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Myocardial Flow Reserve in Patients With a Systemic Right Ventricle After Atrial Switch Repair

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OBJECTIVES The purpose of this study was to assess myocardial blood flow (MBF) and flow reserve in systemic right ventricles (RV) in long-term survivors of the Mustard operation.

BACKGROUND There is a high prevalence of systemic RV dysfunction and impaired exercise performance in long-term survivors of the Mustard operation. A mismatch between myocardial blood supply and systemic ventricular work demand has been proposed as a potential mechanism.

METHODS We assessed MBF at rest and during intravenous adenosine hyperemia in 11 long-term survivors of a Mustard repair (age 18 ± 5 years, median age at repair 0.7 years, follow-up after repair 17 ± 5 years) and 13 healthy control subjects (age 23 ± 7 years), using N-13 ammonia and positron emission tomography imaging.

RESULTS There was no difference in basal MBF between the systemic RV of survivors of the Mustard operation and the systemic left ventricle (LV) of healthy control subjects (0.80 ± 0.19 vs. 0.74 ± 0.15 ml/g/min, respectively, p = NS). However, the hyperemic flows were significantly lower in systemic RVs than they were in systemic LVs (2.34 ± 0.0.69 vs. 3.44 ± 0.62 ml/g/min respectively, $p < 0.01$). As a result, myocardial flow reserve was lower in systemic RVs than it was in systemic LVs (2.93 ± 0.63 vs. 4.74 ± 1.09, respectively, $p < 0.01$).

CONCLUSIONS Myocardial flow reserve is impaired in systemic RVs in survivors of the Mustard operation. This may contribute to systemic ventricular dysfunction in these patients. (J Am Coll Cardiol 2001;37:2120–5) © 2001 by the American College of Cardiology

In children with transposition of the great arteries, the right ventricle (RV) is the systemic ventricle and continues to serve as the systemic pump after the atrial switch surgical correction (Mustard or Senning procedure). Studies of intermediate-term survivors of this operation have shown a high prevalence of RV dilation and mild systolic dysfunction within 5 to 10 years after surgery (1–3). Furthermore, RV dysfunction and impaired chronotropic response during exercise combine to result in impaired exercise performance (4–7). The pathophysiology of systemic RV dysfunction remains poorly understood.

The continuous exposure of the RV to a high resistance systemic circulation results in RV hypertrophy as a compensatory mechanism. In experimental models of pressure overload of either the left ventricle (LV) or the RV, ventricular hypertrophy is associated with a decrease in myocardial capillary density (8,9). Furthermore, coronary vasodilator reserve is frequently impaired in patients with hypertensive heart disease and may contribute to the transition from LV hypertrophy to LV failure (10). A similar mechanism, that is, a mismatch between myocardial blood supply and systemic ventricular work demand has been proposed as a potential mechanism for systemic RV dysfunction (11).

Positron emission tomography (PET) is an imaging modality that allows noninvasive quantification of regional myocardial blood flow (MBF). Quantification of MBF using nitrogen-13 (N-13) ammonia and PET has been validated in animals and in humans and has been shown to be both accurate and reproducible (12–15). Furthermore, flow measurements derived by PET correlate closely with the physiologic severity of coronary artery stenosis in patients with ischemic heart disease (16,17).

The purpose of this study was to assess MBF and flow reserve in systemic RVs in intermediate- and long-term survivors of the Mustard operation. We used PET imaging with N-13 ammonia to assess MBF during baseline conditions and during maximal coronary vasodilation by adenosine.

METHODS

Study population. We used our echocardiography database to select patients >10 years of age who underwent a Mustard repair for simple transposition of the great arteries at our institution and who continue to be followed at our institution. Echocardiography reports or studies were reviewed to exclude patients with current hemodynamically significant abnormalities (LV outflow tract obstruction, more than mild tricuspid regurgitation and pulmonary or systemic venous baffle obstruction). Other exclusion criteria included patients with a history of ventricular septal defect repair and those with ventricular paced rhythm because of the potential effects on myocardial perfusion or its interpretation. Of the 18 eligible patients, 11 (eight men, three women) agreed to participate. Their mean age at the time of

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Abbreviations and Acronyms

ECG = electrocardiogram
FWHM = full-width half maximum
LV = left ventricle or left ventricular
MBF = myocardial blood flow
N-13 = nitrogen 13
PET = positron emission tomography
ROI = region of interest
RV = right ventricle or right ventricular

this study was 18 ± 5 years (median age 18.5 years, range 11 to 30 years). Their median age at surgical repair was eight months (range five months to three years). The mean follow-up time since surgery was 17 ± 5 years (median follow-up 17 years, range 11 to 27 years). Four patients were on digoxin for mild ventricular dysfunction. The other patients were not on medications. The resting rhythm was sinus in six patients and junctional in five patients. Thirteen normal subjects (median age 23 years, range 12 to 35 years) served as control subjects for comparison of MBF data in the systemic RV and systemic LV. There was no significant difference between the study patients and control subjects in age or gender distribution.

Study design. The study protocol was approved by the Human Investigation Committee of Wayne State University, and all patients gave written informed consent. The subjects fasted for 4 h before the study. All subjects refrained from caffeine-containing beverages and theophylline-containing medications for 24 h before the PET study. The study protocol consisted of two parts: 1) assessment of basal MBF, and 2) assessment of hyperemic MBF.

PET. Dynamic PET measurements were performed using a whole-body PET scanner (model Siemens EXACT HR, Knoxville, Tennessee), which acquires 47 contiguous transaxial planes with an image resolution of 3.6 ± 0.23 mm at full-width half maximum (FWHM) in-plane and 3.5 ± 0.18 mm FWHM in the axial direction. It has an interplane spacing of 3.125 mm and covers a 15-cm axial field of view. The images were reconstructed using a Hanning filter with 1.10 cycles/cm cutoff frequency, resulting in an effective resolution of approximately or equal to 6-mm FWHM.

A 15-min transmission scan was acquired for correction of photon attenuation. Beginning with an intravenous bolus administration of N-13 ammonia (0.286 mCi/kg), serial images were acquired for 20 min (12 frames of 10 s each, 4 frames of 30 s, 1 frame of 60 s and 1 frame of 900 s). Thirty minutes later, after the physical decay of N-13 ammonia, 140 μg/kg/min adenosine was infused intravenously for 4 min. Two minutes after initiation of adenosine infusion (maximal hyperemia), a second dose of N-13 ammonia (0.286 mCi/kg) was injected and images recorded in the same acquisition sequence. The radiation exposure to children from this study was low and followed the federal regulations (less than one-tenth of the maximum radiation exposure allowed for research in adults) (18). Sedation was not required for any patient. Patients were instructed to lie still during the image acquisition; fastening a Velcro strap across the patient's chest minimized motion. Heart rate, cuff blood pressure (Dynamap, Criticon Inc., Tampa, Florida) and a 12-lead electrocardiogram (ECG) were monitored continuously throughout the procedure and recorded at baseline, every minute during the infusion and for 5 min after termination of adenosine infusion.

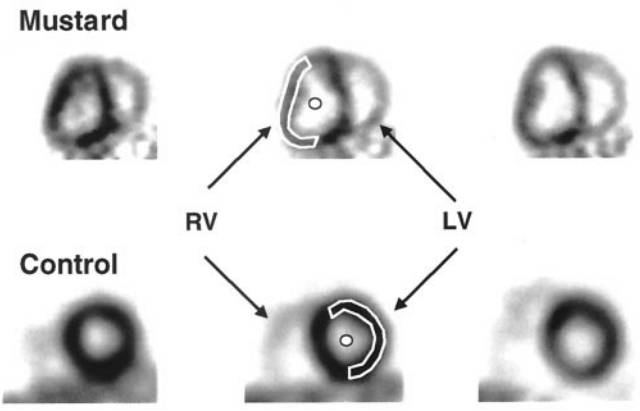

Figure 1. Positron emission tomographic nitrogen 13 ammonia images of the heart in short-axis views obtained at midventricular level in a patient with a systemic right ventricle (RV) **(top row)** and in a control subject with a systemic left ventricle (LV) **(bottom row)**. The images are oriented with the anterior wall on the top and the inferior wall on the bottom. The regions of interest for myocardial blood flow quantification were defined in the systemic ventricular free wall as demonstrated here. The blood pool time-activity curve was generated by selecting a region of interest in the center of the systemic ventricle for each group.

Quantification of MBF. The tomographic slices in each study were reoriented into 12 short-axis slices of the heart extending from the apex to the base of the RV using a SUN SPARC IPX workstation (SUN Microsystems Inc., Palo Alto, California).

In order to quantify regional basal and hyperemic MBF in systemic RVs, sectorial regions of interest (ROI) encompassing RV free wall were automatically assigned to each of the four midventricular short-axis slices of the N-13 ammonia images (Fig. 1). For systemic LVs (control subjects), the sectorial ROIs were assigned to the LV free wall in each of the four midventricular short-axis slices (Fig. 1). The assignment of sectorial ROIs is based on radial activity profiles with a blood volume fraction of 50% to 60%, as previously described (19). To ascertain identical placement of these regions to the rest and hyperemic N-13 ammonia images, the same angle on the circumferential profile served as the starting point for the sectorial ROI on each of the two image sets that were analyzed in each subject. An additional small circular ROI was manually placed in the center of the RV or LV blood pool of the two most basilar ventricular planes to obtain the arterial input function. The ROIs were then copied to the entire serially acquired N-13 ammonia image sequence, and regional myocardial tissue and blood pool time-activity curves were obtained. A single time-activity curve was obtained for the RV free wall in each

Table 1. Hemodynamic Changes With Adenosine

	Mustard Patients (n = 11)		Controls (n = 13)	
	Baseline	Adenosine	Baseline	Adenosine
HR (beats/min)	61 ± 9	87 ± 17*†	66 ± 13	107 ± 14*
Systolic BP (mm Hg)	121 ± 15	126 ± 15	120 ± 16	119 ± 17
Mean aortic BP (mm Hg)	84 ± 9	86 ± 9	83 ± 8	80 ± 9
Rate-pressure product	7,299 ± 1,290	10,987 ± 2,647*	7,815 ± 1,426	12,692 ± 2,384*

*$p < 0.001$ vs. corresponding baseline values; †$p < 0.001$ vs. controls.
BP = blood pressure; HR = heart rate.

patient and the LV free wall in each control subject by averaging the corresponding N-13 ammonia data in adjacent ventricular planes. The time-activity curves were then fitted with a previously validated three-compartment tracer kinetic model (19). The myocardial and blood pool time-activity curves were identical for the systemic RVs (patients) and the systemic LVs (control subjects).

Statistical analyses. The change in cardiac hemodynamics from rest to maximal hyperemia (i.e., heart rate, arterial blood pressure and rate-pressure product) was assessed using a paired Student *t* test. The comparison of systemic ventricular free wall MBFs between the patients and the control subjects was performed using an unpaired *t* test. All values were expressed as mean ± SD. A p value <0.05 was used to define statistical significance.

RESULTS

Hemodynamic findings. Table 1 summarizes the hemodynamic findings at rest and during maximal hyperemia by adenosine in the two groups (patients and control subjects). There was no difference in systolic blood pressure, mean blood pressure (coronary perfusion pressure) and rate-pressure product at baseline between the two groups. There was a significant increase in heart rate and rate-pressure product during adenosine-induced hyperemia in both patients and control subjects. The increase in heart rate was significantly lower in the survivors of the Mustard operation compared with control subjects, most likely due to sinus node dysfunction in these patients. There were no significant changes in systolic and mean arterial blood pressure in either of the two groups.

Regional MBF. **BASAL FLOW.** Basal MBFs were similar in systemic RVs (patients) and systemic LVs (control subjects) (Table 2).

HYPEREMIC FLOW. Myocardial blood flow increased significantly during adenosine-induced hyperemia in both systemic RVs (patients) and systemic LVs (control subjects). However, hyperemic MBFs were lower in systemic RVs compared with systemic LVs (Table 2). As a result, myocardial flow reserve (ratio of hyperemic to basal MBF) was lower in systemic RVs compared with systemic LVs (Table 2, Fig. 2).

MINIMAL CORONARY RESISTANCE. To relate the hyperemic blood flow to one of its major determinants, the coronary driving pressure, the mean aortic blood pressure was divided by the hyperemic blood flow, and an index of minimal coronary vascular resistance was obtained. At baseline, coronary vascular resistance was similar in systemic RVs and systemic LVs. However, the minimal coronary resistance during maximum vasodilation was significantly higher in systemic RVs compared with systemic LVs (Table 2, Fig. 2).

Hyperemic MBFs, myocardial flow reserve and minimal coronary vascular resistance were not related to patient age or duration of follow-up since surgery.

DISCUSSION

Previous studies have demonstrated impaired systemic RV function in survivors of the atrial switch operation. The results of this study demonstrate, for the first time, impaired vasodilator reserve of the coronary microcirculation in systemic RVs of long-term survivors of the atrial switch operation. In this study, the hyperemic MBF in survivors of the Mustard operation was approximately 38% lower compared with control subjects, and the minimum coronary vascular resistance was 67% higher than it was in control subjects. These coronary microcirculation abnormalities may contribute to impairment of ventricular function seen in these patients.

Coronary flow reserve in unrepaired transposition. Marcus (20) obtained measurements of coronary reactive hyperemia by Doppler flow probe (response to transient 20-s coronary occlusion) at the time of cardiac surgery in children with cyanotic heart disease. Marcus (20) demonstrated that coronary flow reserve in hypertrophied RVs of young children with transposition of the great arteries was significantly impaired compared with the RVs of control patients

Table 2. Myocardial Blood Flow and Coronary Vascular Resistance in Systemic Right and Systemic Left Ventricles

Variable	Systemic RV (n = 11)	Systemic LV (n = 13)
MBF (ml/g/min)		
Baseline	0.80 ± 0.19	0.74 ± 0.15
Adenosine	2.34 ± 0.69*	3.44 ± 0.62
Myocardial flow reserve	2.93 ± 0.63*	4.74 ± 1.09
Coronary vascular resistance (mm Hg/ml/min/g)		
Baseline	113 ± 30	116 ± 26
Adenosine	40 ± 15*	24 ± 5

*$p < 0.001$ vs. systemic LV.
LV = left ventricle; MBF = myocardial blood flow; RV = right ventricle.

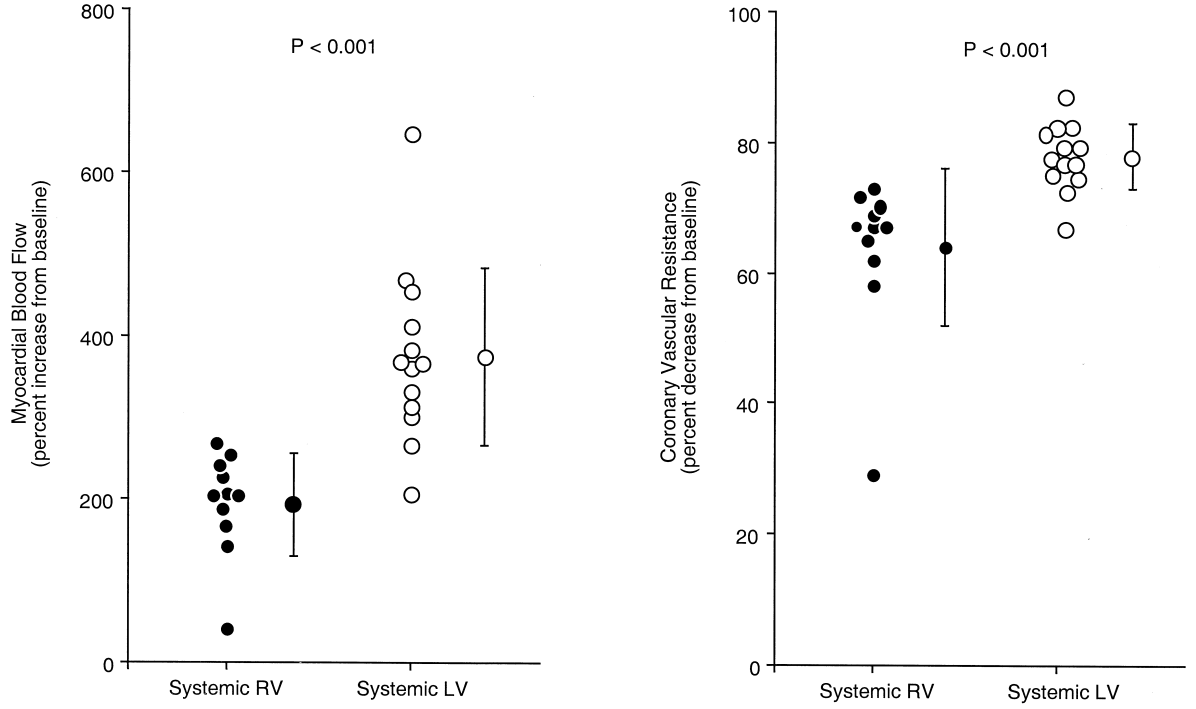

Figure 2. Change in myocardial blood flow and coronary vascular resistance during adenosine infusion in the study patients (systemic right ventricle [RV]) and control subjects (systemic left ventricle [LV]). The **error bars** represent the mean ± SD.

(1.8 ± 0.1 vs. 5.2 ± 0.5 in control patients). The degree of impairment of flow reserve described in systemic RVs in our study is not as severe as it is in the much younger patients with uncorrected transposition described by Marcus (20). This may indicate the effectiveness of physiologic correction by atrial switch surgery in improving the flow reserve in these ventricles. Our study shows that the flow reserve continues to be subnormal in long-term survivors of this operation.

Possible mechanisms. The mechanisms by which coronary flow reserve is impaired in the systemic RVs cannot be determined from this study. However, several potential mechanisms may explain our findings. Myocardial blood flow may be adversely affected in these ventricles because of unfavorable fiber arrangement (11). Alternatively, abnormalities in regional blood flow may be due to myocardial fibrosis secondary to prolonged hypoxemia during infancy while awaiting the atrial switch operation. Finally, prolonged pressure overload as a result of exposure to systemic circulation may result in decreased myocardial capillary density and, therefore, reduced flow reserve (8–10). When RVs are exposed to pressure overload in neonatal experimental models, the myocardial capillary growth tends to keep up with the muscle hypertrophy for several months (21). However, the older animals demonstrate a limited ability for capillary growth in pressure-loaded ventricles that does not match the degree of ventricular hypertrophy. This leads to a reduction in coronary flow reserve (22,23). Long-term survivors of atrial switch repair represent a model of prolonged RV pressure overload with its onset during the neonatal (or intrauterine) period. A similar experimental model has not been described.

Comparison of systemic RVs with systemic LVs. The RV free wall thickness is one-third the thickness of the LV in normal subjects. It is often difficult to visualize with currently available perfusion modalities including PET imaging. Therefore, accurate in vivo quantification of RV MBF is unreliable in healthy control subjects due to a partial volume effect. Similarly, the thinner LV free wall and smaller LV cavity in Mustard repair survivors did not allow reliable quantification of their LV free wall MBFs. However, the vascular density and capillary density are similar in the normal LV and RV (24). The coronary hyperemic response and minimal coronary vascular resistance are similar in the LV and RV in the dog model (22,23,25). These findings have been extended to the swine and to humans (26,27). In two additional human studies, which compared patients with pressure or volume-loaded RVs to control subjects with normal RVs, myocardial flow reserve values in control RVs were similar to the known values of LV myocardial flow reserve in the normal young population (21,28). Therefore, we believe that the LV MBF in healthy subjects is acceptable for comparison with MBFs and flow reserve in this study population.

Clinical significance. Whether these blood flow abnormalities result in clinically significant myocardial ischemia with exercise remains unclear. The presence of substantial RV hypertrophy in these patients leads to an abnormal depolarizarion pattern on their resting ECG. This prevents meaningful interpretation of their exercise ECGs for the

diagnosis of myocardial ischemia. A recent study described perfusion defects, both fixed and reversible, with concurrent wall motion abnormalities by single photon emission computed tomography in this group of patients (29). The investigators suggested that ischemia and infarction were important factors in the pathogenesis of ventricular dysfunction in these patients. In our study group, regional perfusion defects were not seen. However, the possibility that recurrent asymptomatic subendocardial ischemia during exercise due to impaired myocardial flow reserve may lead to subendocardial fibrosis and development of ventricular dysfunction over several decades cannot be excluded.

A previous study has shown that the RV ejection fraction remained stable in a cohort of Mustard operation survivors over a four-year period (30). However, significant concern persists regarding progression of RV dysfunction in survivors of atrial switch repair (29). The majority of long-term survivors are asymptomatic; however, a few have developed progressive ventricular dysfunction requiring a conversion to arterial switch operation or cardiac transplantation (31). Due to these concerns and the presence of a large number of young adults with systemic RVs, further studies to improve the understanding of the pathophysiology of systemic RV dysfunction and to elucidate measures for preserving its function are indicated.

In conclusion, this study demonstrates impaired myocardial flow reserve in systemic RVs in long-term survivors of the Mustard operation. This impairment may contribute to ventricular dysfunction in the intermediate and late survivors of this operation.

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