



Pathophysiology of coronary blood flow in congenital heart disease

Elhadi H. Aburawi^{a,b,*}, Erkki Pesonen^a

^a Department of Pediatrics, Division of Pediatric Cardiology, Lund University, Lund, Sweden

^b Department of Pediatrics, Faculty of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates

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ABSTRACT

Objectives: The aim was to investigate the effects of volume and pressure overload and increased coronary perfusion pressure on coronary flow (CF) in congenital heart disease (CHD) patients.

Background: The effects of CHD on CF are poorly mapped.

Methods: A total of 65 patients with acyanotic CHD and 49 age-matched healthy controls were examined by transthoracic Doppler echocardiography. Posterior descending artery flow was measured in patients with pulmonary valve stenosis (PS) and atrial septal defects (ASDs) i.e. in lesions with right ventricular pressure or volume overload, and left anterior descending artery flow in patients with coarctation of the aorta (CoA) and ventricular septal defect (VSD), in lesions with left ventricular pressure or volume overload. The CF data in each patient group were expressed as the percent of the median for healthy controls from the same age group.

Results: The CF values were in VSD 172%, ASD 185%, PS 233%, and CoA 773% patients. In CoA patients body surface area ($r=0.90$, $p<0.0001$), systolic blood pressure ($r=0.72$, $p<0.0001$), diastolic blood pressure ($r=0.77$, $p<0.0001$), systolic wall tension ($r=-0.77$, $p=0.004$), and signs of inflammation (log CRP, $r=-0.75$, $p=0.007$) correlated with CF.

Conclusions: The increase in CF and velocity was most significant in patients with CoA. In newborns, increased coronary perfusion pressure seems to be the most important factor for increased CF, even if the pressure is not assumed to cause a significant increase in flow over the auto-regulatory range of 70–130 mm Hg. We also showed that inflammation decreases CF.

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1. Introduction

Flow in the coronary arteries is governed by the myocardial workload, myocardial mass, and intramyocardial tension created by the pressure gradient across the vascular bed between the aorta and coronary sinus [1]. The degree of volume and pressure workload affecting CF depends on the type of congenital heart disease (CHD). The increased ventricular pressure and/or ventricular diameter, as well as ventricular hypertrophy, lead to compensatory increases in the CF [2–4].

Increased flow rate augments endothelial cell shear stress, which stimulates the secretion of nitric oxide and prostacyclin from endothelial cells. This has a dilatatory effect on vascular smooth muscle cells [5]. On the other hand, inflammation might decrease CF. The concentration of C-reactive protein (CRP), a marker of the degree of inflammation, has been reported to have a negative correlation with CF after cardiopulmonary bypass [6].

The aim of this study was to provide additional understanding of the pathophysiology of CF in acyanotic CHD by studying the effects of ventricular wall stress, volume, and pressure overload on CF.

2. Methods

2.1. Study subjects

Parameters of CF in the left anterior descending artery (LADCA) and posterior descending artery (PDCA) were determined by transthoracic Doppler echocardiography (TTDE) in 64 patients with different types of acyanotic CHD. The study was performed at admission 1 day before cardiac catheterization or surgical procedures. Seven neonates had severe pulmonary valve stenosis (PS), 12 neonates had coarctation of the aorta (CoA), 18 infants had ventricular septal defect (VSD) of which 13 had pure VSD and five atrioventricular septal defects, and 27 patients had atrial septal defect (ASD). Cardiac catheterization data was available only for patients with PS and 13 patients with ASD before cardiac interventions, balloon pulmonary valvuloplasty or device closure of ASD, respectively. The exclusion criteria were clinical signs of infectious illness or a CRP value >5.0 mg/l prior to the procedure. The patients were studied using TTDE 1–2 days before their surgical or interventional cardiac catheterization procedures.

The age of patients in the diagnostic groups was fairly homogenous because optimal interventional treatment is age-specific. Age-matched healthy controls ($n=49$) were included in every diagnostic group. The patient demographic data is presented in Table 1.

* Corresponding author. Department of Pediatrics, Faculty of Medicine and Health Sciences, P. O. Box 17666, United Arab Emirates University, Al-Ain, United Arab Emirates. Tel.: +971 3 7137 462; fax: +971 3 7672022.

E-mail address: e.aburawi@uaeu.ac.ae (E.H. Aburawi).

Table 1
Measured parameters.

	Age	HR (bpm) (SD)	Systolic BP (SD)	Diastolic BP (SD)	RPP (SD)	LVMI (gm/m ²) (SD)	FS (%) (SD)	CI (l/min/m ²) (SD)	CRP (mg/l) (SD)
PS (n = 7)	Mean, 3.8 days	143	72	38	10,290	86	32	2.5	<0.8
	Range, 2–7 days	(8)	(4.5)	(4.4)	(968)	(15)	(3.4)	(0.8)	
Control (n = 10)	Mean, 5.0 days	123	79	43	9724	52	37	3.0	
	Range, 1–30 days	(17)	(12)	(10)	(2042)	(10)	(5)	(1.4)	–
p-value	–	0.20	0.20	0.20	0.03	0.03	0.10	0.01	–
CoA (n = 12)	Mean, 10.0 days	148	102	55	14,302	62	33	2.1	1.7
	Range, 2–50 days	(7)	(11)	(8)	(1310)	(175)	(4)	(1.0)	
Control (n = 10)	Mean, 5.0 days	123	79	43	9724	52	37	3.0 (1.4)	–
	Range, 1–30 days	(17)	(12)	(10)	(2042)	(10)	(5)		
p-value	–	0.001	0.0004	0.002	0.0001	0.001	0.01	0.001	–
VSD (n = 18)	Mean, 6 months	139	95	53	13,278	75	38	4.5	<0.8
	Range, 3–18 months	(15)	(10)	(8)	(1127)	(18)	(4)	(2.2)	
Control (n = 15)	Mean, 6.5 months	132	89	50	11,940	55	36	3.2	–
	Range, 3–16 months	(10)	(7)	(6)	(1690)	(11)	(4)	(1.3)	
p-value	–	0.02	0.01	0.6	0.02	0.01	0.0001	0.019	–
ASD (n = 27)	Mean, 3.5 years	98	103	56	10,025	56	36	4.0	<0.8
	Range, 2–8 years	(11)	(10)	(7)	(1266)	(15)	(6)	(1.3)	
Control (n = 14)	Mean, 5.1 years	91	101	56	9183	54	41	3.5	
	Range, 2–7 months	(10)	(9)	(6)	(922)	(7)	(4)	(1.1)	–
p-value	–	0.26	0.3	0.2	0.08	0.7	0.06	0.2	–

Data are means (\pm SD) or as indicated.

CI, cardiac index (l/min/m²); FS, fractional shortening; RPP, left ventricular rate-pressure product (mm Hg/min); BP, blood pressure (mm Hg); LVMI (g/m²), left ventricular mass index; HR, heart rate; and bpm, beats per min.

Written consent was obtained from the guardians of the children enrolled in the study. The study protocol conformed to the principles outlined in the Declaration of Helsinki [7]. The ethics committee for human research at Lund University approved the study.

2.2. Transthoracic and Doppler echocardiography

TTDE examination was performed using Sequoia™ C512 (Acuson Mountain View, CA, USA) with a 7–10 MHz transducer. Standard M- and B-mode and Doppler echocardiography studies were performed to determine the anatomy and function of the heart. The diameter of the aorta was measured from a long axis view in M-mode. Left ventricular fractional shortening (FS) was computed from the standard formula [8]. Left ventricular mass (LVM) was calculated from the M-mode in accordance with the American Society of Echocardiography recommendations [9].

Systolic wall stress (i.e. the left ventricular wall tension) was calculated according to the La Place law [10]: wall stress in g/cm² = systolic pressure \times left ventricular internal diameter in systole / (interventricular septal thickness plus posterior wall thickness / 2).

The CoA pressure gradient was evaluated by the flow velocity through the coarctation segment using the simplified Bernoulli equation (pressure gradient = $4 \times$ velocity²). For cardiac output (CO) measurement the velocity time integral across the aortic valve was measured from the apical five-chamber view and averaged over three sequential cardiac cycles. CO was divided by body surface area to obtain the cardiac index (CI).

The method for measuring CF and flow velocity in the LAD was previously described [11,12]. An apical four-chamber view was used to measure flow in the PDCA. The probe was angulated anteriorly and rotated anticlockwise until the right ventricle disappeared from the view. Otherwise, the technique was similar to that used to measure flow in the LAD. Because the PDCA runs almost parallel to the ultrasound beam in the posterior interventricular groove, its diameter could not be measured; instead, the internal dimension of the main right coronary artery (RCA) was measured and used in flow calculations.

The measurements were corrected for the angle between the Doppler beam and the direction of coronary flow. True velocity was defined as the measured velocity divided by the cosine of the angle between the Doppler beam and the direction of the blood flow. The mean (SD) angle was 33° [8] for the LAD and 30° [9] for the PDCA.

The internal dimension of the coronary arteries was measured from the standard parasternal short-axis view of the R-wave. Callipers were applied to the internal borders of the LAD 2–3 mm distal to the bifurcation of the left main coronary artery and close to the ostium of the RCA. The velocity scale was decreased to the minimum range and then gradually increased until the maximal colour intensity inside the vessel lumen, without backscatter, was obtained. The sample volume was adjusted to 0.5–1.0 mm, and the sample volume that gave the highest quality envelope and pure sound throughout the cardiac cycle was chosen. Flow in the LAD was measured at the same site as the LAD diameter. In the PDCA it was measured in its proximal half.

All images were saved on a magnetic-optic disc, reviewed in slow motion, and analysed in single frame advance mode. Arterial blood pressure was measured by an automatic

oscillometer cuff sphygmomanometer (Dynamap, Critikon, Inc., Tampa, Florida, USA). The rate-pressure product was calculated by multiplying heart rate by the systolic blood pressure [13]. The analysis package of the ultrasound unit was used to manually trace the spectral envelope. Diastolic peak flow velocity (PFVd), systolic peak flow velocity (PFVs), the sum peak flow velocity (PFVd + s), diastolic velocity time integral (VTId), systolic velocity time integral (VTIs), and the sum velocity time integral (VTId + s) were measured. The velocity time integral per minute was calculated by multiplying the VTIs + d by heart rate. The CF in millilitres per minute was calculated as VTIs + d \times heart rate \times π (coronary artery radius)², where π (coronary artery radius)² = cross sectional area of the coronary artery.

2.3. Reproducibility

The reproducibility test was performed as previously described [14]. Ten healthy children between 4 and 8 months of age underwent two measurements 15 min apart. The intra-observer coefficient of variation (COV) for LAD diameter was 3.7%, for diastolic peak flow velocity 6.8%, systolic peak flow velocity 5%, velocity time integral 7.7%, LAD blood flow 9%, and heart rate 1%.

2.4. Statistics

ANOVA and unpaired student's t-test was used to compare patients and their age-matched controls. Simple, multiple, and stepwise regression analyses were used to calculate the correlation between CF in the PDCA and right ventricular end diastolic pressure (RVEDP), as well as the pulmonary to systemic flow ratio (Qp/Qs). C-reactive protein was log-transformed given its skewed distribution. The correlation of CF and PFV with body surface area, LVM, systolic and diastolic blood pressure, systolic wall tension, CRP, CI, the pressure gradient across the coarctation segment, and FS % was tested. Statistical analyses were performed using the Stat View (SAS Inst. 5.0) statistical software package. A p-value of <0.05 was considered significant. Results are presented as medians. A reproducibility test was performed according to the British Standards Institution [15].

3. Results

3.1. Hemodynamic findings

The CI (l/min/m²) was increased in VSD shunt patients (p = 0.02) compared to controls and decreased in obstructive lesions (CoA, p = 0.001 and PS 2.5, p = 0.01). The rate-pressure product was highest in CoA patients and VSD patients (p = 0.0001 and p = 0.02, respectively, compared to controls; Table 1).

Table 2

Coronary flow data for the posterior descending coronary artery in patients with pulmonary stenosis (PS) or atrial septal defect (ASD) and age-matched healthy controls.

	PS (n=7)	Controls (n=10)	p	ASD (n=27)	Controls (n=14)	p
RCA, mm	1.2 (0.2)	1.0 (0.11)	0.01	1.7 (0.3)	1.6 (0.2)	0.01
PFVd, cm/s	40 (4.5)	18 (4.7)	0.0001	44 (8)	20 (5)	0.001
PFV %	225	96	0.01	118	90	0.02
VTId + s, cm	15 (2.7)	3.7 (0.3)	0.001	14 (4)	10 (3)	0.001
CF, ml/s	8.4 (1.8)	3.8 (1.3)	0.0001	38 (18)	20 (5)	<0.0001
CF %	233	92	0.01	185	100	0.0001

Right coronary artery (RCA) diameter is used as PDCA diameter. Data are presented as median (\pm SD). The p-value represents the differences between the patients and their controls. PFV, peak flow velocity; PFVd, peak flow velocity in diastole; PFV %, peak flow percentage; VTI, velocity time integral; CF, coronary blood flow; and CF %, blood flow percentage.

3.2. Cardiac anatomy and coronary flow

The diameter of the coronary arteries was increased significantly in patients as compared to controls; $p < 0.001$ for CoA or VSD patients and $p < 0.01$ for PS or ASD patients (Tables 2 and 3). The intraventricular pressure and shunt flow increase correlated to coronary flow velocity and the amount of coronary flow. In patients with PS the median of PFV was 225% ($p = 0.01$) and in patients with CoA 600% ($p = 0.0001$) of controls. In VSD patients PFV was 225% ($p = 0.0001$), and ASD patients 118% of controls ($p = 0.02$; Tables 2 and 3, Fig. 1). The CF was even more increased than PFV due to a simultaneous vasodilatation. In patients with PS, the median CF was 233% ($p = 0.01$) of control, 773% in CoA ($p < 0.0001$), 172% in VSD ($p = 0.0005$), and 185% in ASD ($p = 0.0001$; Tables 2 and 3).

3.2.1. CoA patients

In patients with CoA a simple regression analysis showed significant correlation of LAD CF to body surface area ($r = 0.90$, $p < 0.0001$; Fig. 2), left ventricular mass ($r = 0.85$, $p = 0.0015$), systolic wall tension ($r = -0.77$, $p = 0.004$; Fig. 3), diastolic blood pressure ($r = 0.77$, $p = 0.003$), systolic blood pressure ($r = 0.72$, $p = 0.008$; Fig. 4), log CRP ($r = -0.75$, $p = 0.007$; Fig. 5). The LAD PFV correlated to pressure gradient across the coarctation site ($r = 0.68$, $p = 0.015$). The CI, FS, and rate-pressure product did not correlate significantly with CF parameters (Table 1). In a stepwise regression analysis the order of the parameters was: body surface area ($r = 0.82$, $p = 0.002$), LVM ($r = 0.81$, $p = 0.001$), systolic blood pressure ($r = 0.71$, $p = 0.02$), diastolic blood pressure ($r = 0.68$, $p = 0.02$), systolic wall tension ($r = -0.68$, $p = 0.02$) and CRP ($r = -0.67$, $p = 0.03$).

Table 3

Coronary flow data for the left anterior coronary artery in patients with coarctation of the aorta (CoA) or ventricular septal defect (VSD) and age-matched healthy controls.

	CoA (n=12)	Controls (n=10)	p	VSD (n=18)	Controls (n=18)	p
LAD, mm	1.8 (0.1)	1.2 (0.1)	0.001	1.7 (0.3)	1.5 (0.2)	0.001
PFVd, cm/s	42 (14)	21 (1.4)	<0.0001	36 (10)	37 (5)	ns
PFV %	600	90	0.0001	225	95	0.0001
VTI, cm	11 (4)	5.5 (1.2)	0.001	9 (3)	10 (3)	ns
CF, ml/s	44 (12)	7.4 (2.8)	<0.0001	27 (10)	17 (5)	0.0005
CF %	773	109	<0.0001	172	101	0.0005

Data are presented as median (\pm SD). The p-value represents the differences between the patients and their controls. LAD, left anterior descending artery; PFV, peak flow velocity; PFVd, peak flow velocity in diastole; PFV %, peak flow percentage; VTI, velocity time integral per heart beat; CF, coronary blood flow; CF %, blood flow percentage; and ns, non-significant.

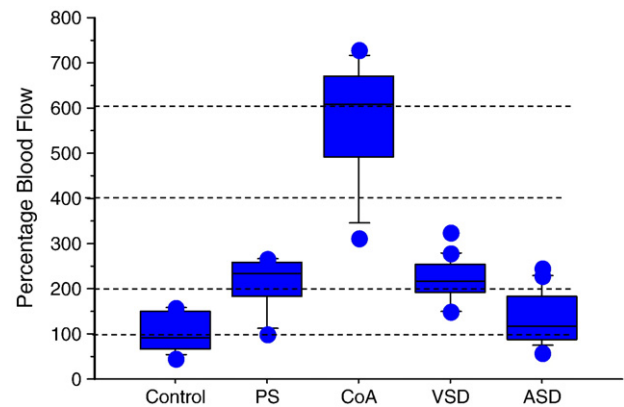


Fig. 1. Median peak flow velocity in patients with congenital heart disease. The values are percentages of the median of the controls. The flow was measured from the LCA in patients with CoA or VSD and from the posterior descending coronary artery in patients with PS or ASD.

3.2.2. ASD patients

In ASD patients, the median Qp/Qs was 1.6 (range 1.4–4). A simple regression analysis showed a positive correlation between CF in the PDCA and right ventricular end diastolic pressure or Qp/Qs ($r = 0.75$, $p = 0.0001$ and $r = 0.52$, $p = 0.06$, respectively).

3.3. Effect of inflammation

The median CRP in patients with CoA was 1.8 mg/l (range 0.8–3.2 mg/l), but normal (< 0.8 mg/l) in other patient groups. CF correlated to log CRP ($r = -0.75$, $p = 0.007$; Fig. 5).

4. Discussion

Increased coronary perfusion pressure was the most significant factor increasing CF. Ventricular volume and pressure overload also increased coronary PFV and CF. Increased systolic wall tension and inflammation seemed to have a negative effect on the amount of CF.

The success rate of measuring CF is significantly operator-dependent. Our success rate for LADCA flow measurement was 100%, but 90% for PDCA. The CF data for different age groups were made comparable by dividing the actual flow values by the median of healthy controls of the same age and multiplied by 100 (i.e. transforming them to percentages of normal).

Coronary flow measurements performed using intracoronary Doppler guide wire and positron emission tomography correlate well with TTDE assessment [11]. The measured PFV is close to the real

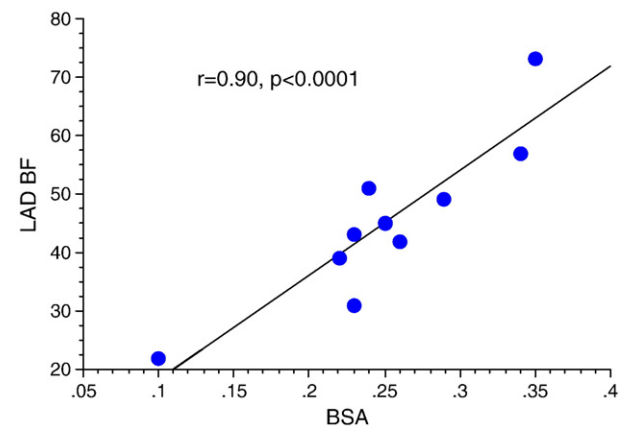


Fig. 2. Median coronary flow and body surface area in patients with coarctation of the aorta.

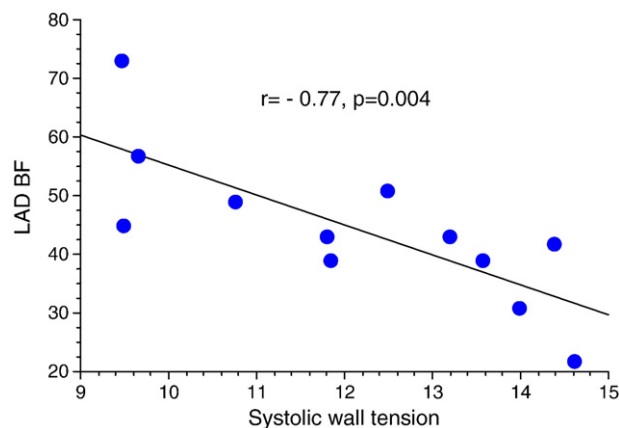


Fig. 3. Median coronary flow and systolic wall tension.

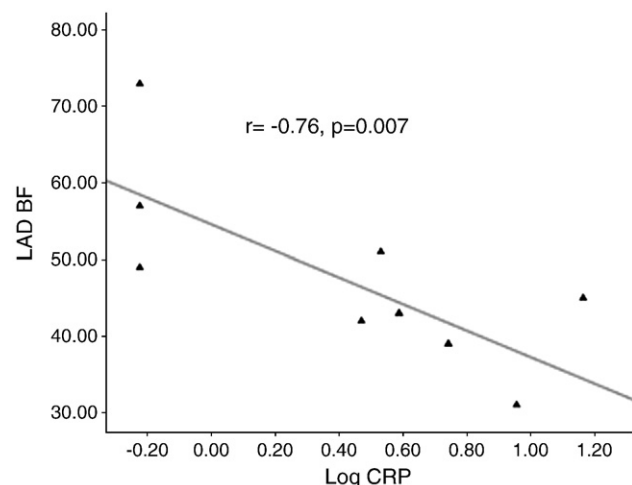


Fig. 5. Median coronary flow and log CRP in patients with coarctation of the aorta.

value, but the flow assessment is less accurate because of the uncertainties in diameter measurements. In principle, details smaller than the wavelength of the ultrasound cannot be seen.

Dimensions that are beyond the resolution limits of ultrasound can be detected accurately and precisely if there is a sufficient difference in acoustic impedance in the biological tissue structure (i.e. if the boundaries are distinct and clearly separated), as is the case between the adventitia and media interface and between the intima and arterial lumen. Differences less than the wavelength have been considered significant in-group comparisons. The visibility of below-resolution structures has been previously discussed in detail [16,17].

The measurement of coronary artery diameter by transthoracic echocardiography correlates well with quantitative coronary angiography measurements [18,19]. Accuracy has been assessed in older patients, even if not in neonates. However, the image resolution is much better in neonates and children than in adults. The theoretical resolution of the ultrasound system using a 7 MHz transducer is considered to be approximately 0.1 mm [20].

In patients with VSD, left ventricular volume overload and increased right ventricular pressure increased CF. In CoA patients the pressure gradient in aorta after the origin of the coronary arteries increased the coronary perfusion pressure and consequently very significantly increased coronary flow. The PFV and CF in the PDCA were increased in patients with ASD or PS because of the increased volume or pressure overload in the right ventricle. Increased right ventricular end diastolic pressure increased the CF, which we also have shown previously [2].

Endothelial vasoactivity has been shown to correlate inversely with CRP in patients with CRP levels up to 45 µg/ml [22]. As we

showed earlier, CF increases after cardiopulmonary bypass [14,23], but this increase is blunted when CRP is elevated, particularly among patients in whom aortic clamping lasted for more than 1 h. A similar negative association was seen in CoA patients from this series [6]. The correlation between CF and CRP was negative, suggesting that elevated CRP decreases CF. Inflammation decreases endothelial nitric oxide synthase [21], which stimulates the secretion of nitric oxide, an important factor inducing arterial vasodilatation.

Wall stress is related to ventricular pressure, chamber diameter, and wall thickness [24]. Wall stress was measured according to the La Place law; left ventricular wall stress showed a significant negative correlation with CF, PFVd + s, and PFV in systole. This finding is similar to our earlier report that the CF in patients with PS decreases linearly with an increasing pressure gradient across the pulmonary valve [2].

Myocardial hypertrophy, pressure and volume overload, and reduced arterial oxygen saturation contribute to myocardial oxygen deprivation and compensatory CF increases [25–28]. Pressure work was increased in PS and CoA patients. In addition, the pressure at the level of the coronary ostia was high in CoA patients, increasing the driving force of the CF to the cardiac vascular bed. The CF was increased more than PFV because the coronary artery diameter was increased in patients with increased endothelial cell shear stress, due to the subsequent liberation of nitric oxide, which dilates the arteries. On the other hand, increased systolic wall tension in CoA patients decreases CF.

The very high CF in the CoA patients was a somewhat unexpected finding. In these neonatal patients with CoA, there seemed to be a very significant increase in flow with a moderate increase in perfusion pressure. The driving force of blood flow in the coronary arteries is the pressure gradient between the aortic root and right atrium. According to Ohm's law, CF is dependent on the pressure gradient across the myocardium. However, the increased pressure is not assumed to cause significantly increased flow over the auto-regulatory range of 70–130 mm Hg in the coronary circulation. Our study provides more understanding of pathophysiology of CF in acyanotic CHD and the effects on ventricular wall stress, volume and pressure overload and increased coronary perfusion pressure on CF.

4.1. Limitations of the study

The data is somehow fragmentary because cardiac catheterization data existed only for patients with PS or ASD, in whom catheterization was done because of cardiac interventions. The PDCA diameter could not be measured, and the main RCA diameter was used to estimate the flow in the PDCA. This leads to some overestimation of flow in the PDCA. Moreover, the measurements of flow in the PDCA may not

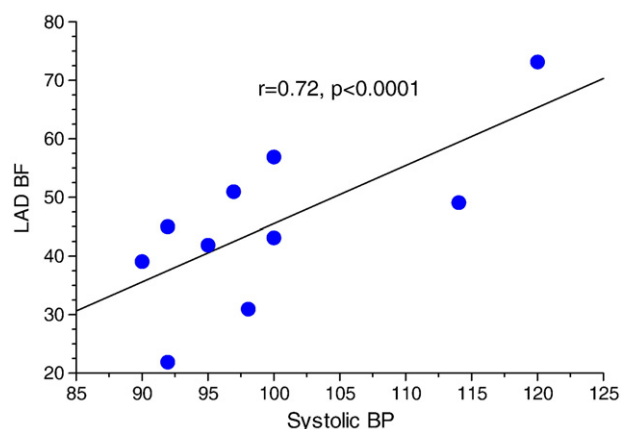


Fig. 4. Median coronary flow and systolic blood pressure (BP) in patients with coarctation of the aorta.

reflect only RCA flow because PDCA gets 30% from branches of the left circumflex coronary artery. This may cause variation in PFV and affect the diameter of PDCA. The origins of the PDCA were not confirmed on cardiac catheterization because neither aortic root injections nor selective coronary angiographies were done.

4.2. Conclusion

The present study showed that CF is increased in patients with CHD due to increasing ventricular volume and pressure overload. Increased perfusion pressure in patients with CoA had a significant effect on CF. The auto-regulatory capacity of CF in neonates with CoA seemed to be unable to maintain close to normal CF. The data also show that inflammation and systolic wall tension decrease CF.

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The authors of this manuscript have certified that they comply with the principles of ethical publishing in the International Journal of Cardiology [29].

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