivo and with technetium-99m human serum albumin. J Nucl Med 1978; 19:796-803.
- 26. Starling MR, Dell'Italia LJ, Walsh RA, et al. Accurate estimates of absolute left ventricular volumes from equilibrium radionuclide angiographic count data using a simple geometric attenuation correction. J Am Coll Cardiol 1984;3:789–798.
- Juni JE, Froelich J, McMeekin J, et al. Effects of heart rate variability on scintigraphic measurement of diastolic function. *Circulation* 1983;68:111-296.
- Juni JE, Chen CC. Effects of gating modes on the analysis of left ventricular function in the presence of heart rate variation. J Nucl Med 1988;29: 1272-1278.
- Bacharach SL, Green MV, Vitale D, et al. Optimum Fourier filtering of cardiac data. J Nucl Med 1988;24:1176-1184.
- Betocchi S, Cuocolo A, Pace L, et al. Effects of intravenous verapamil administration on left ventricular diastolic function in systemic hypertension. *Am J Cardiol* 1987;59:624-629.
- Bonow RO, Kent KM, Rosing DR, et al. Improved left ventricular diastolic filling in patients with coronary artery disease after percutaneous transluminal coronary angioplasty. *Circulation* 1982;66:1159-1167.
- 32. Yamagishi T, Ozaki M, Kumada T, et al. Asynchronous left ventricular diastolic filling in patients with isolated disease of the left anterior descending coronary artery: assessment with radionuclide ventriculography. *Circulation* 1984;69:933–942.
- Ishida Y, Meisner JS, Katsuhiko T, et al. Left ventricular filling dynamics: influence of left ventricular relaxation and left atrial pressure. *Circulation* 1986;74:187-196.