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Stress Echocardiography: Abnormal Response of Tissue Doppler–Derived Indices to Dobutamine in the Absence of Obstructive Coronary Artery Disease in Patients with Chronic Renal Failure

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Background: Abnormal tissue Doppler (TD)–derived indices during dobutamine stress echocardiography (DSE) can predict the presence of coronary artery disease (CAD) in patients with normal renal function. These indices include a reduction in annular systolic velocity (S′), a decrease in early diastolic annular velocity (E′), and prolongation of the time to E′. However, the ability of these indices to detect or exclude CAD in patients with chronic renal failure (CRF) is unclear. Objective: To examine the ability of TD-derived indices to detect or exclude the presence of CAD in patients with CRF. Methods: We evaluated a total of 30 patients (13 males, mean age 57 ± 15 years) using both DSE and coronary angiography. This cohort consisted of 12 control patients with normal renal function (mean creatinine 0.5 mg/dL) and 18 patient with CRF (mean creatinine 2.5 mg/dL). At each stage of the DSE, left ventricular (LV) diastolic function was assessed using conventional (peak early (E) and late (A) transmitral, E/A ratio, E-wave deceleration time (DT), and isovolumic relaxation time (IVRT)) and TD-derived indices (lateral annular systolic (S′), early diastolic (E′), and late atrial velocities (A′), time to E′ and E/E′). Results: All 30 patients had a normal DSE based on systolic regional function and a normal coronary angiogram. There was no difference in E, A, E/A, DT or IVRT between the two groups at each stage. Despite normal coronaries, patients with CRF demonstrated lower S′ and E′ velocities at peak stress compared to the control patients (8.0 ± 2.2 cm/sec vs 15.1 ± 2.6, $P < 0.05$ and 6.7 ± 1.6 cm/sec vs 13.3 ± 3.1, $P < 0.05$, respectively). During DSE, the time to E′ at peak stress in CRF patients was also prolonged compared to control (400 ± 44 ms vs 329 ± 51, $P < 0.05$). Patients with CRF also had increased filling pressures (as estimated by E/E′) as compared to controls at peak stress (14.7 ± 5.2 vs 7.4 ± 1.5, $P < 0.05$, respectively). Conclusion: In patients with CRF, a reduction in TD derived indices does not predict the presence of obstructive CAD. (ECHOCARDIOGRAPHY, Volume 24, July 2007)

diastolic dysfunction, stress echocardiography, renal disease

Background

Dobutamine stress echocardiography (DSE) is an accurate and noninvasive technique that is widely used for the detection of underlying coronary artery disease (CAD).[1,2,26] Conventional interpretation of DSE involves the assessment of regional or global systolic function and is dependent on the quality of the images and experience of the observers.[3] In order to quantitatively evaluate the echocardiographic response to stress and, due to the observation that diastolic dysfunction precedes the development of systolic dysfunction during

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ischemia,[4] tissue Doppler–derived indices of systolic and diastolic function have been applied during DSE for the detection of CAD.[5–10] Using tissue Doppler imaging (TDI), a dobutamine-induced reduction in the peak annular velocities in systole and diastole has been demonstrated to identify CAD in patients with normal renal function.[8–10]

In patients with chronic renal failure (CRF), the leading cause of death is CAD and noninvasive screening using DSE is an important aspect of patient selection for potential renal transplantation.[11] In patients with normal renal function, DSE has a sensitivity and specificity of 90% for the detection of obstructive CAD.[12] However, in patients with CRF, the sensitivity and specificity is reduced at 75% and 71%, respectively.[13] Little is known about the response of TD-derived indices in patients with CRF undergoing DSE.

Therefore, the aim of the current study was to examine serial changes in both conventional and TDI-derived indices of systolic and diastolic function in patients with CRF during DSE in whom no evidence of CAD was present on coronary angiography.

Methods

Patient Population

Between 2004 and 2006, 30 patients were prospectively evaluated who underwent both DSE and coronary angiography. This population included 12 patients (5 males, mean age 59 ± 13 years) referred to rule out CAD with normal renal function (Cr $<$ 2.0 mg/dL) and 18 patients (8 males, mean age 55 ± 12 years) with CRF (Cr $>$ 2.0 mg/dL) on hemodialysis referred for prerenal transplant workup. The study protocol was approved by the local institutional review board.

Dobutamine Stress Protocol

Beta-adrenergic blocking agents were withdrawn for the preceding 24 hours prior to the study. Dobutamine was infused at doses of 5, 10, 20, 30, and 40 μg/kg/min for 3 minutes each. Images were analyzed using the standard 16-segment model. A 12-lead electrocardiogram, blood pressure, and two-dimensional(2D) echocardiograms were taken at baseline, at low-dose dobutamine, peak dobutamine, and at recovery. The stress test was terminated when 85% of the maximal predicted heart rate was reached, or earlier if the patient had progressive or severe chest discomfort, serious ventricular arrhythmia, systolic blood pressure $>$240 mm Hg, symptomatic hypotension or systolic blood pressure $<$ 80 mm Hg or intolerable side effects.

Echocardiography

At each stage of the DSE, parasternal and apical views were obtained using a standard echocardiograph (Philips Sonos 7500, Andover, MA, USA) with a multifrequency transducer and tissue Doppler capability. Standard 2D, spectral-Doppler and tissue Doppler imaging were performed at each stage. A single observer (DSJ) blinded to the clinical data, analyzed the echocardiographic images offline.

LV interventricular septal thickness (IVS), posterior wall thickness (PWT), and LV ejection fraction (EF) were determined from 2D images according to established criteria.[14] LV diastolic function was assessed using both conventional and novel diastolic parameters at each stage. Transmitral LV filling velocity at the tips of the mitral valve leaflets was obtained from the apical four-chamber view using pulsed wave Doppler echocardiography. The transmitral left ventricular (LV) filling signal was traced manually and the following variables were obtained: peak early (E) and late (A) transmitral velocities, E/A ratio, and E-wave deceleration time (DT). Isovolumic relaxation time (IVRT) was determined by the time interval between the end of the aortic outflow during systole and the onset of mitral inflow during diastole.

Tissue Doppler–derived indices were recorded at the lateral mitral annulus. These indices included systolic velocities (S'), early diastole (E') velocities, and late diastolic (A') velocities. The time interval from the R-wave on the electrocardiogram to the peak of the E' was also measured. Finally, the dimensionless index of E/E' was calculated.[15]

Coronary Angiography

The absence of CAD was established during routine coronary angiography after DSE. Despite a normal DSE based on systolic function, either a high pretest probability of CAD or a positive nuclear stress test accounted for the performance of a cardiac catheterization in these patients. All lesions occurring in the major coronary artery segments or their proximal branches were visually identified, and an initial qualitative assessment was made. Coronary stenosis was quantitated with edge detection software and a diameter reduction >50% was considered significant.

Statistics

The data are summarized as mean ± SD or number (percentage). Chi-square's or Fisher's exact tests were applied to compare categorical variables. A Student's *t*-test was used to compare parameters between both groups at baseline. Comparisons over time were made using an ANOVA for repeated measurements. If the interaction of time was significant, groups were compared at the same time points using Student's *t*-tests. $P < 0.05$ was considered significant. The Statistical Analysis System 8.01 (SAS Insitute, Cary, NC, USA) was used to perform the analysis.

Results

Baseline Characteristics

The total population included 30 patients (13 males with a mean age of 57 ± 15 years, range 32 to 88 years), who underwent DSE. No patient demonstrated evidence of obstructive CAD on cardiac catheterization. Baseline patient characteristics are shown in Table I. There were no differences in cardiovascular risk factors or 2D echocardiographic parameters between groups.

TABLE I

Clinical and 2D Echocardiographic Findings in All Patients (n = 30)

Characteristics	Control (n = 12)	CRF (n = 18)	P-value
Age, y	59 ± 13	55 ± 12	0.67
Male gender (%)	5 (42)	8 (44)	1.00
Diabetes mellitus (%)	4 (33)	7 (38)	0.95
Hypertension (%)	9 (75)	14 (77)	1.00
Dyslipidemia (%)	4 (33)	5 (28)	0.92
Smoking history (%)	3 (25)	5 (28)	0.90
Baseline Cr (mg/dL)	1.1 ± 0.3	6.4 ± 2.3*	< 0.001
Baseline GFR (ml/min/1.73 m^2)	69 ± 23	10 ± 4*	< 0.001
Left heart dimensions			
IVS (mm)	12 ± 2	12 ± 2	1.00
PWT (mm)	11 ± 2	11 ± 1	0.90
EF (%)	65 ± 9	67 ± 7	0.92

Values are mean ± SD (percentage). CRF = chronic renal failure; IVS = interventricular septal thickness; PWT = posterior wall thickness; EF = ejection fraction. P-values were calculated by the *t*-test for difference in means and the Fisher's exact test for difference in proportions. $^*P < 0.05$ was considered significant.

TABLE II

Hemodynamic Data during DSE For All Patients (n = 30)

		Dobutamine Stress Echo Stage		
Characteristics	Group	Baseline	Peak	Recovery
HR (bpm)	Control	66 ± 14	129 ± 19*	85 ± 11*
	CRF	70 ± 7	134 ± 15*	99 ± 15*
SBP (mmHg)	Control	143 ± 29	163 ± 46	141 ± 15
	CRF	147 ± 28	164 ± 36	135 ± 20
DBP (mmHg)	Control	70 ± 13	71 ± 23	68 ± 10
	CRF	76 ± 11	74 ± 14	70 ± 12

Values are mean ± SD. HR = heart rate; CRF = chronic renal failure; SBP = systolic blood pressure; DBP = diastolic blood pressure. P-values were calculated by repeated-measures ANOVA with baseline adjustment. $^*P < 0.05$ vs. at baseline. $P < 0.05$ vs. control at same time point.

Hemodynamic Data

All patients completed the DSE protocol without complications (maximal dose 35 ± 10 μg/kg/min). Complete hemodynamic data including heart rate and blood pressure at each stage for both groups were available. At baseline, the heart rates were 66 ± 14 and 70 ± 7 beats / min for the control and CRF groups and increased to a maximum of 129 ± 19 (100 ± 14% of maximal predicted heart rate) and 134 ± 15 beats/min (97 ± 9%, of maximal predicted heart rate) respectively, with peak stress. Systolic and diastolic blood pressures for both groups at each stage were similar (Table II).

Conventional Doppler Echocardiographic

No patient had a resting or inducible wall motion abnormality. All patients had normal diastolic function at baseline (Table III). At peak stress, the mitral E and A velocities increased, whereas the E/A ratio, deceleration time, and IVRT decreased in both groups. There was no difference in conventional indices of diastolic function between groups at each stage of the DSE.

Tissue-Doppler-Derived Echocardiographic Data

TDI could be performed in all patients at each stage of the DSE. Figure 1 illustrates examples of lateral S′, E′, and A′ at baseline,

TABLE III

Dobutamine Stress Doppler Echocardiographic Data (n = 30)

		Dobutamine Stress Echo Stage		
Characteristics	Group	Baseline	Peak	Recovery
Mitral E velocity (cm/sec)	Control	79 ± 15	95 ± 15*	76 ± 17
	CRF	86 ± 28	94 ± 29*	86 ± 17
Mitral A velocity (cm/sec)	Control	84 ± 28	120 ± 20*	86 ± 21
	CRF	84 ± 26	111 ± 44*	98 ± 20
E/A ratio	Control	1.00 ± 0.2	0.82 ± 0.2*	0.90 ± 0.1
	CRF	1.07 ± 0.4	0.90 ± 0.3*	0.91 ± 0.3
E deceleration time (ms)	Control	227 ± 37	104 ± 30*	205 ± 30
	CRF	233 ± 68	108 ± 33*	189 ±32
IVRT (ms)	Control	108 ± 11	61 ± 8*	97 ± 11
	CRF	107 ± 10	55 ± 11*	95 ± 11

Values are mean ± SD. CRF = chronic renal failure; IVRT = isovolumic relaxation time. P-values were calculated by repeated-measures ANOVA with baseline adjustment. *P < 0.05 vs. at baseline. P < 0.05 vs. control at same time point.

peak, and recovery DSE stages in a patient with normal renal function and a patient with CRF. In controls, the mean values for S′, E′, and A′ velocities increased during dobutamine stress (Table IV). In CRF patients, the mean values for S′ and E′ decreased at peak stress as compared to both baseline and to the controls (Table IV). Although the time to E′ decreased in both groups at peak stress compared to baseline, the mean value was prolonged in the CRF patients compared to the control group (400 ± 49 ms vs. 329 ± 51 respectively). Finally, left atrial pressure as measured by E/E′ was elevated in the CRF group at peak stress, as compared to the controls where E/E′ remained unchanged.

Discussion

Tissue Doppler imaging is a modification of conventional blood-flow Doppler to image tissue-derived, high amplitude, and low-velocity Doppler signals that has been recently applied during DSE for the quantitative evaluation of both systolic and diastolic function.[5,16] A spectrum of abnormalities including a decrease in annular systolic velocity, decrease in early diastolic annular velocity, and prolongation of time to E′ with stress are associated with ischemia in patients with normal renal function.[9,17,18] In this study, serial evaluation of both conventional and TDI indices during DSE was performed in controls and CRF patients without evidence of obstructive coronary artery disease. As compared to controls, CRF patients had decreased S′ and E′ velocities, longer duration of time to E′ and elevated E/E′ at peak stress. Therefore, systolic and diastolic regional velocities as measured by TDI during DSE are abnormal in patients with renal disease and may not be useful in the detection of CAD.

Conventional Diastolic Parameters during DSE

Many noninvasive approaches have been used to detect diastolic dysfunction and of these, analysis of the transmitral velocity has become the most widely used technique. Transmitral velocity measures changes in global LV function, and as all of the patients in our study demonstrated preserved systolic function with stress, the transmitral Doppler variables of E-wave, A-wave, E/A, DT, and IVRT were not different between both groups at each stage of the DSE. However, in patients with CRF, the E′ decreased at peak stress as compared to the controls. The disparity between the transmitral Doppler indices and E′ may relate to their sensitivity to loading conditions which are altered during DSE. Whereas transmitral Doppler is load-sensitive,[19] mitral annular velocity has been reported to be a relatively load-independent index of LV relaxation and may thus serve as a better marker of diastolic dysfunction during stress.[20]

Doppler Tissue Imaging during DSE

Tissue Doppler–derived indices have been shown to predict the presence of obstructive coronary disease in patients with normal renal

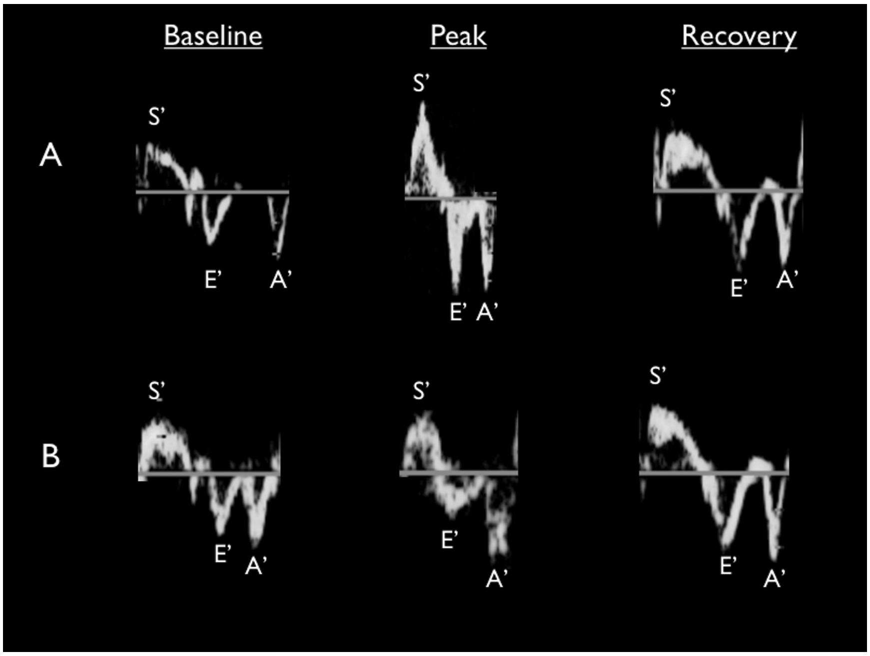

Figure 1. *Representative TDI annular velocities including S′, E′, and A′ at each stage of the DSE in a normal patient (A) and in a patient with chronic renal failure (B). Whereas the S′ and E′ increase at peak stress in the normal patient, the S′ and E′ decrease in the patient with CRF at peak stress.*

function.[9,17,18] Peak systolic (S′) and early diastolic (E′) velocities are decreased in ischemic as compared to nonischemic segments.[17,18] While systolic annular velocities have been shown to be more sensitive than LVEF at detecting early dysfunction,[21] the finding of a low E′ at peak stress has been attributed to ischemia leading to energy depletion (as early diastolic relaxation is energy dependent).[10] Furthermore, the lusitropric effects of dobutamine are more prominent in healthy participants than in patients with ischemia, and thus the time interval from the R-wave on the electrocardiogram to the peak of E′ is prolonged in ischemic regions during DSE.[9]

In our study, however, patients with CRF demonstrated a decrease in S′ and E′ with a prolongation of the time to E′ at peak stress in the setting of normal coronaries. Marwick and colleagues similarly demonstrated that subclinical LV dysfunction may be detected in the absence of significant CAD in patients with renal dysfunction at baseline during DSE.[22] However, unlike in our study, their patients with CRF demonstrated an increased LV thickness and mass at baseline as compared to controls, serial changes in TDI at each DSE stage were not measured, and cardiac catheterization was not performed to rule out significant CAD.[22]

The potential mechanisms for these abnormalities in our study may relate to the subendocardial small vessel disease, increased interstitial fibrosis, and decrease in myocardial relaxation inherent in patients with renal dysfunction that may be exacerbated with stress. CRF patients demonstrate increased homocysteine levels and global endothelial dysfunction, that may lead to disturbances in coronary vascular function independent of significant epicardial coronary artery disease.[27] As longitudinally arranged subendocardial fibers are most vulnerable to subclinical ischemia, LV base-apex contraction may be a sensitive marker of small vessel disease and endothelial dysfunction inherent in the CRF population, that is exacerbated when myocardial oxygen requirements are increased and flow reserve is exhausted, such as in stress echocardiography.[22] It is also possible that the reduction in systolic and early diastolic velocities observed in our CRF patients may in part relate to interstitial fibrosis. Previous studies have demonstrated a strong correlation between reduced systolic Doppler velocity and interstitial fibrosis in patients with regional LV dysfunction who underwent TDI and myocardial biopsy.[28] A combination of small vessel disease, interstitial

TABLE IV

Dobutamine Stress Tissue Doppler Imaging Echocardiographic Data (n = 30)

Characteristics	Group	Dobutamine Stress Echo Stage		
		Baseline	Peak	Recovery
Lateral S′ (cm/sec)	Control	8.7 ± 1.4	15.1 ± 2.6*	9.2 ± 1.2
	CRF	9.0 ± 1.5	8.0 ± 2.2*†	9.4 ± 2.1
Lateral E′ (cm/sec)	Control	10.8 ± 2.0	13.3 ± 3.1*	10.9 ± 3.1
	CRF	11.6 ± 1.6	6.7 ± 1.6*†	10.6 ± 2.7
Lateral A′ (cm/sec)	Control	12.0 ± 2.2	15.1 ± 2.7*	13.7 ± 3.1
	CRF	11.3 ± 1.6	12.6 ± 3.1*†	13.2 ± 2.7
Time to E′ (ms)	Control	508 ± 62	329 ± 51*	492 ± 45
	CRF	501 ± 41	400 ± 44*†	494 ± 36
E/E′	Control	7.6 ± 2.2	7.4 ± 1.5	7.7 ± 2.9
	CRF	7.7 ± 2.8	14.7 ± 5.2*†	8.5 ± 2.5

Values are mean ± SD. CRF = chronic renal failure; IVRT = isovolumic relaxation time. P-values were calculated by repeated-measures ANOVA with baseline adjustment. *$P < 0.05$ vs at baseline. †$P < 0.05$ vs control at same time point.

fibrosis, and diastolic dysfunction exacerbated by stress may account for the decrease in S′ and E′ with prolongation of time to E′ in our CRF population.

The ratio of E/E′ has been demonstrated to be a reliable noninvasive means of predicting an elevated LV diastolic pressure at rest and during exercise.[23,24] While the control subjects maintained and even augmented their diastolic function with stress, the CRF patients exhibited an increase in their E/E′ ratio consistent with a stress-induced increase in LV filling pressures. This inability to augment diastolic function with stress likely reflects an underlying subclinical myocardial structural or metabolic abnormality as described previously. In CRF patients with early myocardial diastolic abnormalities, the assessment of mitral annular velocity during diastole by TDI is useful in evaluating diastolic function, overcoming some of the difficulties inherent in assessing diastolic function using mitral inflow velocities alone.

Study Limitations

Similar to other studies using TDI, this methodology is affected by the quality of 2D images and cardiac translation, rotation or both that is exacerbated by dobutamine. We only measured lateral annular velocities as septal annular velocities may be subjected to the influence of the right ventricle. However, lateral velocities may be affected by both translational effects and beam angle.[25] Tissue velocity data, including strain and strain rate, was not assessed, which may be less influenced by cardiac movement than TDI. Additionally, the current study could potentially be affected by selection bias as patients underwent diagnostic coronary angiography despite normal DSE.

Conclusions

In patients with CRF undergoing DSE, there is a reduction in TDI-derived annular velocities in patients with normal coronary angiograms. This may limit the utility of these indices in the detection of obstructive epicardial coronary disease in patients with CRF.

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