ORIGINAL ARTICLE

Pharmacological vs Exercise Stress Echocardiography for Detection of Cardiac Allograft Vasculopathy

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Abstract

Objective: To test the hypothesis that exercise and dobutamine would provide levels of cardiac stress that are comparable to those achieved in a general stress test population, and to one another, in heart transplant recipients.

Patients and Methods: From February 10, 2015, to December 31, 2017, 81 patients underwent exercise stress (N=45) or dobutamine stress (N=36) echocardiography at a mean ± SD of 11±14 years (range, 1-29 years) after heart transplant. Hemodynamic and inotropic responses were compared between groups, and to a prior test, longitudinally. The primary outcome was peak heart rate (HR) × systolic blood pressure (SBP).

Results: Peak exercise HR × SBP × 10^{-3} was a mean ± SD of 24.9±4.9 mm Hg/min for exercise stress vs 21.2±3.4 mm Hg/min during dobutamine stress ($P<.001$). In 35 patients who underwent a dobutamine stress test followed later by another dobutamine stress test, peak HR × SBP changed by 4.2%±16% ($P=.05$). In 25 patients who underwent a dobutamine stress test followed later by an exercise stress test, peak HR × SBP increased by 12%±23% ($P=.002$ vs serial dobutamine stress tests). Peak exercise HR did not correlate with time since heart transplant, patient age, or graft age. Peak dobutamine HR correlated modestly with patient age ($r^2=0.28$). Inotropic responses were similar in both groups. Overall, patients preferred exercise stress testing to dobutamine stress tests. Dobutamine stress testing was more expensive than exercise stress tests.

Conclusion: Exercise induces a level of cardiac stress that is equal to or greater than dobutamine-induced stress, at lower cost, in heart transplant recipients who express preference for exercise stress testing.

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The prognostic importance of cardiac allograft vasculopathy (CAV) mandates vigilant surveillance in the early years after transplant utilizing invasive coronary angiography with or without intravascular ultrasound.[1] Late after transplant, a patient subset emerges for whom risk/benefit analysis no longer favors frequent invasive surveillance for CAV.

Dobutamine stress echocardiography, which provides limited sensitivity for detection of early mild CAV[2] and moderate sensitivity for more advanced disease, can provide indirect assessment of graft microcirculatory function and short-term prognostic information.[3]

For the broader cohort of patients undergoing stress echocardiography to detect physiologically important discrete epicardial coronary stenoses, the American Society of Echocardiography guidelines strongly favor exercise over dobutamine as the stressor, when feasible.[4] However, chronotropic responses are altered after heart transplant. Uncertainty regarding patients' ability to achieve adequate cardiovascular stress during exercise[5-10] may skew the decision toward pharmacological stress in heart transplant

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recipients. Standard formulae to predict maximum heart rate (HR) (eg, 220 − age) have not been validated in heart transplant recipients. Further, standard age-based formulae do not discriminate between the recipient's age vs chronological graft age.

We report the results of a prospective study designed to test the hypothesis that in heart transplant recipients who prefer to undergo exercise stress testing, exercise can induce a level of stress that is comparable to that of dobutamine stress testing.

PATIENTS AND METHODS

The study was approved by the University of Iowa Institutional Review Board. The primary aim of the study was to determine whether exercise stress echocardiography provides clinical information that is equivalent to or exceeds the information provided by dobutamine stress echocardiography in patients who prefer to exercise. The primary outcome of this study was change in peak HR × systolic blood pressure (SBP) in patients who underwent both tests in succession.

Study Hypotheses and Site Survey

Hypothesis 1: Peak HR × SBP achieved during exercise stress will be equal to or greater than peak HR × SBP achieved during dobutamine stress in patients who have undergone both tests in succession.

Hypothesis 2: Echocardiographic image quality sufficient for a clinical determination is achieved as often with exercise stress as with dobutamine stress.

Hypothesis 3: Resource allocation required to perform dobutamine stress echocardiography exceeds that required to perform exercise stress echocardiography.

Hypothesis 4: A significant number of patients who have an active lifestyle after heart transplant would prefer to walk on a treadmill over dobutamine infusion.

Site survey: We queried 12 US heart transplant centers (see Acknowledgments section), "For heart transplant recipients who undergo noninvasive testing for CAV at your center, what is the preferred modality?"

Study Population

From February 10, 2015, to December 31, 2017, 191 living adult heart transplant recipients were followed up clinically at the University of Iowa in Iowa City. Of those patients, 88 underwent invasive coronary angiography for routine CAV surveillance. The remaining 103 patients were offered participation in the present study, at the discretion of their transplant clinicians, based on the following inclusion criteria: older than 18 years, time from transplant more than 1 year, ability to perform sufficient treadmill exercise, as judged by each patient's clinician, after discussion with the patient. Of the 191 patients, 81 provided informed consent and completed the research protocol.

Study Protocol

Clinical data were obtained from the electronic medical record. Each patient was asked whether he or she preferred exercise stress vs dobutamine stress. Forty-five patients preferred to exercise and 36 patients preferred dobutamine. Previous dobutamine stress echocardiograms were available for comparison for 26 of the 45 patients who preferred exercise stress for the present study and for 35 of the 36 patients who chose dobutamine stress for the present study. No patients had undergone prior exercise stress testing followed by study-driven dobutamine stress testing.

All patients receiving β-adrenergic blockers were asked to withhold those medications for 24 hours before the stress test. Exercise was performed using a symptom-limited modified Bruce protocol.[11] Age-predicted metabolic equivalent was calculated using the Calculate app by QxMD.[12] According to the American Society of Echocardiography standards, echocardiographic images were obtained within 60 seconds after peak exercise. Dobutamine stress echocardiography was performed using standard protocols.[13] Briefly, intravenous dobutamine infusion was initiated at 10 μg/kg per minute and incremented by 10 μg/kg per minute at 3-minute intervals until 85% of the patient's age-adjusted maximum predicted HR (MPHR) was achieved or until the maximum dose of 50 μg/kg per minute was infused for 3 minutes, whichever occurred first. Atropine, 0.5 to 2.0 mg, was administered intravenously when target HR was not achieved during maximal dobutamine infusion. Echocardiographic images were obtained at peak

TABLE 1. Transplant Recipient and Donor Characteristics[a,b]

Recipient and donor characteristics	Exercise		Dobutamine		
	No. (%) of patients[c]	Value (mean ± SD)	No. (%) of patients[c]	Value (mean ± SD)	*P* value
Heart transplant patient age (y)	45	47±19	36	59±16	.004
Sex	45	NA	36	NA	
Male	29 (64.4)	NA	28 (77.8)	NA	.26
Female	16 (35.6)	NA	8 (22.2)	NA	
Race/ethnicity	45	NA	36	NA	
White	38 (84.4)	NA	34 (94.4)	NA	.29
African American	4 (8.9)	NA	2 (5.6)	NA	.93
Hispanic	3 (6.7)	NA	0	NA	.30
BMI (kg/m^2)	45	27±5	36	30±5	.008
Etiology of heart failure	45	NA	36	NA	
Ischemic cardiomyopathy	13 (28.9)	NA	16 (44.4)	NA	.21
Nonischemic cardiomyopathy	20 (44.4)	NA	17 (47.2)	NA	.96
Congenital heart disease	12 (26.7)	NA	3 (8.3)	NA	.06
No. of transplants	45	NA	36	NA	
1	43 (95.6)	NA	34 (94.4)	NA	.92
2	2 (4.4)	NA	2 (5.6)	NA	.92
Time from the last transplant (y)	45	10±7	36	12±6	.09
Donor age (y)					
At time of transplant	39	25±15	29	31±13	.07
At time of test	39	35±13	29	43±13	.02
Donor sex	41	NA	29	NA	
Male	27 (65.9)	NA	19 (65.5)	NA	.79
Female	14 (34.1)	NA	10 (34.5)	NA	.79
Ischemic time (min)	27	194±54	15	189±73	.81
Time from last coronary angiography (y)	45	3±3	33	3±2	.54
Allograft coronary vasculopathy	43	NA	33	NA	
No evidence of disease	35 (81.4)	NA	23 (69.7)	NA	.34
Nonobstructive coronary disease (<50%)	7 (16.3)	NA	10 (30.3)	NA	.22
Obstructive coronary disease	1 (2.3)	NA	0	NA	.78
Allograft rejection[d]	3 (7)		0 (0)		.30
Selected medications	45	NA	36	NA	
Immunosuppression therapy					
Azathioprine	5 (11.1)	NA	5 (13.9)	NA	.95
Cyclosporine	2 (4.4)	NA	5 (13.9)	NA	.23
Mycophenolate	32 (71.1)	NA	22 (61.1)	NA	.48
Prednisone	11 (24.4)	NA	12 (33.3)	NA	.52
Sirolimus	9 (20.0)	NA	4 (11.1)	NA	.51
Tacrolimus	39 (86.7)	NA	29 (80.6)	NA	.67
Aspirin	38 (84.4)	NA	31 (86.1)	NA	.95
Clopidogrel	1 (2.2)	NA	0	NA	.83
β-Blocker	7 (15.6)	NA	6 (16.7)	NA	.86
Calcium channel blocker	14 (31.1)	NA	17 (47.2)	NA	.21
Statin	37 (82.2)	NA	32 (88.9)	NA	.57
Atorvastatin	3 (6.7)	NA	7 (19.4)	NA	.20
Pravastatin	21 (46.7)	NA	17 (47.2)	NA	.82
Rosuvastatin	3 (6.7)	NA	5 (13.9)	NA	.50
Simvastatin	10 (22.2)	NA	3 (8.3)	NA	.16

Continued on next page

TABLE 1. Continued

Recipient and donor characteristics	Exercise No. (%) of patients[c]	Exercise Value (mean ± SD)	Dobutamine No. (%) of patients[c]	Dobutamine Value (mean ± SD)	*P* value
Selected medications, continued					
Ezetimibe	0	NA	2 (5.6)	NA	.33
Fenofibrate	2 (4.4)	NA	1 (2.8)	NA	.72
Gemfibrozil	0	NA	2 (5.6)	NA	.33
Niacin	1 (2.2)	NA	0	NA	.83
Basic laboratory data					
HbA_{1c} (%)	45	5.6±1	36	6.2±1	.02
Creatinine (mg/dL)	45	1.3±0.4	36	1.7±1	.02
GFR (mL/min/1.73 m^2)	45	58±20	36	47±18	.01
LDL (mg/dL)	45	82±27	36	83±38	.92
HDL (mg/dL)	45	55±18	36	48±14	.06

[a]BMI = body mass index; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein cholesterol; ISHLT = International Society for Heart and Lung Transplantation; LDL = low-density lipoprotein cholesterol; NA = not applicable.
[b]SI conversion factors: To convert creatinine values to μmol/L, multiply by 88.4; to convert LDL and HDL values to mmol/L, multiply by 0.0259.
[c]Patients with information available for the characteristic.
[d]Allograft rejection episodes ISHLT grade ≥1R within 12 months before index stress test.

stress. Echocardiographic contrast material (DEFINITY [Lantheus Medical Imaging, Inc], 2-4 mL intravenously) was utilized at the attending echocardiographer's discretion.[14]

Left ventricular ejection fraction (LVEF) was calculated using the biplane method of disks convention. Segmental wall motion was evaluated visually. Stress echocardiography was interpreted as "positive" when at least one of the following was present: 1 mm or greater horizontal ST-segment depression in contiguous electrocardiographic leads induced by stress, stress-induced decrease in LVEF to less than 0.55, or induction by stress of at least one segmental wall motion abnormality. All image sets were later adjudicated by 2 of the authors (M.A.G., R.M.W.). There was agreement between the authors and the original clinical interpretation in 80 of the 81 studies.

After stress echocardiography, each patient was asked 4 survey questions:

- Which type of stress test would you prefer to undergo in the future?
- How many minutes per week have you been exercising within the past 3 months?
- How likely are you to increase your exercise routine within the next year?
- Would you like a prescription for an exercise program?

The primary clinical outcome was death or hospitalization for cardiac indications within 12 months after the index stress echocardiography.

Statistical Analyses

Group data reporting continuous variables are presented as mean ± SD. Comparisons between groups were performed using unpaired *t* tests. Comparisons of past findings with new study findings in the same patients were performed using paired *t* tests. Least squares fit linear regression analysis was used to depict relationships between donor age or recipient age, respectively (independent variables) and peak HR (dependent variable). Proportions of group patients exhibiting a binary characteristic (eg, sex) were compared using *z* testing.[15] The null hypothesis was rejected when the *P* value was .05 or less. Data analysis was performed using *Primer of Biostatistics* statistical software.[15]

The primary outcome of this study was longitudinal change in peak HR × SBP in patients who underwent dobutamine stress testing followed by exercise stress testing. The null hypothesis was that longitudinal performance of equivalent tests in the same patients would produce a change of less than

10% in peak HR × SBP. Before study onset, characteristics of exercise stress were not known for this study group. Thus, we used characteristics of dobutamine stress, where SD/mean for peak HR × SBP = 0.16. We projected[15] that inclusion of 25 patients who underwent dobutamine stress testing followed by exercise stress testing would allow detection of a change of ±10% with 95% confidence at a power of 0.85, using a paired *t* test.

RESULTS

Site Survey

The majority of centers reported stress echocardiography as the preferred noninvasive modality for assessment of CAV, among which dobutamine was the preferred stressor at 5 centers and exercise was preferred at 2 centers (Supplemental Figure 1, available online at http://mcpiqojournal.org).

Baseline Patient Characteristics

Patients who preferred exercise stress were younger, received younger donor hearts, had lower body mass index and hemoglobin A_{1c} level, and had less renal impairment than patients who preferred dobutamine (Table 1). There were no significant differences between groups for sex (*P*=.26) or time since transplant (*P*=.09) or history of transplant rejection (*P*=.30). Race/ethnicity, heart failure etiology, and medication usage are depicted in Table 1.

Cardiac Stressors

Patients who preferred exercise stress walked for a mean ± SD of 12±4 minutes on a modified Bruce protocol, corresponding, on average, to completion of Bruce stage 2 (Table 2). Patients who preferred exercise stress achieved a peak workload of 9±3 metabolic equivalents, which is commensurate with the predicted workload for individuals without cardiac disease.[16]

In patients who preferred dobutamine stress, average peak dose was 32±13 μg/kg per minute (Table 2). Eight patients received injection of atropine, for the purpose of HR

TABLE 2. Stress Test Results[a]

Stress test characteristics	Exercise: No. of patients[b]	Exercise: Value (mean ± SD)	Dobutamine: No. of patients[b]	Dobutamine: Value (mean ± SD)	*P* value
Resting HR (beats/min^{-1})	45	85±11	36	86±11	.64
Resting SBP (mm Hg)	45	129±16	36	133±18	.24
Resting HR × SBP × 10^{-3} (mm Hg/min)	45	11.1±1.8	35	11.4±1.9	.56
Exercise time (min)	45	12±4	NA	NA	
METs achieved	45	9±3	NA	NA	
METs predicted based on recipient's age	45	9±2	NA	NA	
MPHR at peak stress (%)	43	86±12	35	87±8	.60
Peak HR achieved (beats/min^{-1})	43	148±18	35	138±13	.01
Peak SBP (mm Hg)	43	167±24	35	154±23	.01
Peak DBP (mm Hg)	43	80±13	35	77±18	.38
Peak HR × SBP × 10^{-3} (mm Hg/min)	43	24.9±4.9	35	21.2±3.4	<.001
Recovery time (min)	45	9±4	36	10±2	.22
Average dobutamine dose (μg/kg/min)	NA	NA	36	32±13	
Ultrasound contrast required, No. (%)	4/45 (8.9)	NA	12/36 (33.3)	NA	
Wall motion abnormalities, No. (%)	45	NA	36	NA	
Yes	2 (4.4)	NA	1 (2.8)	NA	
No	43 (93.5)	NA	35 (97.2)	NA	

[a]DBP = diastolic blood pressure; HR = heart rate; METs = metabolic equivalents; MPHR = maximum age-predicted heart rate; NA = not applicable; SBP = systolic blood pressure.
[b]Patients with information available for the characteristic.

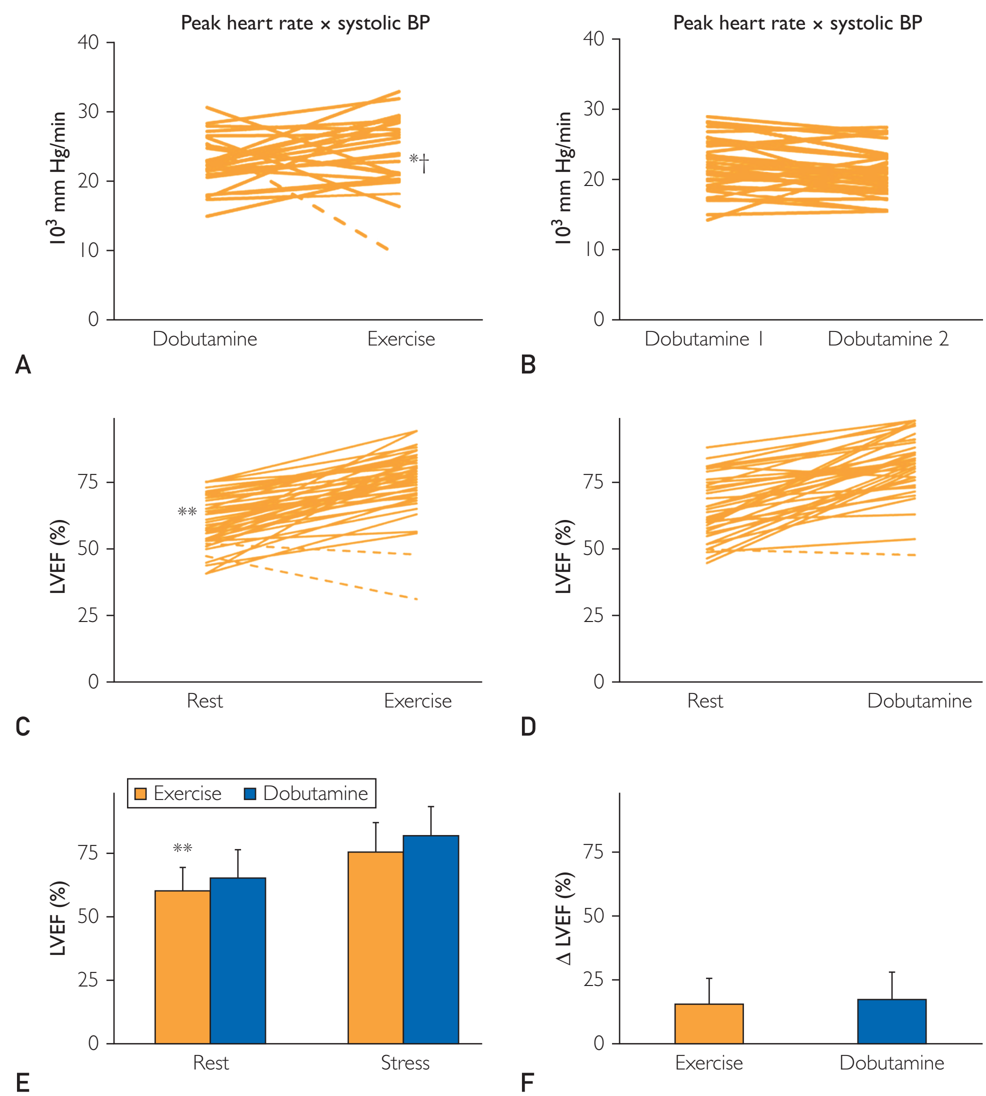

FIGURE 1. Peak cardiac stress and inotropic responses. A, Peak heart rate × systolic blood pressure (BP) for patients who underwent prior dobutamine stress testing, then chose exercise stress testing for the present study (N=25). B, Peak heart rate × systolic BP for patients who underwent prior dobutamine stress testing, then chose dobutamine stress testing for the present study (N=35). C, Individual left ventricular ejection fraction (LVEF) responses to exercise. Dashed lines indicate patients with "positive" stress echocardiograms. D, Individual LVEF responses to dobutamine. E and F, Group LVEF data. **P*=.047 vs dobutamine. †*P*=.002 for longitudinal change with exercise vs longitudinal change for previous dobutamine test (dobutamine 1)/current dobutamine test (dobutamine 2). ***P*=.04 for resting LVEF vs resting LVEF before dobutamine. There was no significant difference in the increase in LVEF induced by exercise vs that induced by dobutamine (*P*=.51).

augmentation (Supplemental Table 1, available online at http://mcpiqojournal.org). Two patients received esmolol for treatment of post–stress test anxiety.

Peak Cardiac Stress

In all 45 patients who preferred exercise stress, mean ± SD resting HR × SBP × 10^{-3} was 11.1±1.8 mm Hg/min and

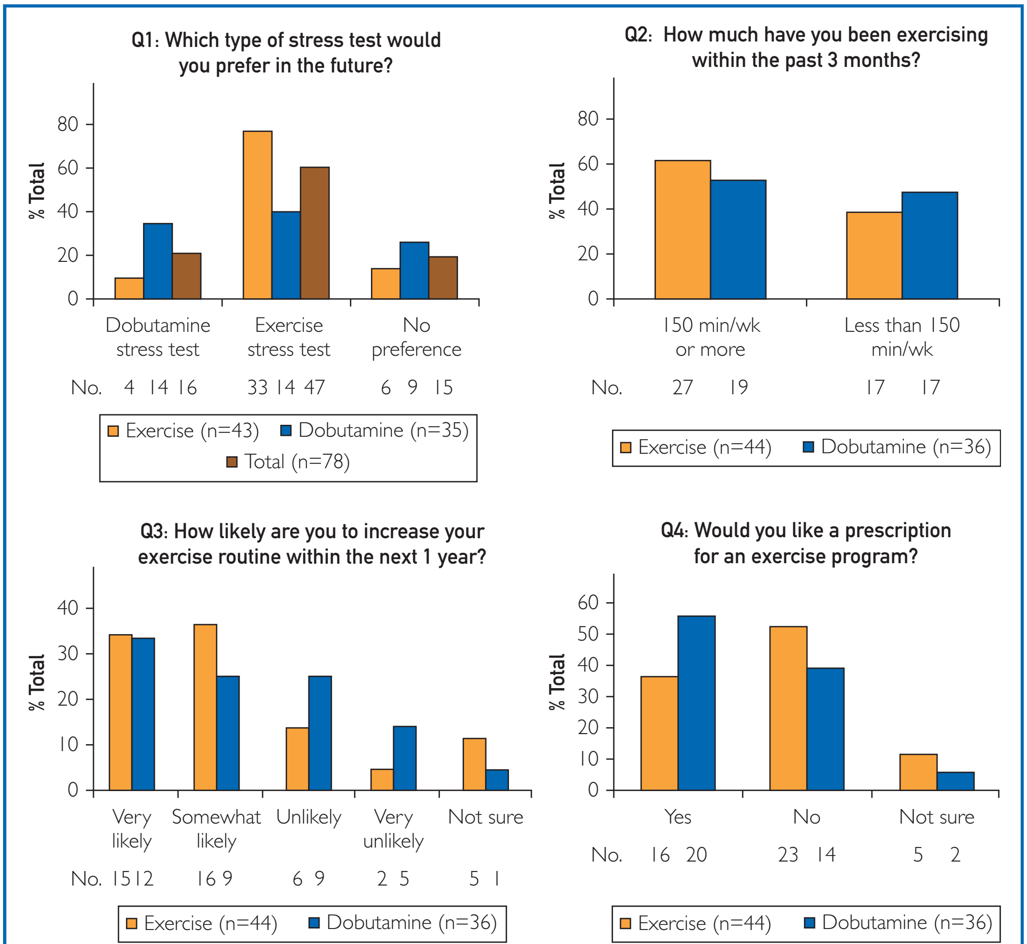

FIGURE 2. Patient survey results. Q = question.

increased to 24.9±4.9 during stress (Table 2). In patients who preferred dobutamine, resting HR × SBP × 10^{-3} was 11.4±1.9 mm Hg/min (P=.56 vs exercise) and increased to 21.2±3.4 mm Hg/min during dobutamine/atropine administration (P<.001 vs exercise). Excluding a patient with a grossly positive study, whose test was stopped before symptom onset because of hypotension, the 25 remaining patients who preferred exercise increased peak HR × SBP by 12%±23% compared with their previous dobutamine stress test (P=.047; 95% CI, 0.1%-19.0%; Figure 1A and B). In 35 patients who preferred dobutamine stress testing, peak HR × SBP decreased by 4%±16% compared with their previous dobutamine stress test (P=.002; 95% CI, 6%-26% for difference in longitudinal trend for exercise stress vs longitudinal trend for dobutamine stress [unpaired t test]).

To understand more completely the factors contributing to peak cardiac stress, we studied HR responses to stress. Resting HR was similar in patients who preferred exercise stress vs dobutamine stress (Table 2). Peak exercise HR achieved was statistically significantly higher by 10 beats/min compared with peak dobutamine HR (P=.01; 95% CI for difference in peak HR, 2-17 beats/min). Individual HR responses are shown in Supplemental Figure 2A and B (available online at http://mcpiqojournal.org). In the 26 patients who underwent prior dobutamine stress echocardiography followed by study exercise echocardiography, 17 achieved greater than 85% MPHR during prior dobutamine stress vs 18 who achieved greater than

85% MPHR during subsequent exercise stress (P=.99).

There was no statistically significant relationship between age and peak exercise HR (Supplemental Figure 2E [P=.09] and G [P=.29]). There was modest correlation between peak dobutamine HR and patient age (r^2=0.28; P<.001), but not donor age (P=.08; Supplemental Figure 2F and H). The slopes of regression lines, which depict the relationship between recipient age and peak HR, were not statistically significantly different for exercise vs dobutamine (P=.35).

Blood Pressure Responses to Stress

Resting SBP was similar for patients who preferred exercise vs dobutamine (Table 2). Exercise produced higher peak SBP than dobutamine (P=.01; Supplemental Figure 2C and D).

Echocardiographic Findings

Image quality was sufficient to reach a diagnostic conclusion in all patients. Contrast medium was utilized in 4 of the 45 exercise patients and in 12 of the 36 dobutamine patients. Resting LVEF was 60%±9% in exercise patients and 65%±1% in dobutamine patients (P=.04; Figure 1C through F). The LVEF increased by 15%±10% after exercise and by 17%±11% at peak dobutamine (P=.51; 95% CI for differences in augmentation of LVEF, −6% to +3%).

The test was interpreted as positive in 3 patients. In one, LVEF decreased from 47% to 32% after exercise. Subsequent angiography revealed flow-limiting discrete stenoses in the left main and right coronary arteries, which were stented. In 2 patients, who had previously documented moderate diffuse CAV not amenable to revascularization, exercise induced a decrease in LVEF to less than 55%. Those patients were managed medically, without subsequent invasive assessment. There were no sustained arrhythmias with either stressor.

Clinical Outcomes

Three patients died of cardiac causes in the 12 months following the index stress echocardiogram, 2 of whom had positive exercise stress echocardiograms (Supplemental Table 2, available online at http://mcpiqojournal.org). No patients in the dobutamine stress group died of cardiac causes in that time frame. An additional 5 patients required hospitalization for cardiac indications in the 12 months following index stress echocardiography (allograft rejection [1], heart failure [1], both [2], hypertensive urgency [1]), none of whom had a positive exercise or dobutamine stress echocardiogram. No patients were hospitalized during this time period for acute coronary syndrome or arrhythmia.

Conversely, exercise echocardiography was positive in only 2 of 45 patients, both of whom died (one each of heart failure and end-stage renal disease). Exercise stress echocardiography was negative in the other 43 patients, 1 of whom died suddenly and 3 who required hospital admission for cardiac reasons in the 12 months following the test (1 each for acute rejection, fluid overload, and elevated blood pressure). Dobutamine stress echocardiography was positive in 2 of 36 patients, both of whom remained alive without hospitalization for cardiac reasons over the ensuing 12 months. Dobutamine stress echocardiography was negative in the other 34/ patients, none of whom died and 2 of whom required hospitalization for cardiac reasons in the 12 months following the index test.

Patient Survey Results

The survey response rate was 96.3% (78 of the 81 patients). After the index stress echocardiogram, 60.3% of patients (47 of 78 respondents) expressed preference for future exercise testing over dobutamine testing (Figure 2). Surprisingly, perhaps, patients who preferred dobutamine stress testing for the index study were approximately evenly divided between future preference for exercise stress and preference for dobutamine stress (34.3% [12 of 35 respondents] vs 40.0% [14]; P=.78). Patients who chose exercise stress tests were approximately equally likely to report exercising 150 min/wk or more compared with patients who chose dobutamine (61.4% [27 of 44 respondents] vs 52.8% [19 of 36 respondents]; P=.62). Patients who preferred exercise tests and patients who preferred dobutamine tests were approximately equally likely to forecast an increase in exercise in the coming year (P=.39) and a desire for an exercise prescription (P=.14).

Resource Allocation

For study purposes, allocation of time for a cardiologist, sonographer, and electrocardiography technologist were considered to be approximately equivalent for exercise stress vs dobutamine stress (Supplemental Table 1). The presence of a registered nurse was required for dobutamine stress tests. Intravenous access was required in 8.9% of exercise studies (4 of 45) and in all of the dobutamine studies. Additional costs for saline infusion, dobutamine, atropine, and esmolol were prorated for frequency of use. On average, additional costs for dobutamine stress totaled $501 per study.

DISCUSSION

The most important finding of this study is that in heart transplant recipients who are referred for noninvasive testing for CAV and who prefer to exercise, treadmill exercise produces levels of cardiac stress that are equal to or greater than levels of cardiac stress achieved during dobutamine/atropine stress testing. We also found that most patients who exercise 150 min/wk or more and who are offered the choice prefer exercise stress over dobutamine stress. Resource utilization is lower for exercise stress testing than for dobutamine stress testing.

Total Cardiac Stress

We found that exercise produced higher peak SBP, higher peak HR, and thus higher peak HR × SBP than dobutamine. The findings are not wholly explained by patient selection bias because the trends held for patients who underwent both tests in succession.

HR Responses to Stress

Surprisingly, perhaps, we found no statistically significant relationship between patient age and peak exercise HR (P=.09) and only a modest correlation with peak dobutamine HR (r^2=0.28; P<.001). The findings suggest that standard formulae for estimating maximum HR (220 − age) are not highly predictive for transplant recipients when based on either recipient age or chronological age of the donor heart. Age of the donor heart, which would not influence the decision to end a dobutamine stress study, was not statistically related to peak HR during pharmacological stress (P=.08).

Patient Preferences and Resource Utilization

We found that most patients, including many who preferred dobutamine stress for this study, would prefer exercise stress over dobutamine stress for future evaluations. In concert with other findings of our study, including lower cost for exercise stress, we believe that consideration of patient preference is warranted.

Study Limitations

Our survey of clinical sites was not designed to be exhaustive or even necessarily representative. Rather, the survey was intended to document the diversity of preferences for noninvasive testing and that preference for exercise vs pharmacological stress can differ between institutions.

This study was prospective but not randomized. Study patients, all of whom were deemed able to exercise, were offered the choice of exercise stress or dobutamine stress, resulting in important differences between groups, including recipient age. Thus, the primary outcome, with respect to level of cardiac stress, was specified as the change in peak HR × SBP in patients who preferred exercise stress testing and who had previously undergone dobutamine stress testing. That strategy facilitates comparison of the 2 stressors while minimizing the contribution of confounding variables. Comparisons between outcomes of exercise vs dobutamine performed contemporaneously in different study patients are provided for context, acknowledging similarities and differences in patient characteristics between the 2 groups. Thus, our findings would not support the conclusion that all transplant recipients who are referred for stress echocardiography should perform exercise stress tests. Rather, we conclude that exercise is an advantageous stressor for heart transplant receipients who express that preference.

Our finding that patients who chose dobutamine stress testing were more likely to require ultrasound-enhancing agents in order to achieve acceptable image quality almost certainly reflects selection bias. Diagnostic accuracy (vs invasive angiography and intravascular ultrasonography) could not be quantified because contemporary invasive studies were not available for most patients. The incidence of positive studies was too low to infer prognostic power, a finding that is common among patients referred for noninvasive surveillance for CAV.[2]

CONCLUSION

Together, our findings indicate that exercise provides levels of cardiac stress and image quality that are equal to or superior to dobutamine-induced stress in heart transplant recipients who are referred for noninvasive CAV surveillance and who express preference for exercise testing. Standard formulae for estimating maximum HR (220 − age) are not highly predictive for transplant recipients when based on either recipient age or the chronological age of the donor heart. A substantial number of heart transplant recipients prefer exercise stress to dobutamine stress. Exercise stress costs less than dobutamine stress.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CAV** = cardiac allograft vasculopathy; **HR** = heart rate; **LVEF** = left ventricular ejection fraction; **MPHR** = maximum predicted HR; **SBP** = systolic blood pressure

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