Original Article

Abnormal myocardial blood flow in children with mild/moderate aortic stenosis

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Abstract *Objective:* To quantify myocardial blood flow in infants and children with mild or moderate aortic stenosis using adenosine-infusion cardiac magnetic resonance. *Background:* It is unclear whether asymptomatic children with mild/moderate aortic stenosis have myocardial abnormalities. In addition, cardiac magnetic resonance-determined normative myocardial blood flow data in children have not been reported. *Methods:* We studied 31 infants and children with either haemodynamically normal hearts (n = 20, controls) or mild/moderate aortic stenosis (n = 11). The left ventricular myocardium was divided into six segments, and the change in average segmental signal intensity during contrast transit was used to quantify absolute flow (ml/g/minute) at rest and during adenosine infusion by deconvolution of the tissue curves with the arterial input of contrast. *Results:* In all the cases, adenosine was well tolerated without complications. The mean pressure gradient between the left ventricle and the ascending aorta was higher in the aortic stenosis group compared with controls (24 versus 3 mmHg, p < 0.001). Left ventricular wall mass was slightly higher in the aortic stenosis group compared with controls (65 versus 50 g/m^2, p < 0.05). After adenosine treatment, both the absolute increase in myocardial blood flow (p < 0.0001) and the hyperaemic flow significantly decreased (p < 0.001) in children with mild/moderate aortic stenosis compared with controls. *Conclusion:* Abnormal myocardial blood flow in children with mild/moderate aortic stenosis may be an important therapeutic target.

Keywords: Congenital heart disease; aortic stenosis; perfusion; fibrosis; contrast media

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MILD OR MODERATE AORTIC STENOSIS IS MANAGED conservatively in infants and children because most paediatric cardiologists believe it is well-tolerated and are reluctant to employ treatment strategies such as balloon angioplasty or aortic valve replacement that carry significant risks. Yet, it remains unclear whether myocardial injury exists during the earliest stages of left-heart obstruction. In adults, there is accumulating evidence that

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diffuse myocardial fibrosis does not regress after aortic valve replacement, despite otherwise favourable myocardial remodelling.[1–3] Accordingly, it may be important to treat afterload-induced heart disease during its earliest phases. As maladaptive cardiac growth and interstitial fibrosis result from underlying abnormalities of the microcirculation,[4] we hypothesised that children with mild or moderate aortic stenosis would have abnormal myocardial perfusion, despite having no clinical symptoms, no evidence of fibrosis, and normal-appearing coronary arteries.

Recently, quantitative myocardial perfusion using cardiac magnetic resonance imaging has proven to

provide excellent spatial and temporally resolved information in adults.[5,6] In the present study, we take advantage of this new technique to quantify resting and adenosine-induced hyperaemic myocardial blood flow using adenosine-infusion cardiac magnetic resonance imaging in haemodynamically normal children and compared them to a group with mild or moderate aortic stenosis.

Methods

The protocol was approved by the Oregon Health & Science University's institutional review board. Written and dated informed consent was obtained from all parents or guardians of all the patients, and informed assent was obtained from all children and adolescents older than 9 years.

Study subjects (Table 1)

In the present study, two groups of children – all greater than 3 months of age – were enrolled. Caveats by the human subjects committee precluded enrolling children without cardiac findings. Therefore, one group included children with haemodynamically trivial congenital heart malformations – the control group. The second group included those with unrepaired mild or moderate aortic stenosis, defined as Doppler-determined mean pressure gradients of <40 Torr. Overall, the study population consisted of 31 individuals, none of whom had any signs or symptoms of haemodynamically significant heart disease, nine were referred for concerns unrelated to cardiac haemodynamics, and 22 consented to participate solely in order to contribute to this research effort (see results Patient Characteristics for additional details).

Table 1. Patient characteristics, diagnoses, aortic valve Doppler of experimental groups.

		Age at AI-cMR	Gender	Diagnosis	LVOT Gradient (mean)
Control	1	0.3	Male	Vascular ring	2
	2	1	Female	Vascular ring	4
	3	1.1	Male	Vascular ring	3.2
	4	1.9	Male	Vascular ring	5
	5	3.5	Female	ASD	4.5
	6	4.1	Male	VSD	3.6
	7	4.8	Female	Nl coronary eval	2.5
	8	7.5	Male	VSD	2
	9	7.7	Male	PS	2.8
	10	8.4	Female	VSD	3
	11	8.4	Female	VSD	2.1
	12	8.4	Female	VSD	2
	13	10.6	Female	VSD	4.2
	14	11.4	Male	VSD	3
	15	12.5	Female	Nl coronary eval	4.5
	16	12.8	Male	Hx of Coarct.	4.4
	17	13	Male	ASD	5.5
	18	13	Male	VSD	2
	19	13	Female	PS	1
	20	15.9	Male	Chest pain	3
	Average	8.0 ± 4.8			3.2 ± 1.5
Aortic stenosis	1	4.2	Male	BAV Ang	28.1
	2	9.9	Male	BAV	8
	3	12.9	Male	BAV	31
	4	8.2	Male	BAV/AI	32
	5	12	Female	SubAs	34
	6	10.6	Male	BAV/AI	28.6
	7	11.2	Male	BAV/Ang	15.3
	8	1.2	Male	BAV	15.7
	9	11.1	Female	BAV	37.8
	10	7	Male	BAV	20.2
	11	11.4	Male	BAV Coarct	16.6
	Average	9.1 ± 3.6			24.3 ± 9.5*

AI = aortic insufficiency; Ang = balloon angioplasty; ASD = atrial septal defect (<2 mm); BAV = bicuspid aortic valve; cMR = cardiovascular magnetic resonance imaging; Hx of Coarct. = repair at one year of age with no echo evidence of residual obstruction; LVOT = left ventricular outflow tract; Nl coronary eval = normal coronary anatomy demonstrated by MRI; PS = mild pulmonary stenosis (Doppler velocity <2 m/second); VSD = small ventricular septal defect
*$p < 0.05$ by Student's t-test. Other non-significant comparisons include the following: BSA, SV, CI, LV Vol, HR, systolic/diastolic BPs, and RPP (both resting and hyperaemic)
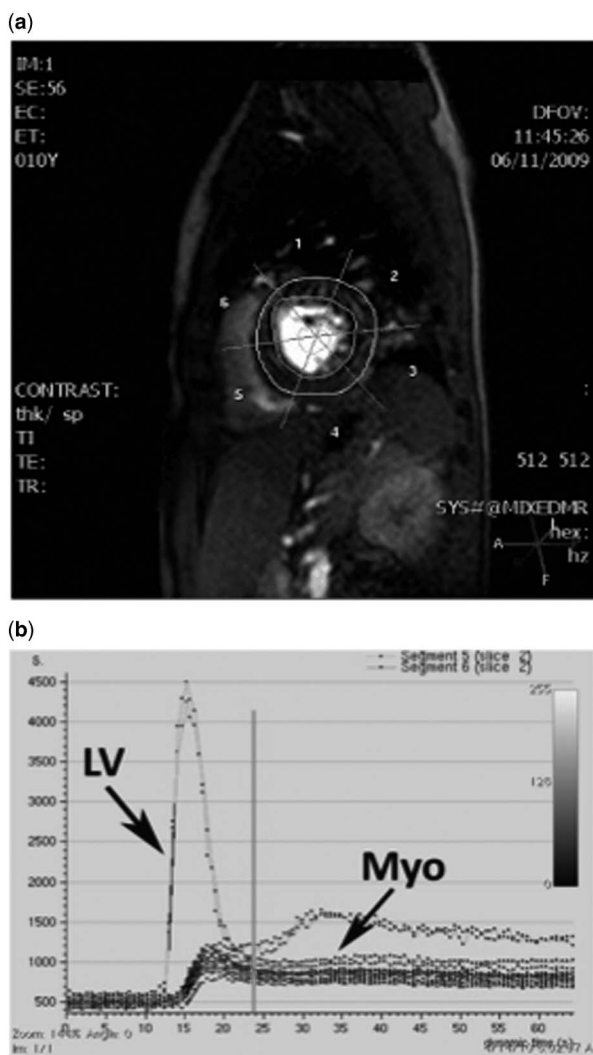
(a)

(b)

Figure 1.
(a) User traced endocardial and epicardial contours, and regions of interest in the centre of the left ventricular cavity (1 = anterior, 2 = lateral, 3 = posterior, 4 = inferior, 5 = inferior septal, and 6 = anterior septal). (b) Signal intensity curves for the blood pool within the left ventricular cavity (LV) and the interstitial compartments of six segments from two short-axis slices of the myocardium (Myo).

95% confidence interval failed to overlap. All data analysess were performed using R statistical software version 2.12.1.[10]

Results

Patient characteristics (Table 1)

Adenosine-infusion cardiac magnetic resonance imaging studies were performed in 31 children – 20 haemodynamically normal controls and 11 with aortic stenosis. None of the children were thought to have any symptoms referable to the cardiovascular system. All the children had normal-appearing coronary arteries

and normal cardiac function as assessed by routine echocardiography. Some had trivial congenital heart disease such as a small ventricular septal defect, with Doppler-determined blood flow velocity >4 m/second, a vascular ring, a patent foramen ovale, or mild pulmonary stenosis, with Doppler-determined blood flow velocity <2 m/second.

The control group (n = 20) consisted of children referred for the study and ultimately shown to have normal hearts or children with trivial congenital heart malformations. Among all, seven controls were referred for magnetic resonance imaging (MRI) because of concerns unrelated to cardiac haemodynamics: question of vascular ring with structurally normal heart and normal cardiac function in four, two children with question of abnormal coronary artery origin prompted by echocardiography were proven to have normal coronary anatomy, and chest pain in one who had a normal exercise stress test was ultimately given a non-cardiac diagnosis. The remaining 13 controls did not have clinical indications for the study but consented to participate after being approached by the investigators. All 13 participants had clinical evidence and echocardiography indicating haemodynamically insignificant cardiac malformations – tiny ventricular septal defect in seven, tiny atrial septal defect in two, trivial pulmonary stenosis in two, and a 13-year-old boy with coarctation repair at one year of age who had echo evidence of trileaflet aortic valve and no residual obstruction by echocardiography. The aortic stenosis group (n = 11) included those with unrepaired mild or moderate aortic stenosis, defined as Doppler-determined mean pressure gradients of <40 Torr. These participants had no complaints, symptoms, or signs of heart disease, and after discussion with the investigators consented to participate in this research.

Median age and sex were not different between the groups (aortic stenosis 8.4 versus control 10.6 years, 82 versus 55% males). Mean pressure gradient between the left ventricle and the ascending aorta was higher in the aortic stenosis group compared with controls (24 versus 3 mmHg, $p < 0.001$). The left ventricular wall mass index was higher in the aortic stenosis group compared with controls (65 versus 50 g/m^2, $p < 0.05$, Table 2). Ejection fraction was also higher in the aortic stenosis group compared with controls (75 versus 70%, $p < 0.05$).

Physiological response to adenosine infusion

Adenosine infusion was well tolerated in all patients. In seven patients, less than five seconds of self-limited apnoea was observed moments after discontinuing the adenosine infusion. No intervention was required in any instance. In total, the adenosine infusion part of the study took ~30–45 minutes to be completed.

Table 2. cMR characteristics of experimental groups.

	AS (n = 11)	Control (n = 20)	p-value
Male	82% (9)	55% (11)	0.135[*]
Age	10.6[**] (7.6[***], 11.3[****])	8.4 (4.0, 12.6)	0.747[*****]
BSA	1.10 (0.88, 1.47)	1.15 (0.84, 1.30)	0.686[*****]
EF	75.2% (70.0, 77.0)	69.5% (65.4, 72.0)	0.009[*****]
SV	39.4 (28.6, 58.6)	39.3 (26.2, 49.0)	0.748[*****]
CO	3.3 (3.1, 5.0)	3.0 (2.6, 3.9)	0.163[*****]
CI	3.2 (2.6,3.7)	2.9 (2.5, 3.4)	0.254[*****]
LVMass	65.6 (52.9, 78.4)	49.4 (41.1, 57.0)	0.011[*****]
LVVol	43.2 (40.2, 60.4)	52.9 (44.2, 60.4)	0.657[*****]
rHR	83 (77,93)	83 (72, 94)	0.968[*****]
rBPs %tile	13 (3.3, 59)	5.7 (1.35, 41)	0.719[*****]
rBPd %tile	4.4 (0.7, 11.6)	4.4 (0.7, 4.4)	0.554[*****]
hHR	109 (101, 114)	110 (101, 124)	0.518[*****]
hBPs %tile	9 (3, 45)	4 (1.3, 37)	0.66[*****]
hBPd %tile	0.15 (0.2, 0.55)	3.7 (0.6, 9)	0.63[*****]
rRPP	7761 (5995, 8447	7840 (6804, 8800)	0.492[*****]
hRPP	8640 (7560, 9100)	6878 (6115, 10,866)	0.518[*****]
cRPP	316 (–364, 1088)	333 (–1051, 2137)	0.418[*****]

BSA = body surface area; CI = cardiac index; cMR = cardiovascular magnetic resonance imaging; CO = cardiac output; cRPP = change between resting and hyperaemic rate pressure products; EF = ejection fraction; h = hyperaemic; LVMass = left ventricle mass; LVVol = left ventricle volume; r = resting; SV = stroke volume; %tile = blood pressure percentiles
*Pearson's test
**Median
***Lower quartile
****Upper quartile for continuous variables
*****Wilcoxon's test

Furthermore, during the 15-minute interval between rest and adenosine infusion, additional image acquisition was possible. When the control and aortic stenosis groups were compared, adenosine-induced hyperaemia had mild effects on blood pressure and heart rate, but the differences between groups were not different (Table 2). During adenosine infusion, the median heart rate increased from 83 to 109 beats per minute ($p < 0.001$), and systolic blood pressure decreased from the median value of 89 to 70 mmHg ($p < 0.001$). Blood pressures in both the resting and hyperaemic states were converted to percentile ranks based on age, gender, and height.[11] The decrease in blood pressure percentile was significant within both control and aortic stenosis groups, but the difference between the groups was not significant. We noted that the percentile ranks for blood pressure were all lower than the normal range. We ascribed this observation to the fact that all the patients were under deep sedation during the studies. The change in the rate pressure product (RPP) was not different between the groups (median 316 versus 333, $p = 0.4$). Focal regions of gadolinium late enhancement were not observed in either group.

Myocardial blood flow

Normal resting and adenosine-induced hyperaemic flows obtained from 20 haemodynamically normal children (controls) are shown in Table 4. Overall, we found that the main effect of the adenosine treatment was significant, as myocardial blood flow went up in both the groups, and the main effects of group were also significant – that is, the change caused by adenosine-induced hyperaemia as well as the absolute value of maximal myocardial blood flow were different between the aortic stenosis and control groups. The aortic stenosis group's adenosine-induced myocardial blood flow change compared with the resting state was significantly smaller than the decrease from adenosine infusion to rest in controls (Tables 3a and 4) (–0.72 ml/g/minute; 95% confidence interval: –0.50, –0.93 versus –1.14, 0.95, 1.34, $p < 0.0001$). In addition, the hyperaemic flow adjusted for resting flow (Fig 2) was significantly lower in the aortic stenosis group compared with controls (2.15 ml/g/minute; interquartile range 1.5, 2.3 versus 2.51 (1.8, 3.3), $p < 0.001$). When the model was analysed without adjusting resting flow for rate pressure product, the results were the same. In addition, when gender, left ventricle wall mass, or severity of stenosis was included in the model, the results were unchanged.

A mixed linear effects model was created to account for both between and within-patient variation allowing for differences between groups – that is, aortic stenosis and control – and within-group treatments – resting, hyperaemia – the six

Table 3a. AI-cMR-determined regional quantitative regional myocardial blood flow comparing children with aortic stenosis and haemodynamically normal hearts (group) at rest or during adenosine-induced hyperaemia (treatment).

	Flow (ml/g/minute)	95% CI	p-value
Baseline*	2.15	(1.95, 2.35)	<0.0001
Main effects		Difference from baseline	
Group (control)	0.37	(0.11, 0.62)	0.0067
Treatment (resting)	−0.72	(−0.93, −0.50)	<0.0001
Region			
Lateral	0.09	(−0.09, 0.28)	0.3032
Posterior	−0.12	(−0.31, 0.06)	0.1974
Inferior	−0.25	(−0.44, −0.07)	0.0084
Inferior septal	−0.40	(−0.59, −0.21)	<0.0001
Anterior septal	−0.08	(−0.26, 0.11)	0.4330
Slice (basal)	−0.10	(−0.17, −0.02)	0.0121
Interaction terms		Difference from baseline and Main Effects	
Group (control) and treatment (resting)	−0.42	(−0.58, −0.27)	<0.0001
Treatment (resting) and region			
Lateral	−0.18	(−0.45, 0.08)	0.1679
Posterior	0.02	(−0.24, 0.28)	0.8725
Inferior	0.15	(−0.11, 0.41)	0.2568
Inferior septal	0.37	(0.10, 0.63)	0.0065
Anterior septal	0.13	(−0.13, 0.39)	0.3282

*Baseline is for AS in hypaeremic state in the anterior region and apical slice. The prediction of flow (ml/g/minute) can be accomplished by summing baseline flow and the main effects (group, treatment, region, and slice) and the interaction terms (group and treatment and/or treatment and region)

Table 3b. Summing main effects and interaction terms from Table 3a to predict myocardial blood flow at rest and during adenosine-induced hyperaemia in control and aortic stenosis (AS) groups.

	Rest	Adenosine
Control	2.15* −0.72** + 0.37*** −0.43**** = 1.37	2.15 + 0.37 = 2.52
Aortic stenosis	2.15 −0.72 = 1.43	2.15

All values are expressed in ml/g/minute. Non-significant main effects or interactions should not be included in the prediction model
*Baseline reference flow is AS in hyperaemic state, anterior region, apical slice
**Main effect-treatment in resting state
***Main effect-group in controls
****Interaction term-control group and resting treatment

Table 4. Resting and hyperemic flows in aortic stenosis and control groups

	Region	Resting	Hyperemic	Delta (Resting minus Hyperemic)
	Anterior	1.39 (1.20, 1.58)*	2.10 (1.91, 2.29)	− 0.72 (−0.93, −0.50)
	Lateral	1.30 (1.11, 1.49)	2.20 (2.00, 2.39)	− 0.90 (−1.11, −0.69)
	Posterior	1.29 (1.10, 1.48)	1.98 (1.79, 2.17)	− 0.69 (−0.91, −0.48)
Aortic stenosis (n = 11)	Inferior	1.29 (1.10, 1.48)	1.85 (1.66, 2.04)	− 0.56 (−0.78, −0.35)
	Inferior septal	1.35 (1.16, 1.54)	1.70 (1.50, 1.89)	− 0.35 (−0.56, −0.13)
	Anterior septal	1.44 (1.25, 1.63)	2.03 (1.83, 2.22)	− 0.58 (−0.80, −0.37)
	Average	1.34 (1.19, 1.49)	1.98 (1.82, 2.13)	− 0.63 (−0.76, −0.51)
	Anterior	1.32 (1.10, 1.55)	2.47 (2.24, 2.70)	− 1.14 (−1.34, −0.95)
	Lateral	1.23 (1.01, 1.46)	2.56 (2.33, 2.79)	− 1.33 (−1.52, −1.14)
	Posterior	1.22 (0.99, 1.45)	2.35 (2.12, 2.57)	− 1.12 (−1.32, −0.93)
Control (n = 20)	Inferior	1.22 (1.00, 1.45)	2.22 (1.99, 2.45)	− 0.99 (−1.19, −0.80)
	Inferior septal	1.29 (1.06, 1.52)	2.06 (1.84, 2.29)	− 0.78 (−0.97, −0.58)
	Anterior septal	1.38 (1.15, 1.61)	2.39 (2.16, 2.62)	− 1.01 (−1.21, −0.82)
	Average	1.28 (1.08, 1.47)	2.34 (2.15, 2.54)	− 1.06 (−1.16, −0.97)

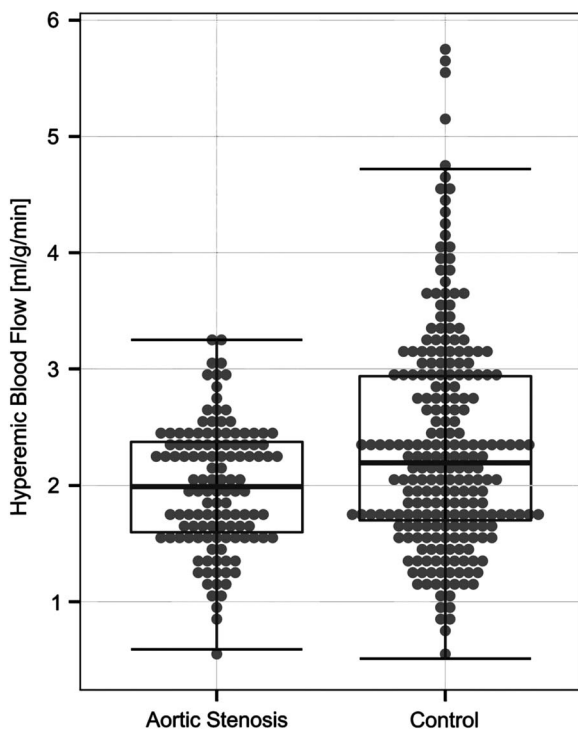* all values are ml/gm/min (95% confidence limits)

Figure 2.
Children with mild/moderate aortic stenosis (AS) have significantly (p < 0.001) lower hyperaemic myocardial blood flow (hMBF) than haemodynamically normal children. Dots represent resting MBF-adjusted values from each slice and region of the heart (AS, n = 132 and control, n = 240). When the identical model was re-analysed, where resting flows were not rate pressure product-adjusted, the results were the same.

In addition, the basal slice consistently had lower flow than the apical slice (–0.10 ml/g/minute, 95% confidence interval: –0.02, –0.17, p = 0.0121), but again there was no difference identified between the control and aortic stenosis groups.

Discussion

The major finding of this study is that asymptomatic children with mild or moderate aortic stenosis have significantly decreased myocardial perfusion in response to adenosine infusion compared with healthy children. In adults with suspected coronary artery disease, the ability of adenosine-infusion cardiac magnetic resonance imaging to predict significant cardiac events is established.[12] The fact that children with mild or moderate aortic stenosis remain asymptomatic for many years does not exclude the possibilities that latent disease exists in these children or that significant injury occurs during the period of latency. The observation of decreased myocardial blood flow in response to adenosine stress in young aortic stenosis patients suggests that, in children with minimally after-loaded hearts, there is a disorder of the microcirculation that could be the substrate for later development of diffuse myocardial fibrosis.[3]

This report also provides the first quantitative information about resting and adenosine-induced regional myocardial blood flow in healthy children with haemodynamically normal hearts, data that will be applicable to other studies in children who require normative comparisons. It is notable that hyperaemic flow was relatively decreased in the inferior wall segments of both control and aortic stenosis group individuals. The same observation has been made in asymptomatic adults.[13,14] Although the mechanism for these differences is unclear, it is interesting that Puchalski et al[15] also observed regional wall motion abnormalities and gadolinium delayed enhancement in the inferior myocardial regions of asymptomatic children with Duchenne muscular dystrophy. They concluded that these findings heralded the onset of global disease in these children. Taken together, these data suggest that the posterior cardiac segments may be particularly vulnerable to ischaemic injury.

There is an increasing body of literature suggesting that microvascular dysfunction is the proximate cause of acute myocardial fibrosis.[9] Recent evidence suggests that diffuse myocardial fibrosis identified before aortic valve replacement may be the best predictor of long-term poor outcome.[2] Thus, early treatments that target precursors of cardiac fibrosis such as pathological angiogenesis or coronary vascular reactivity may prove useful. Our data suggest that myocardial abnormalities may occur in the setting of even mild or moderate aortic stenosis and

myocardial regions, and the two slices – apical and basal. Initially all possible interactions were analysed. Significant interactions were identified between group and treatment (p < 0.0001) and between treatment and region (p = 0.0006); the interactions between group and region, between group and slice, and all higher-order interactions were not significant.

As shown in Tables 3a, 3b, and 4, adenosine-induced flows were significantly decreased in the aortic stenosis group compared with controls (0.37 ml/g/minute, CI 0.11, 0.62, p = 0.0067), using the anterior region and the apical slice as reference. This effect can be generalised to all regions as there was no significant interaction between regional flow and the aortic stenosis and control groups. Rest flows in the aortic stenosis group were unchanged compared with controls (–0.06 ml/g/minute, 95% confidence interval: –0.31, 0.19), again using the anterior region and the apical slice as reference. The inferior and inferior septal regions, compared with the anterior region, demonstrated decreased flow during hyperaemia (p < 0.01), but this effect was not different between the groups.

begin as early as childhood. Whether this disorder of the microcirculation is a consequence of afterload-induced injury or a primary developmental phenomenon, independent of the severity of left-heart obstruction, deserves further investigation.

Studies of the immature myocardial microcirculation in humans are limited, because until the advent of cardiac magnetic resonance imaging there has not been a safe, non-invasive, and quantitative method to address this question. There is evidence from experimental animal models suggesting that maximal coronary blood flow is decreased in the after-loaded myocardium.[16,17] In addition, Rakusan et al[17,18] studied pressure-overloaded left ventricular hypertrophy in post-mortem human hearts. In those studies, children with aortic stenosis had proportional capillary angiogenesis, meaning that capillary density was directly related to the degree of myocyte hypertrophy. On the other hand, in post-mortem hearts from adults with aortic stenosis, hypertrophy appeared to be associated with failure of compensatory capillary growth. Consistent with Rakusan et al's studies in children with aortic stenosis, we found that resting blood flow per gram of tissue is preserved in the non-hyperaemic state; however, we found decreased adenosine-induced hyperaemia in the mildly/moderately after-loaded heart, an observation that would be impossible to make in a post-mortem study. Whether impaired hyperaemic blood flow in these asymptomatic children represents failure to recruit a potential vascular bed, or abnormal vascular reactivity perhaps caused by downregulation of the adenosine receptor, is unclear.[19] Our findings lay the groundwork for future studies in animals and humans aimed at understanding the developmental relationships between angiogenesis, myocardial fibrosis, and myocardial dysfunction in children. Furthermore, the potential benefit of currently available therapies such as angiotensin or mineralocorticoid inhibitors, or the value of novel therapies that might prevent early fibrosis[20–24] in the mildly after-loaded heart, are completely unknown.

Limitations

These studies were carried out using a 3-T magnet in order to maximise signal strength while quantifying myocardial blood flow. In none of these studies were we able to visually appreciate perfusion differences between the control group and aortic stenosis patients, nor were we able to identify evidence of regional gadolinium late enhancement. It is possible that regional differences will become more apparent with newer 3 T scanners that avoid previously described acquisition artefacts,[25] or with newer quantitative techniques.[3] Importantly, we could not find a linear correlation between quantitative regional blood flow and stenosis severity or left ventricular mass. Thus, the clinical applicability of adenosine-infusion cardiac magnetic resonance imaging to risk stratify abnormal myocardial perfusion in children is probably limited at present because of the variable flows that resulted in overlap between the aortic stenosis and control individuals. Refined techniques and better scanners may solve this limitation. It is also possible that perfusion abnormalities may, in part, occur independently of the severity of aortic stenosis and other, perhaps modifiable, factors may play a role. Finally, Hoffman[17] demonstrated in animal models that maximal coronary flow is dependent on perfusion pressure, and therefore defined coronary flow reserve over a range of pressures. This was not possible in our studies; however, we were able to show that the change in diastolic blood pressure or the change in the rate pressure product before and after inducing maximal dilation with adenosine was not different between the two experimental groups. Thus, it is likely that both the groups were studied at a similar level of coronary perfusion pressure.

Conclusion

In this report, we provide evidence that there may be significant abnormalities of the microcirculation in asymptomatic infants and children with even mild or moderate aortic stenosis. Whether myocardial perfusion abnormalities exist in other forms of left ventricle afterload in pre-clinical phases such as in early systemic hypertension or mild cardiomyopathy awaits future study. Very little is known about the adaptive and maladaptive responses, as they relate to myocardial perfusion in infants and children affected by cardiac hypertrophy, chronic hypoxaemia, and the effect of prolonged exposure to heart failure-inducing neuroendocrine hormones. As angiogenesis is a key component of the heart's adaptation to ischaemia,[26] quantitative adenosine-infusion cardiac magnetic resonance imaging holds the unique promise of being able to monitor this process in infants and children.

Conflicts of Interest

There are no relevant conflicts of interest for any of the authors.

Ethical Standards

The authors assert that all the procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Federal regulation 45CFR46, the federal policy for the protection of human subjects [the common rule]) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Oregon Health & Science University Institutional Review Board.

References

1. Azevedo CF, Nigri M, Higuchi ML, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol 2010; 56: 278–287.
2. Weidemann F, Herrmann S, Stork S, et al. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. Circulation 2009; 120: 577–584.
3. Flett AS, Sado DM, Quarta G, et al. Diffuse myocardial fibrosis in severe aortic stenosis: an equilibrium contrast cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging 2012; 13: 819–826.
4. Marcus ML, Harrison DG, Chilian WM, et al. Alterations in the coronary circulation in hypertrophied ventricles. Circulation 1987; 75: I19–I25.
5. Constantine G, Shan K, Flamm SD, Sivananthan MU. Role of MRI in clinical cardiology. The Lancet 2004; 363: 2162–2171.
6. Wang L, Jerosch-Herold M, Jacobs DR Jr, Shahar E, Folsom AR. Coronary risk factors and myocardial perfusion in asymptomatic adults: the multi-ethnic study of atherosclerosis (mesa). J Am Coll Cardiol 2006; 47: 565–572.
7. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (cMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson 2008; 10: 35.
8. Jerosch-Herold M, Seethamraju RT, Swingen CM, Wilke NM, Stillman AE. Analysis of myocardial perfusion MRI. J Magn Reson Imaging 2004; 19: 758–770.
9. Petersen SE, Jerosch-Herold M, Hudsmith LE, et al. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. Circulation 2007; 115: 2418–2425.
10. Team RDC. R: A language and environment for statistical computing (http://www.R-project.Org/). R Foundation for Statistical Computing; Institute for Statistics and Mathematics, Wirtschaftsuniversität Wien Welthandelsplatz 1, Vienna, Austria, 2010.
11. Roccella E. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114: 555–576.
12. Jahnke C, Nagel E, Gebker R, et al. Prognostic value of cardiac magnetic resonance stress tests: adenosine stress perfusion and dobutamine stress wall motion imaging. Circulation 2007; 115: 1769–1776.
13. Chareonthaitawee P, Kaufmann PA, Rimoldi O, Camici PG. Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans. Cardiovasc Res 2001; 50: 151–161.
14. Rosen BD, Lima JA, Nasir K, et al. Lower myocardial perfusion reserve is associated with decreased regional left ventricular function in asymptomatic participants of the multi-ethnic study of atherosclerosis. Circulation 2006; 114: 289–297.
15. Puchalski MD, Williams RV, Askovich B, et al. Late gadolinium enhancement: precursor to cardiomyopathy in duchenne muscular dystrophy? Int J Cardiovasc Imaging 2009; 25: 57–63.
16. Wicker P, Tarazi RC. Coronary blood flow in left ventricular hypertrophy: a review of experimental data. Eur Heart J 1982; 3 (Suppl A): 111–118.
17. Hoffman JI. Problems of coronary flow reserve. Ann Biomed Eng 2000; 28: 884–896.
18. Rakusan K, Flanagan MF, Geva T, Southern J, Van Praagh R. Morphometry of human coronary capillaries during normal growth and the effect of age in left ventricular pressure-overload hypertrophy. Circulation 1992; 86: 38–46.
19. Feldman AM, Cheksis-Feiner E, Hamad E, Chan T. Adenosine receptor subtypes and the heart failure phenotype: translating lessons from mice to man. Trans Am Clin Climatol Assoc 2011; 122: 198–214.
20. Funabiki K, Onishi K, Dohi K, et al. Combined angiotensin receptor blocker and ace inhibitor on myocardial fibrosis and left ventricular stiffness in dogs with heart failure. Am J Physiol Heart Circ Physiol 2004; 287: H2487–H2492.
21. Hudson MP, Armstrong PW, Ruzyllo W, et al. Effects of selective matrix metalloproteinase inhibitor (pg-116800) to prevent ventricular remodeling after myocardial infarction: results of the premier (prevention of myocardial infarction early remodeling) trial. J Am Coll Cardiol 2006; 48: 15–20.
22. Kaye DM, Krum H. Drug discovery for heart failure: a new era or the end of the pipeline? *Nature reviews*. Drug Disc 2007; 6: 127–139.
23. Sata Y, Krum H. The future of pharmacological therapy for heart failure. Circ J 2010; 74: 809–817.
24. Young MJ, Lam EY, Rickard AJ. Mineralocorticoid receptor activation and cardiac fibrosis. Clin Sci (Lond) 2007; 112: 467–475.
25. Dietrich O, Reiser MF, Schoenberg SO. Artifacts in 3-T MRI: physical background and reduction strategies. Eur J Radiol 2008; 65: 29–35.
26. Berry C, Balachandran KP, L'Allier PL, Lesperance J, Bonan R, Oldroyd KG. Importance of collateral circulation in coronary heart disease. Eur Heart J 2007; 28: 278–291.