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RESEARCH

Dobutamine stress echocardiography after cardiac transplantation: implications of donor–recipient age difference

Patrick H Gibson BMBCh MD, Fernando Riesgo MD[1], Jonathan B Choy MD[1], Daniel H Kim MD[1] and Harald Becher MD[1]

Royal Infirmary of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SA, UK
[1]Mazankowski Alberta Heart Institute, University of Alberta Hospital, Edmonton, Alberta, Canada

Correspondence should be addressed to P H Gibson
Email
Patrick.gibson@nhslothian.scot.nhs.uk

Abstract

Dobutamine stress echocardiography (DSE) is widely used during follow-up after cardiac transplant for the diagnosis of allograft vasculopathy. We investigated the effect of donor–recipient age difference on the ability to reach target heart rate (HR) during DSE. All cardiac transplant patients who were undergoing DSE over a 3-year period in a single institution were reviewed. Target HR was specified as 85%×(220 – patient age). Further patient and donor demographics were obtained from the local transplant database. 61 patients (45 male, 55±12 years) were stressed with a median dose of 40 mcg/kg per min dobutamine. Only 37 patients (61%) achieved target HR. Donor hearts were mostly younger (mean 41±14 years, $P<0.001$), with only 11 patients (18%) having donors who were older than they were. Patients with older donors required higher doses of dobutamine (median 50 vs 30 mcg/kg per min, $P<0.001$) but achieved a lower percentage target HR (mean 93% vs 101%, $P=0.003$) than those with younger donors did. Patients with older donors were less likely to achieve target HR (18% vs 67%, $P=0.003$). In conclusion, donor–recipient age difference affects the likelihood of achieving target HR and should be considered when a patient is consistently unable to achieve 'adequate' stress according to the patient's age.

Key Words
- age
- target heart rate
- dobutamine stress echo
- DSE
- cardiac transplant

Introduction

Dobutamine stress echocardiography (DSE) is commonly performed during follow-up after cardiac transplantation as part of surveillance for the diagnosis of cardiac allograft vasculopathy (CAV). Previous studies have demonstrated the sensitivity of DSE to be sufficient to reduce the frequency of invasive investigation by coronary angiography or intravascular ultrasound (IVUS) in patients with a normal test (1, 2, 3, 4). However, the sensitivity of DSE in an individual depends on the patient being adequately stressed to exclude prognostically significant subclinical disease. The adequacy of dobutamine stress is usually determined according to the maximum heart rate (HR) achieved, with a pre-specified target that is 85% of the maximum predicted according to the patient's age (5).

However, the factors that influence HR response in the post-transplant population may be complicated compared with patients undergoing routine DSE for the diagnosis of coronary artery disease. As a result of the surgical denervation of the transplanted heart, some patients may reach their target HR with relatively low doses of

dobutamine. In others, target HRs may be difficult to achieve despite maximum doses, and the additional use of atropine in these instances has been found to be of limited value (6, 7). Furthermore, although the target HR is usually determined by the patient's age, it is conceivable that chronotropic response to dobutamine depends also on the age of the donor heart. If there is a significant mismatch between the recipient and donor age, this may have implications for the level of stress required. For example, an older patient that receives a young donor heart may be inadequately stressed for confident exclusion of CAV if the target HR is too low according to the patient's age. Conversely, more aggressive stress in a younger patient to achieve a higher target HR may be inappropriate if the donor heart is significantly older. The present study aimed to assess the effect of patient–donor age difference on the ability to reach target HR during DSE.

Methods

Study population

In a retrospective analysis, patients in the Alberta Heart Transplant Program who were being followed routinely with DSE during a 3-year period were reviewed. Repeat investigations were not included in the analysis. Relevant patient demographic data, including the age and sex of the donor heart, was acquired from the patient chart. Data regarding stress and echocardiographic variables were obtained from the local echocardiographic database. The study protocol was reviewed and approved by the Health Research Ethics Board at the University of Alberta (ID no. Pro00039405).

Dobutamine stress

Rate-control medication was not routinely discontinued before stress echocardiography. i.v. dobutamine was infused at an initial dose of 5–10 mcg/kg per min and increased every 3–5 min to a maximum dose of 50 mcg/kg per min. i.v. atropine was administered in the later stages at the discretion of the supervising physician in divided doses (0.3–0.6 mg) up to a maximum of 1.2 mg. The target HR was pre-specified at 85% of the maximal predicted HR, which was calculated as 220 − patient age. HR reserve (HRR) was calculated as (peak − resting HR)/(220 − age − resting HR). Dobutamine was discontinued when any of the following criteria were reached: i) target HR; ii) obvious stress-induced wall motion abnormality; iii) significant hypertension (blood pressure of >240/120 mmHg); iv) severe angina; or v) patient request because of intolerance of side effects. i.v. metoprolol (2.5–5 mg) was administered when necessary to reverse the side effects of dobutamine.

Statistical analysis

Continuous variables are reported as means and S.D. or, where skewed, as medians and interquartile ranges (IQR). Groups of patients were compared using Student's t tests, and Mann–Whitney U tests were used for non-normally distributed data. Categorical data were analysed using Pearson's χ^2 tests. Spearman's ρ was used to assess the relationship between resting HR and patient and donor age. Patients in tertiles of (target – maximum) HR were compared using the χ^2 test for trend and the Jonckheere–Terpstra test. A P value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Study population

Sixty-one patients (44 male, 17 female, median age 57 years) underwent stress echocardiography at a median of 5.3 years (IQR 3.1–6.9 years) post-transplant. All of the patients were in sinus rhythm, and none had an implanted pacemaker or defibrillator device. All of the patients were taking standard immunosuppressive therapy, including mycophenolate plus either cyclosporine or tacrolimus in 90% of the cases. Sixteen patients (26%) had a previous diagnosis of rejection (nine occurring within 6 months of transplant), and 22 patients (36%) were taking oral corticosteroids at time of DSE. Fourteen patients (23%) had an existing diagnosis of CAV on coronary angiography at a median of 11 months post-transplant, as per the International Society of Heart Lung Transplantation (ISHLT) CAV Grading (4).

Stress echocardiography

Only 37 patients (61%) achieved their target HR, with 54 patients (89%) achieving at least 90% of the target. The median dobutamine dose was 40 mcg/kg per min. Characteristics of patients who did and did not reach their target HR are given in Table 1. Two tests were discontinued early because of side effects of dobutamine (headache and nausea), but there were no significant complications. The prevalence of stress-induced ischaemia

Table 1 Patient demographics and comparison of patients who did or did not reach target heart rate.

	Achieved target heart rate			
	Total ($n=61$)	Yes ($n=37$)	No ($n=24$)	*P* value
Male sex	44 (72%)	26 (70%)	18 (75%)	0.69
Donor male sex	43 (71%)	28 (76%)	15 (63%)	0.27
Diabetes	21 (34%)	12 (32%)	9 (38%)	0.68
Hypertension	56 (92%)	33 (89%)	23 (96%)	0.36
Body mass index (kg/m^2)	28.5±5.5	28.4±5.1	28.7±6.2	0.83
Time since transplant (years)	5.3 (3.1–6.9)	5.3 (3.3–6.3)	5.5 (3.0–7.0)	0.88
Documented CAV	14 (23%)	8 (22%)	6 (25%)	0.76
Previous rejection	16 (26%)	8 (22%)	8 (33%)	0.31
Rate-limiting medication	34 (56%)	18 (49%)	16 (67%)	0.17
Atropine use	12 (20%)	5 (14%)	7 (30%)	0.13
Patient age at DSE	57 (49–65)	60 (53–66)	54 (46–61)	0.06
Donor age at DSE	40 (29–53)	39 (28–52)	46 (29–58)	0.28
Patient age – donor age	15±17	19±15	8±18	0.02
Patient younger than donor	10 (17%)	2 (6%)	8 (33%)	0.005
Target HR	139 (132–145)	136 (131–142)	141 (135–148)	0.07
Percent target HR achieved (%)	101 (96–103)	103 (101–107)	95 (88–98)	<0.001
Resting heart rate	84±12	86±13	81±10	0.14
Maximum heart rate	139±13	143±9	132±14	0.001
Maximum resting HR	55±14	58±14	51±15	0.06
Heart rate reserve[a] (%)	71 (65–76)	75 (71–78)	60 (51–67)	<0.001
Peak double product	21 409±4558	22 297±4432	20 042±4498	0.06

CAV, cardiac allograft vasculopathy; HR, heart rate; DSE, dobutamine stress echocardiogram.
[a]Calculated as (peak HR − HR at rest)/(220 − age − HR at rest) × 100.

was low – one patient developed a new wall motion abnormality in the right coronary territory and a further four demonstrated nonspecific findings (involving one to two myocardial segments only).

Patient–donor age difference

Transplant patients were generally older than their donor hearts (median 57 vs 40 years, $P<0.001$), with only ten patients (16%) having donors older than they were. The distribution of the absolute age difference is provided in Fig. 1. Two patients were the same age as their donors. Patients with older donors were less likely to achieve their target HR than those with younger donors (20 vs 67%, $P=0.005$). Accordingly, patients with older donors received higher doses of dobutamine (median 50 vs 30 mcg/kg per min, $P<0.001$), but they achieved a lower percentage target HR (mean 93 vs 101%, $P=0.003$) than those with younger donors. If target HR is considered by donor age (i.e., 85% of 220 − *donor* age at the time of DSE), only 11 patients achieved this level of stress; this was more common in patients with younger donors (50 vs 8%, $P=0.001$). Resting HR was modestly correlated with donor age ($\rho=-0.41$, $P=0.001$), but there was no correlation between resting HR and patient age ($\rho=-0.02$, $P=0.85$).

The effect of the patient–donor age difference was further analysed according to the difference between peak and target HR in order to assess the groups of patients who attained their target HR with relative ease as compared to

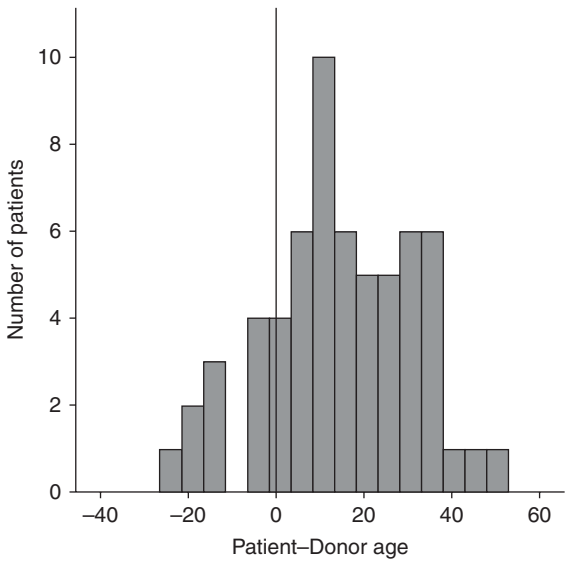

Figure 1
Distribution of patient age – donor age ($n=61$). The mean age difference is 15±17 years.

those who did not attain their target. This was performed by dividing the cohort of patients into tertiles of (maximum – target) HR (Table 2).

All of the patients in tertile 3 achieved their target HR compared to none in tertile 1, and required much lower doses of dobutamine (median 25 vs 50 mcg/kg per min, $P<0.001$). Patients who achieved target HR easily were more senior than their donors (tertiles 3 vs 1: mean age difference +21 vs +6 years, $P=0.023$). This is reflected in a trend toward older patients in patients in tertile 3 (61 vs 53 years, $P=0.083$) with younger donor hearts (median 36 vs 46 years, $P=0.072$).

Discussion

The main finding of the present study is that recipient–donor age difference may be a significant factor that influences the ability of cardiac transplant patients to achieve their target HR during DSE. Even before stress, resting HR was (modestly) related to donor, but not patient, age. Older patients with younger hearts and a larger age difference achieved their target readily with relatively short stress. However, a significant proportion of the study population did not achieve their target HR despite high doses of dobutamine. These patients demonstrated a smaller age difference and tended to be younger but with older donor hearts.

There have been relatively few studies that assessed the utility of DSE in patients with cardiac transplant as compared with the non-transplant population. However, comparable studies indicated the sensitivity and specificity to be in the region of 70–80% for the detection coronary stenosis (2, 3), which was similar to the findings of a meta-analysis in non-transplant patients (8). Likewise, DSE has been shown to provide prognostic information in the transplant population, including the need for revascularisation and risk of myocardial infarction and death, although the number of events was relatively small (1, 3).

There is limited prior data regarding the degree of recipient–donor age difference in heart transplant populations that are undergoing DSE. Two previous studies documented a similar mismatch to the present cohort, with recipients being older than donors by a mean of around 20 years (1, 2). However, there have been no previous reports regarding the implications of this on the maximum HR or on the ability to achieve target HR.

Given the extent of the age difference observed, the target HR should theoretically be achieved easily in most cases and greater chronotropy should be expected of younger hearts. The overall chronotropic response that was noted in the present population was therefore surprising, with only 61% of patients achieving their target HR. Previous studies of transplant patients that were undergoing DSE have reported rates from 72 to 94% reaching target with variable use of atropine (2, 3, 6, 7, 9). In the present study, 89% of the population came within 90% of the target; 17 patients who achieved between 90

Table 2 Comparison of patients by tertile of (maximum – target) heart rate.

	Tertile 1	Tertile 2	Tertile 3	*P* value for trend
	n=20 ('poorer' response)	*n*=21	*n*=20 ('better' response)	
Maximum – target HR	−13±11	+1±2	+10±6	<0.001
Time since transplant (years)	5.5 (3.1–6.8)	5.0 (3.0–6.0)	5.5 (4.4–7.2)	0.62
Diabetes	7 (35%)	7 (33%)	7 (35%)	1.00
Rate-limiting medication	13 (65%)	11 (52%)	10 (50%)	0.34
Documented CAV	6 (30%)	4 (19%)	4 (20%)	0.47
Previous rejection	7 (35%)	5 (24%)	4 (20%)	0.29
Maximum dobutamine dose (mcg/kg per min)	50 (40–50)	40 (30–50)	25 (20–40)	<0.001
Patient age	50 (46–61)	60 (53–66)	61 (53–67)	0.08
Donor age	46 (32–59)	38 (31–52)	36 (24–50)	0.07
Patient–donor age	6±19	17±14	21±15	0.02
Patient older than donor	12 (60%)	18 (90%)	19 (100%)	0.002
Resting HR	80±11	80±10	92±13	0.004
Target HR	142 (136–148)	136 (131–142)	136 (130–142)	0.09
Target HR achieved	0 (0%)	17 (81%)	20 (100%)	<0.001
Maximum – Resting HR	51±15	59±13	56±15	0.21
Heart rate reserve[a] (%)	59 (49–67)	71 (67–74)	78 (75–82)	<0.001

CAV, cardiac allograft vasculopathy; HR, heart rate.
[a]Calculated as (peak HR − HR at rest)/(220 − age − HR at rest) × 100.

and 100% of their target received a median of 40 (IQR 40–50) mcg/kg per min dobutamine, which suggests that they were not under-stressed pharmacologically. Only four of these patients received atropine, and it is possible that some of the patients may have achieved a higher peak HR with further vagal suppression. However, the effect of atropine in the transplant population is not well defined – one previous retrospective study showed that atropine administration allowed 48% of patients who had been below target with dobutamine alone to reach their target HR (7). In another cohort of 50 patients, the absolute response to atropine was muted as compared to non-transplanted controls (6).

The effect of atropine may depend on effective parasympathetic function after cardiac transplant, although there is conflicting data regarding the extent of re-innervation and its effect on chronotropic response. For example, a study by Bacal *et al*. (10), which assessed HR variability on Holter monitoring as a marker of re-innervation in 20 transplant patients, found no relation to peak HRs obtained at 40 mcg/kg per min dobutamine. In a study by Flox *et al*. (6), resting HRs and early response to dobutamine were greater in transplanted patients than they were in non-transplant controls. However, fewer patients achieved target HR, which suggests that the factors that govern the chronotropic response may be more complicated in this group.

In the present study, older patients with younger donor hearts were more likely to achieve their target HR, and it is unclear what proportion of these would have achieved a higher target HR based on the *donor* age. However, given the varying influences on HR and chronotropy, which include the patient–donor age difference, it is reasonable to question whether the current standard means of assessing 'adequate' stress is still appropriate in the transplant population. Using the traditional formula of 85% $\times$(220 – age) to define a target HR is relatively straightforward, and this has been widely adopted particularly in the setting of dobutamine stress, compared with more physiological performance measures such as power, which may be assessed with exercise. Two relatively recent studies that assessed maximum HRs with exercise confirmed a strong dependence on age, but they refined and remodelled the relationship such that patients older than 40 years of age have a higher maximum predicted HR than they would according to the currently used formula (11, 12). The use of these new formulae would raise the target HR for many transplant patients; this implies even greater chronotropic limitation in the present study cohort, which is stressed according to patient age. However, there are still problems with such an age-related approach. Formulae are based on regression models in large populations with significant individual variability, and recent guidelines caution against the use of target HRs in isolation as a termination criterion, at least with exercise stress (13).

Other, more sophisticated, age-related formulae, such as the HRR, which is defined as (peak − resting HR)/(220 − age − resting HR), have been derived. An HRR of $<$70% has been demonstrated to have prognostic significance that is independent of echocardiographic ischaemia in a large population undergoing DSE (14). However, the utility of these methods has not previously been studied in the transplant population. Peak double product (HR $\times$ systolic blood pressure) may be used as an alternative measure of stress with dobutamine, but it likewise has not been validated in this setting. In patients that are able to exercise maximally, the clinical information obtained in addition to the echocardiographic assessment may be useful even if sub-target HRs were to be achieved, and maximal exertion could facilitate the derivation of an individualised target that could be used with subsequent DSE.

Thus, although a clearly defined marker of 'adequate' stress may be lacking based on HR alone, strict adherence to target HR according to recipient age as a sole test endpoint in the transplant population seems somewhat arbitrary (15). For example, it may risk providing an insufficient challenge to a young donor heart if doing so can be easily achieved with a low dose of dobutamine. In such instances, it could be considered whether patients should be stressed further to a maximum pharmacologic dose of dobutamine (40–50 mcg/kg per min). On the other hand, it is unclear whether DSE retains its diagnostic or prognostic utility in patients who are maximally stressed pharmacologically but fail to achieve their target HR.

For patients who are persistently unable to reach an acceptable target, or where stress is inadequate for other reasons, such as intolerance of dobutamine, other non-invasive tests may be considered. In combination with resting echocardiography, myocardial perfusion scintigraphy with dipyridamole stress has shown similar sensitivity and specificity to DSE for the diagnosis of coronary disease in cardiac transplants (16). Computed tomography (CT) coronary angiography has demonstrated close agreement with invasive coronary angiography and IVUS, and it is emerging as a useful tool for visualising the arterial wall in addition to coronary luminal stenosis (9, 17, 18, 19). However, the radiation involved may render these investigations less attractive for serial follow-up, particularly in younger patients.

Myocardial perfusion has also been assessed in small populations by magnetic resonance imaging (MRI) that measures myocardial perfusion reserve (20) and contrast-enhanced echocardiography that measures resting relative myocardial blood volume (21) or coronary flow reserve in the left anterior descending artery (22). However, the clinical role of perfusion assessment by such means remains to be established in this population.

Some limitations should be acknowledged in relation to the present study. This is a retrospective analysis with a relatively small number of patients. However, the cohort is comparable to other studies that have assessed transplant patients with DSE. There is no protocol regarding the administration of atropine following heart transplant in our institution, and the number of study patients who received atropine was relatively low. This reflects some uncertainty regarding the role of this drug in this setting, as described earlier in the present study. Likewise, there is no policy regarding the use of isometric stress (e.g., handgrip exercise). The effect of recipient–donor age difference on maximum HRs could not be defined because the majority of the tests were discontinued when the patients achieved their target HR. This would ideally be studied with maximal exercise testing with peak oxygen consumption. Finally, no outcome measures are presented in relation to the diagnostic or prognostic utility of stress echocardiograms in this cohort. This reflects the primary goal of the study, which was to assess the influence of age difference on the ability to reach a specified target HR with dobutamine stress.

Conclusion

Patients that undergo DSE after cardiac transplant tend to have younger donor hearts, with a minority receiving hearts from older donors. Despite this, they may demonstrate chronotropic incompetence, which is likely complex and multifactorial. Donor–recipient age difference affects the likelihood of achieving a patient-derived target HR in this population. Although the implications of the chronotropic response are uncertain for the diagnosis of CAV or the assessment of prognosis, the patient–donor age difference should be considered when patients are consistently unable to achieve 'adequate' stress at DSE; other forms of noninvasive testing may also be appropriate.

Declaration of interest

Drs P H Gibson, F Riesgo and D H Kim declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. Dr H Becher has received non-financial support from Lantheus and personal fees from Bracco and Acusphere. Dr J B Choy reports grants from Philips Healthcare.

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