

Original Research

Dobutamine Stress Echocardiography for the Evaluation of Cardiac Reserve Late After Fontan Operation

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Introduction: This study aimed to assess the potential role and safety of dobutamine stress echocardiography (DSE) in the evaluation of cardiac reserve in asymptomatic patients several years after a Fontan operation.

Methods: We studied 10 asymptomatic patients, 28 ± 5 years old, 14 ± 6 years after their Fontan operation. All patients and 10 healthy, matched controls underwent two-dimensional and Doppler echocardiography at baseline and throughout dobutamine infusion (given in 3-minute increments of 5, 10, 20, 30, and 40 $\mu\text{g}/\text{kg}/\text{min}$). Multivariate analysis for repeated measurements was used to detect differences between patients and controls.

Results: There were no adverse events during dobutamine infusion. Heart rate increased appropriately in both patients and controls. Patients reached peak stroke volume at infusion rates of 20 $\mu\text{g}/\text{kg}/\text{min}$, whereas controls peaked at 10 $\mu\text{g}/\text{kg}/\text{min}$. Mean stroke volume, cardiac output and cardiac index were significantly different between the two groups only up to infusion rates of 10 $\mu\text{g}/\text{kg}/\text{min}$. The velocity time integral of the left ventricular outflow tract flow was significantly lower in patients than controls throughout the study.

Conclusion: DSE is a safe method of stress testing for the assessment of adult Fontan patients and provides insights into the pathophysiology of their cardiac performance. Cardiac reserve in these patients is impaired compared to healthy controls.

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Despite successful palliation after Fontan procedures even “asymptomatic” patients have limited effort capacity and an abnormal cardiorespiratory response to exercise.¹⁻⁵ This functional impairment mainly relates to the presence of a unique single-ventricle physiology, where both the haemodynamic efficiency of the Fontan circulation and systemic ventricular function are major determinants of cardiac output.^{6,7}

Stress echocardiography, an established form of stress testing (physical or pharmacological) combined with simultaneous echocardiographic imaging, provides

a wealth of information and has prognostic implications in patients with other cardiovascular diseases.⁸⁻¹¹ One of the forms of stress echocardiography employs dobutamine, a synthetic catecholamine that has primarily positive inotropic effects at doses of 5-15 $\mu\text{g}/\text{kg}/\text{min}$ with a positive chronotropic effect at higher doses (20-50 $\mu\text{g}/\text{kg}/\text{min}$).¹² To our knowledge, there are no data available at present concerning dobutamine stress echocardiography (DSE) in adults with previous Fontan procedures, or the possible role of DSE in contributing to a better understanding of the pathophysiology of their decreased cardiopul-

monary performance and in guiding therapy. We therefore aimed to assess the feasibility and safety of DSE as an alternative method for detecting cardiac reserve in adult patients late after a Fontan palliation, and to compare their response to that of healthy controls.

Methods

Participants

The study population consisted of 10 patients (5 males and 5 females, age 28 ± 5 years) with previous Fontan procedures followed up in our clinic, and 10 healthy volunteers matched by sex, age and body surface (control group). None of the Fontan patients had evidence of right-sided obstruction and all healthy controls had a negative screening for congenital or any other cardiovascular disease. Patients had a background diagnosis of tricuspid atresia (6) or double-inlet left ventricle (4) and were assessed for the study 14 ± 6 years after their Fontan modification. Eight of them had undergone an atriopulmonary connection, 1 an atrioventricular and 1 a total cavopulmonary connection. Eight of the patients were in sinus rhythm, whereas 2 patients were in chronic atrial fibrillation with a satisfactory ventricular response. All patients were in New York Heart Association (NYHA) class I-II. Left ventricular (LV) ejection fraction at rest assessed by echocardiography ranged from 35% to 55%. All 4 patients with double-inlet left ventricle had mild (3) or moderate (1) mitral regurgitation.

The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all subjects before examination.

Study design

All patients and controls underwent a baseline two-dimensional and Doppler echocardiographic examination using a 2500 HP Sonos echo machine. Standard parasternal long-axis, short-axis and apical 2-, 4- and 5-chamber views were recorded. LV outflow tract diameter was measured from the parasternal long-axis view, whereas LV outflow tract flow velocity and the corresponding velocity-time integral (VTI) were measured using pulsed wave Doppler recordings from the apical long-axis view. LV end-diastolic volume, LV end-systolic volume and LV ejection fraction were calculated with the use of the modified Simpson's biplane (2- and 4-chamber) method of disks.¹³ All trac-

ings of the LV endocardial border were performed manually. Stroke volume, cardiac output and cardiac index were calculated using the equations:

$$\text{stroke volume} = (\text{LVOT diameter})^2 \times 0.785 \times \text{LVOT VTI}$$

$$\text{cardiac output} = \text{stroke volume} \times \text{heart rate}$$

$$\text{cardiac index} = \text{cardiac output} / \text{body surface area}$$

Attention was paid to the presence of any new wall motion abnormalities throughout the study.

A 12-lead electrocardiogram, arterial blood pressure, and O₂ saturation by pulse oximetry were also recorded.

Dobutamine was infused via peripheral venous access in serial incremental doses of 5, 10, 20, 30, and 40 $\mu\text{g}/\text{kg}/\text{min}$ in 3 min stages. Infusions were performed under continuous monitoring with electrocardiogram, pulse oximetry and automated blood pressure measurements. The endpoint for termination of dobutamine infusion was a target heart rate of 130 beats/min. This was chosen to reflect an adequate amount of stress, corresponding to a physical activity of submaximal intensity frequently achieved by these patients in their daily life, and to induce a primarily inotropic rather than chronotropic effect. Incidence of major side effects, such as hypotension, sustained arrhythmia or serious patient discomfort, was also considered as a reason for study termination. At the end of each stage, before dose increment, the same recordings as at baseline were obtained and heart rate, blood pressure and O₂ saturations were recorded. All studies were stored on videotape. Two experienced investigators performed blindly all two-dimensional and Doppler measurements; 5 consecutive beats were averaged for patients in sinus rhythm and all controls, whereas 10 consecutive beats were employed for the 2 patients in atrial fibrillation.

Statistical analysis

All continuous variables are presented as mean values \pm standard deviation. Comparisons between different variables were performed by repeated measurements of multi-way analysis of variance (RMANOVA). Pulsar analysis was applied in order to evaluate the variation of the continuous measurements, as done by Merriam et al.¹⁴ All reported p-values are based on two-sided t-tests and compared to a significance level of <0.05 . We used SPSS 10.1 software (SPSS Inc. 2002, Chicago, Illinois) for statistical analysis.

Results

The examination was well tolerated by all subjects with no adverse events. In particular, none of the Fontan patients had episodes of hypotension or sustained arrhythmia leading to early termination of DSE. Moreover, none of the participants experienced headache, chest pain or palpitations, and no ST-T changes or premature ventricular complexes were recorded on the electrocardiogram.

Mean values of heart rate, systolic blood pressure, O₂ saturation, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, LV outflow tract diameter, VTI and Doppler derived stroke volume, cardiac output and cardiac index, at baseline and at each stage of dobutamine infusion, are listed in Table 1. According to the data analysis, only systolic blood pressure, VTI, O₂ saturation, LV end-diastolic volume, LV end-systolic volume and LV ejection fraction differed significantly between patients and controls at all stages. Systolic blood pressure increased significantly from baseline to peak exercise in both groups. However, the percentage increase in systolic blood pressure from

baseline to peak was lower in Fontan patients compared to controls (8% vs. 23% respectively, $p < 0.05$).

Oxygen saturation did not change in patients or controls during the study. Heart rate increased in both patients and controls with no significant difference between the two groups. Target heart rate was achieved with 30 µg/kg/min of dobutamine infusion in 4 patients and in 7 controls. The remaining subjects achieved target heart rate with 40 µg/kg/min of dobutamine infusion (Figure 1).

Maximal stroke volume was achieved in Fontan patients with infusion rates of 20 µg/kg/min versus 10 µg/kg/min in healthy controls. Stroke volume was significantly different between patients and controls from baseline up to the 10 µg/kg/min stage. Similar results were observed for cardiac output and cardiac index, with the peak of both being achieved at 30 µg/kg/min of dobutamine infusion for patients and at 20 µg/kg/min for controls (Figure 1). Patients had significantly greater LV end-diastolic volume and LV end-systolic volume throughout the study, whereas LV ejection fraction was significantly lower in patients than in controls. No wall motion abnormalities were

Table 1. Variables recorded in patients and controls at baseline and at serial stages of dobutamine infusion (mean ± standard deviation).

Variables		Infusion rates (µg/kg/min)						p-value
		0	5	10	20	30	40	
SBP (mmHg)	Controls	116 ± 7	122 ± 8	128 ± 9	130 ± 8	133 ± 5	139 ± 4	<0.01
	Patients	103 ± 3	106 ± 3	110 ± 3	112 ± 3	115 ± 3	115 ± 4	
Heart rate (beats/min)	Controls	66 ± 5	78 ± 5	92 ± 7*	111 ± 7	127 ± 6	132 ± 2	0.867
	Patients	67 ± 4	73 ± 6	81 ± 6	103 ± 6	121 ± 7	132 ± 3	
Stroke volume (ml)	Controls	93 ± 34*	97 ± 29*	99 ± 26*	90 ± 78	76 ± 20	65 ± 17	0.343
	Patients	60 ± 14	68 ± 18	68 ± 15	75 ± 16	69 ± 18	55 ± 12	
Cardiac output (l/min)	Controls	6 ± 2*	7.6 ± 2*	9.1 ± 3*	10 ± 3	9.7 ± 3	8.5 ± 2	0.336
	Patients	4.1 ± 1	4.9 ± 1	5.5 ± 1	7.6 ± 2	7.9 ± 2	7.9 ± 3	
Cardiac index (l/min/m ²)	Controls	3.6 ± 1*	4.6 ± 1*	5.5 ± 2*	6 ± 2	5.9 ± 1	5.2 ± 1	0.3
	Patients	2.5 ± 1	2.9 ± 1	3.5 ± 1	4.7 ± 1	5 ± 1	4.7 ± 2	
LVOT-d (cm)	Controls	2.2 ± 0.1	2.2 ± 0.1	2.2 ± 0.2	2.1 ± 0.2	2 ± 0.1	1.9 ± 0.1	0.456
	Patients	2.3 ± 0.2	2.4 ± 0.2	2.4 ± 0.1	2.4 ± 0.2	2.3 ± 0.2	2.2 ± 0.1	
VTI (cm)	Controls	22.1 ± 3	23.4 ± 3	23.9 ± 3	24.3 ± 3	23.3 ± 3	22.5 ± 3	<0.01
	Patients	14.1 ± 2	14.8 ± 3	15.3 ± 2	16.2 ± 2	15.7 ± 2	14.2 ± 1	
O ₂ sat (%)	Controls	99 ± 1	98 ± 1	98 ± 1	99 ± 0.5	98 ± 1	99 ± 1	<0.01
	Patients	94 ± 1	94 ± 1	94 ± 1	94 ± 1	94 ± 1	94 ± 1	
LVEDV (ml)	Controls	128 ± 6	123 ± 6	120 ± 6	116 ± 5	110 ± 5	106 ± 4	<0.001
	Patients	162 ± 16	160 ± 16	158 ± 16	136 ± 11	132 ± 12	134 ± 15	
LVESV (ml)	Controls	48 ± 4	44 ± 4	38 ± 3	34 ± 3	32 ± 3	30 ± 2	<0.001
	Patients	98 ± 12	94 ± 12	92 ± 12	76 ± 14	70 ± 10	68 ± 8	
LVEF (%)	Controls	63 ± 4	65 ± 4	68 ± 3	70 ± 3	71 ± 2	72 ± 1	<0.001
	Patients	39 ± 5	41 ± 5	42 ± 5	45 ± 6	47 ± 6	50 ± 4	

LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; LVEF – left ventricular ejection fraction; LVOT-d – left ventricular outflow tract diameter; O₂ sat – O₂ saturation; SBP – systolic blood pressure; VTI – velocity time integral.

*Statistically significant differences ($p < 0.05$) between patients and controls at individual stages.

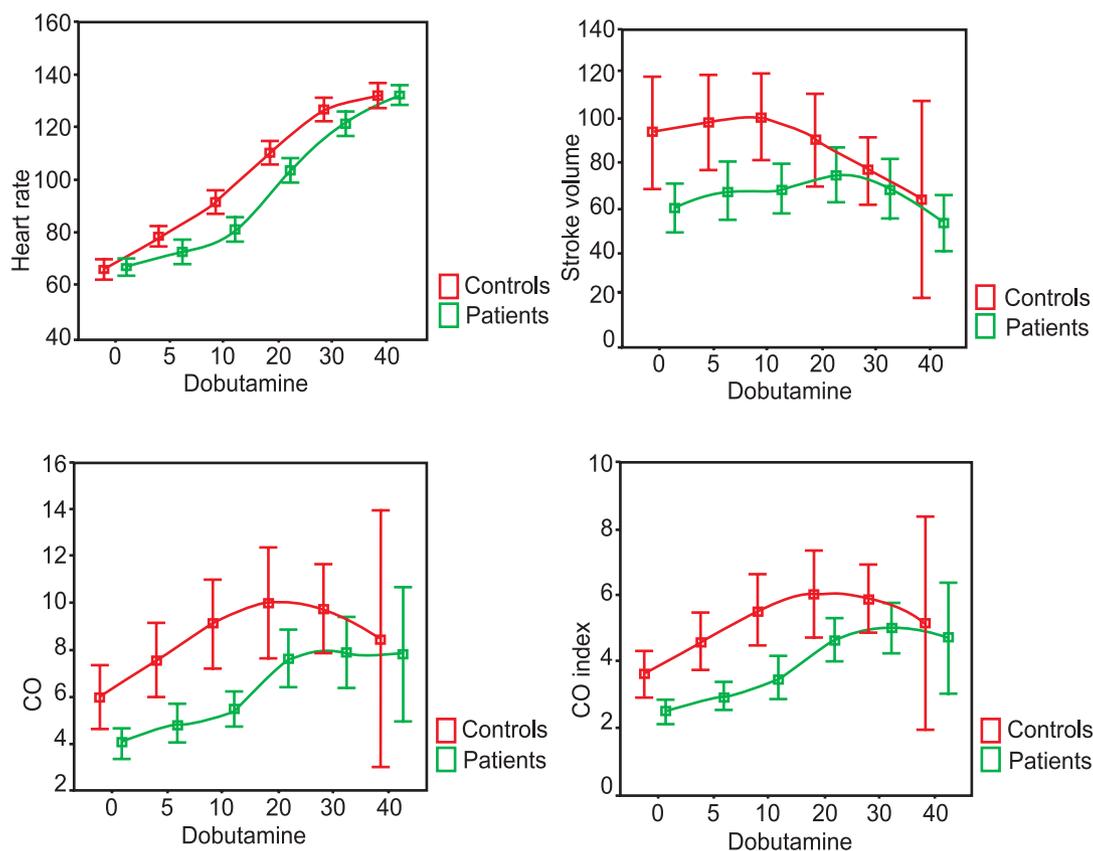


Figure 1. Heart rate, stroke volume, cardiac output (CO), and CO index. Mean values and 95% confidence intervals in patients and controls, at baseline and at serial stages of dobutamine infusion. Continuous lines represent 3rd order (cubic) splines.

observed in any patient or healthy subject. Finally, mitral regurgitation remained stable in 8 patients, while in the remaining 2 patients the degree of regurgitation slightly increased from mild to mild-moderate.

Discussion

This study demonstrates that DSE is feasible and safe in adult patients several years after the Fontan operation. Fontan patients required higher dobutamine infusion rates to reach peak stroke volumes compared to healthy controls, indicative of decreased inotropic reserve. In addition, stroke volume, cardiac output and cardiac index were all lower in patients compared to controls, although the difference was significant only up to dobutamine infusion rates of 10 $\mu\text{g/kg/min}$. We suggest this primarily reflects the earlier and greater decrease of the LV outflow tract diameter in controls than in patients, due to increased contractility. LV ejection fraction, similarly, was consistently lower in

the Fontan group compared to controls. However, it continued to augment with serial increments of dobutamine infusion in all subjects without a substantial increase in the degree of mitral regurgitation in the majority of patients, conveying a positive message for our Fontan population. There was a lower percentage increase in systolic blood pressure in patients than in controls, which may also be indicative of a suboptimal inotropic performance in the Fontan group. However, this is speculative, since complex ventriculo-arterial interactions would be involved and such were not the subject of our study.

It is of interest that no arrhythmic events, such as atrioventricular block or tachyarrhythmia, were observed in our patients during the study and that patients' heart rate increased appropriately with dobutamine infusion. The latter suggests that sinus node dysfunction was not a primary problem in our patient population¹⁵ and is in agreement with the findings of Gewillig et al, who reported that the heart rate re-

sponse in patients after Fontan was similar to that of healthy subjects at submaximal workloads.⁴

To our knowledge, this is the first study in the literature to assess cardiac reserve using DSE in patients with previous Fontan procedures. DSE and dobutamine magnetic resonance imaging have been employed to assess cardiac reserve in other forms of congenital heart disease.¹⁶ On the other hand, there are numerous studies evaluating the haemodynamic and cardiopulmonary response to exercise and the aerobic capacity in patients with Fontan circulation.^{1-4,17-22} Recently, the haemodynamic effect of beta-adrenergic stimulation in patients with Fontan circulation has been studied using invasive methods.²³ Our results are in agreement with these investigators.

Our primary aim, however, was to explore whether DSE offers a safe alternative in the physician's hands for estimating the global haemodynamic status of Fontan patients without exposing the patients to strenuous exercise. Although our protocol did not directly address the Fontan circulation *per se*, during dobutamine infusion this was estimated indirectly by evaluating stroke volume. We believe that the evaluation of the haemodynamic efficiency of patients who have undergone Fontan repair with the use of DSE is objective and indicative of their functional capacity. The status of systemic ventricular function has prognostic implications for these patients with single ventricle physiology.²⁴ Inotropic and chronotropic challenge with dobutamine may, therefore, unmask subtle haemodynamic and arrhythmogenic disturbances (i.e. atrioventricular block, sinus dysfunction), with the additional benefit of easy recording of blood pressure and oxygen saturations. Patients with fenestrated Fontan are desaturated during exercise or during tachycardia.^{1-4,25} The evaluation of these patients with DSE may easily detect the phenomenon and the clinician has a clear view of their functional status. Finally, the haemodynamic response of the Fontan circulation to the increased heart rate can easily be evaluated.

Maximum graded exercise testing, in contrast, consists of continuous exercise that usually lasts for about 10 min and at least half of this time is spent in the high intensity exercise range.²⁶ Achievement of a true maximum oxygen uptake does not usually occur, even in healthy, well-motivated subjects.²⁷ DSE cannot be directly compared with muscular exertion in a supine or an upright position, as preload is decreased with dobutamine and the increase in systolic blood pressure is of different magnitude during exercise testing. Nevertheless, a satisfactory increase in heart

rate was achieved in our patients, and our protocol was safe and easy to administer.

In conclusion, DSE provides a global estimate of patients with Fontan circulation – including haemodynamics, propensity to arrhythmia and cardiac reserve – independent of their level of physical conditioning. DSE was safe and may be considered for the outpatient evaluation of adult patients with previous Fontan procedures. Further studies are required to assess its prognostic implications.

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