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Vascular Dysfunction in Patients with Coarctation of the Aorta

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Abstract
Introduction: *Coarctation of the aorta is more commonly a discrete stenosis of the proximal thoracic aorta. The long-term prognosis may be affected by several clinical and hemodynamic conditions like residual or recurrent coarctation, systemic arterial hypertension and an associated increase in premature atherosclerotic cardiovascular events, development of aneurysm at repaired site, dissection of aorta, intracranial hemorrhage. Studies showing that a disappointingly high prevalence of hypertension even after correction of arch obstruction. Increased stiffness and abnormal smooth muscle response of the arterial wall can contribute to the development of hypertension. Therefore, we have studied vascular responses to endothelium dependent and endothelium independent stimuli in brachial artery in patients late after the surgical repair of aortic coarctation performed at different ages.*
Aim : *To assess the vascular function by assessment of the flow mediated dilatation (FMD) in brachial artery, dilatation in response to nitroglycerine (NTG) in patients after successful coarctation repair and to assess the influence of age at surgery on vascular function.*
Materials And Methods: *We studied 24 patients who underwent surgical repair of coarctation of aorta and 22 age, sex matched control subjects. It was taken care that subjects did not exert or exercise and not to ingest substances that might affect FMD. Height, weight and blood pressure in right arm and right leg were recorded. Adult subjects were considered to be hypertensive if their systolic blood pressure was >140 mm Hg and/or their diastolic blood pressure was >90 mm Hg. Children and adolescents were considered to be hypertensive if their blood pressure values were above the normal values of the 95th percentile of their age group according to the nomogram. Echocardiography was performed to confirm that there were no associated lesions or re coarctation. All subjects underwent noninvasive assessment of endothelium dependent dilatation (flow-mediated dilatation [FMD]) and endothelium-independent dilatation (dilatation to sublingual nitroglycerin [NTG]) of the brachial artery according to the task force guidelines.*
Results: *Among the patients 21% (5) of them were hypertensive. All of them were operated beyond 5 yrs of age. Among control subjects one was hypertensive. The mean echocardiographic gradient at coarct segment was 17 mmHg (SD 2.61).*
The mean brachial artery diameter in cases is 3.04 mm (SD 0.61). The mean absolute brachial FMD, percentage FMD, absolute post NTG dilatation, percentage post NTG dilatation parameters were significantly higher in control subjects when compared to the cases. Among cases, univariate analysis showed that brachial FMD was related to baseline vessel diameter (p =.01) and age at surgery (p= .001). None of the other parameters were significant determinants of the flow mediated dilatation. Age at surgery had a negative correlation coefficient. Brachial NTG response was related to age (p =.001), baseline vessel diameter (p =.001), age at the time of repair (p =.001). Again age at surgery had a negative correlation coefficient. None of the other parameters were significant determinants of the NTG mediated dilatation.
Conclusion : *Patients with repaired aortic coarctation have impaired vascular function in the upper part of the body, with abnormal responses to flow and NTG when compared to the age and sex matched control subjects. Impaired endothelial function may also contribute to the vascular dysfunction. Early repair is associated with improved reactivity .*

I. Introduction

Coarctation of the aorta occurs in approximately 6% to 8% of patients with congenital heart disease (1). Coarctation of the aorta is more commonly a discrete stenosis of the proximal thoracic aorta. The apparent anatomic simplicity is misleading. The long-term prognosis may be affected by several clinical and hemodynamic conditions like residual or recurrent coarctation, systemic arterial hypertension and an associated increase in premature atherosclerotic cardiovascular events, development of aneurysm at repaired site, dissection of aorta, intracranial hemorrhage (2,3). Studies showing that a disappointingly high prevalence of hypertension (19%) even after correction of arch obstruction (5-7). Endothelial function of conduit arteries is understood to be a key initiating event in atherogenesis. Increased stiffness and abnormal smooth muscle response of the arterial wall can contribute to the development of hypertension(12,14,16). However, little information is known about vascular function and its determinants in patients after repair of coarctation.

Therefore, we have studied vascular responses to endothelium dependent and endothelium independent stimuli in brachial artery in patients late after the surgical repair of aortic coarctation performed at different ages.

II. Aim

To assess the vascular function by assessment of the flow mediated dilatation (FMD) in brachial artery, dilatation in response to nitroglycerine (NTG) in patients after successful coarctation repair and to assess the influence of age at surgery on vascular function.

III. Materials And Methods

Study design: Prospective case control study.
Sample size: 24 patients and 22 control subjects
Inclusion criteria: Patients who underwent successful surgical repair of coarctation of the aorta in our institute.
Exclusion criteria: Major associated cardiovascular abnormalities, such as ventricular septal defect, aortic stenosis, aortic regurgitation and mitral stenosis or regurgitation.
Evidence of aortic aneurysm.
Re coarctation (Defined as more than 20 mm Hg pressure gradient with continuous wave Doppler at the level of coarctation)
Medications: All the patients were advised to withhold the vasoactive medications for at least one week.
Study Protocol: Written informed consent was taken from all the subjects and from the parents if the subject was minor. Patients attended in the morning after fasting for 12 hours. Height and weight were recorded. It was taken care that subjects did not exert or exercise and not to ingest substances that might affect FMD (caffeine, high-fat foods or use of tobacco) for at least 4 to 6 h before the study. Supine systolic and diastolic blood pressures were measured in the right arm and in the right leg after a 5-minute rest period. Adult subjects were considered to be hypertensive if their systolic blood pressure was >140 mm Hg and/or their diastolic blood pressure was >90 mm Hg. Children and adolescents were considered to be hypertensive if their blood pressure values were above the normal values of the 95th percentile of their age group according to the CDC nomogram (17).

Echocardiography was performed to confirm that there were no associated lesions or re coarctation as mentioned in the exclusion criteria. All subjects underwent noninvasive assessment of endothelium dependent dilatation (flow-mediated dilatation [FMD]) and endothelium-independent dilatation (dilatation to sublingual nitroglycerin [NTG]) of the brachial artery. The International Brachial Artery Reactivity Task Force has published guidelines for the ultrasound assessment of flow-mediated vasodilation of the brachial artery (1). Study was done according to the guidelines.

All subjects were studied while they were at rest in the supine position. Vascular ultrasound assessment of the endothelium dependent and endothelium independent dilatation of the brachial artery was performed in all patients. A B-mode scan of the right brachial artery was obtained in longitudinal section between 5 and 10 cm above the elbow by use of 8.5 MHz linear array transducer (GE Logiq MD 500 system). The artery was identified when the clearest picture of the anterior and posterior wall was obtained, and the transducer was kept at the same point throughout the study. A sphygmomanometric (blood pressure) cuff is first placed above the ante cubital fossa. A baseline rest image is acquired. Brachial artery diameter was measured during the same time of the cardiac cycle (the onset of the R-wave). Arterial occlusion is created by cuff inflated to at least 50 mm Hg above systolic pressure to occlude arterial inflow for 5 minutes. After 5 min the cuff was deflated. The longitudinal image of the artery is recorded at every 15 sec interval from 15 s after cuff deflation until 120 sec post deflation. Images were recorded and analyzed offline. Brachial artery diameter was assessed in all the images. After 10 min of rest another image is acquired to confirm the reestablishment of baseline conditions.

A single high dose (0.4 mg for adult and equivalent weight adjusted dose in case of children) of nitroglycerin (NTG) sublingual tablet was been given to determine the maximum obtainable vasodilator response. Images acquired at 15 sec interval starting from 2 minutes to 6 minutes.

All analyses were performed by a single operator. Baseline vessel size was taken as the mean of the measures obtained during the first minute. Flow mediated dilatation was calculated as absolute and percentage maximum increase in vessel size from baseline. NTG response was also calculated as absolute and percentage maximum increase in vessel size from baseline. Blood investigations (fasting blood sugar, lipid profile) were done on the day of Doppler study in our clinical lab.

IV. Statistical Analysis

Data analysis was performed by using the SPSS statistical package. Data are presented as mean ± SD. Data not showing a normal distribution are presented as median (range).

The comparison between mean of continuous variables was performed by the ANOVA test. Univariate linear regression model was used to assess the independent determinants of vascular parameters. A value of $P<0.05$ was considered to be statistically significant.

V. Results

Study population included 24 patients who underwent coarctation repair at various ages and 22 age and sex matched control subjects who were either siblings of the patients or hospital staff. Mean age and sex ratio was not significantly different between the cases and controls. Mean BMI was not significantly different between the two groups. Mean fasting blood sugar & total cholesterol was not significantly different between the two groups (Table 1). Among the patients 21% (5) of them were hypertensive. All of them were operated beyond 5 yrs of age. Among the control subjects one was hypertensive.

Echocardiography parameters

The mean echocardiographic gradient at coarct segment was 17 mmHg (SD 2.61). None had the gradient of > 20 mmHg. Other details of the echocardiograhic parameters are noted in the table 2. None of the patients had any hemodynamically significant mitral or aortic valve lesions .

Surgical details

Eighteen (75 %) patients out of 24 underwent resection and end to end anastamosis of the coarctation segment, 5 patients underwent coarctation resection and patent ductus arteriosus ligation and division, 1 patient underwent coarctation resection with dacron patch augmentation**.** Age at surgery varied from 6 months to 31 yrs (mean : 11 yrs). Only two patients underwent surgery during infancy.

Upper Limb Vascular Phenotype

The mean brachial artery diameter in cases is 3.04 mm (SD 0.61). The mean brachial artery diameter in control subjects was 3.05 mm (SD 0.64) and is not significantly different between the two groups (p 0.94) .

The mean absolute brachial FMD, percentage FMD, absolute post NTG dilatation, percentage post NTG dilatation among cases and controls were shown table 3. All the four parameters were significantly higher in control subjects when compared to the cases .

Figure 1,2,3 and 4 showing the peak FMD and post NTG dilatation among cases and control subjects respectively. Majority (66%) of the cases and controls had the peak FMD at 60 sec. Peak NTG mediated dilatation was noted at 4 to 5 min in the majority (63%) of subjects .

Determinants of Vascular Responses

Among cases, univariate analysis showed that brachial FMD was related to baseline vessel diameter (p =.01) and age at surgery (p= .001). None of the other parameters were significant determinants of the flow mediated dilatation. Age at surgery had a negative correlation coefficient. Brachial NTG response was related to age (p =.001), baseline vessel diameter (p =.001), age at the time of repair (p =.001). Again age at surgery had a negative correlation coefficient. None of the other parameters were significant determinants of the NTG mediated dilatation. Among control subjects, brachial FMD was related baseline vessel diameter (p =.001). Brachial NTG response was related to age (p = .001), baseline vessel diameter (p =.001).

VI. Discussion

The present study is assessing the vascular function after the repair of coarctation and influence of age at surgery on the vascular function. There was no significant difference in the demographic profile, fasting blood sugar, total cholesterol among the cases and controls. Mean age of surgery was 11 years and only 2 patients underwent surgery during infancy. This is significantly higher when compared to the recommended age of surgery which is due to later age of presentation. Majority of the patients underwent resection and end to end anastamosis of the coarctation segment.

Twenty percentage of the patients were hypertensive, all of them were operated beyond 5 years of age. This is in concordance with the study by Peter A. Seirafi et al (7), 27 % of the patients operated beyond infancy had late hypertension on 25 years follow up. Considering the mean age of surgery, the prevalence of hypertension in our patient population is lower when compared to other studies, this could probably be related to the duration of follow up. The maximum follow up in our study was 8 years post surgery .The prelvalence of the hypertension in our study population is likely to increase as the duration of follow up increases.

The basal brachial artery diameter was not significantly different between the two groups. Since there was wide variation of age among the patients and basal brachial artery diameter varied according to the age, we preferred to use percentage of flow mediated dilatation in relation to the basal brachial artery diameter. Absolute flow mediated dilatation and percentage of flow mediated dilatation were significantly higher in control

subjects when compared to cases . In the same way absolute NTG mediated dilatation and percentage of NTG mediated dilatation was significantly lower in patients when compared to the control subjects. Our study results were in concordance with the previous studies by Gardiner (9) and Marcello de Divitiis (10).

HM Gardiner et al (9) had studied the similar cohort of patients who underwent successful repair of coarctation in childhood and assessed the flow mediated dilatation and to glyceryl trinitrate. FMD was significantly lower in coarctation subjects, as were GTN response reflecting abnormal dilatory capacity in arteries.

Marcello de Divitiis et al (10) has studied the similar cohort of the patients who underwent coarctation repair at various ages. Flow-mediated dilatation (FMD) and the dilatation after sublingual nitroglycerin were measured In brachial artery and posterior tibial artery. Arterial stiffness was determined by pulse-wave velocity (PWV) of the brachioradial and femoral-dorsalis pedis tracts. Patients, compared with control subjects, had lower brachial FMD and NTG and higher brachioradial PWV. In contrast, posterior tibial FMD, NTG, and lower limb PWV were comparable and concluded that patients with repaired aortic coarctation have impaired conduit artery function, with abnormal responses to flow and NTG, and increased vascular stiffness confined to the upper part of the body.

Similar FMD findings have been demonstrated in other cohorts of young subjects with coronary risk factors such as hypercholesterolemia, cigarette smoking and diabetes by Mullen M et al (12). Rajesh K. Kharbanda et al (16) has shown that dilatation after brief episodes of hyperemia is mediated by release of nitric oxide, hypercholesterolemia seems to affect these pathways with impairment of the nitric oxide–dependent pathway. Neuenteufl T et al (14) has shown that reduced brachial artery FMD has been related to adverse cardiovascular outcome in coronary artery disease patients.

However, the FMD findings must be interpreted with caution in coarctation patients, in view of reduced dilatation to NTG (NO donor) also. This may be due to reduced capacity for relaxation of vascular smooth muscle cells and/or to structural changes in the arterial wall that limit its ability to dilate indicating an increase in resting arterial stiffness.

The present study shows that in patients with repaired coarctation of the aorta, vascular reactivity and mechanical properties of large conduit arteries are impaired even late after successful repair. Reduced FMD and NTG responses were observed in the upper limb. This pattern of persistent abnormalities of conduit arteries in the upper limb during long-term follow-up suggests that aortic coarctation is associated with extensive arterial dysfunction and that, at least in part, vascular changes are acquired as a result of the abnormal hemodynamics present in the upper part of the body before surgery.

In univariate analysis age at surgery is related to the flow mediated dilatation as well as NTG mediated dilatation, and has the negative correlation coefficient. Which indicates that if the surgery is done at younger age, the flow mediated dilatation and NTG mediated dilatation was more. This is in contrast to the study done by Marcello de Divitiis, et al (10), where the age at surgery was not a determinant of the flow mediated as well as NTG mediated dilatation .

Clinical implications

Aortic coarctation is associated with persistent abnormalities of arterial function during long-term follow-up , likely to contribute to the development of late systolic hypertension, and therefore may contribute to atherosclerosis, which is responsible for reduced life expectancy and morbid events. Early repair may preserve the elastic properties of conduit arteries, and this may explain, at least in part, the known relationship between the timing of repair and prognosis. We recommend to assess the vascular function test for patients with operated for CoA especially at a older age with normal blood pressure as a routine test on follow up. This will identify the patients with high risk of vascular complication in future, so that a frequent follow up plan can be made for them. Role of measures that improve the endothelial function in post coarct surgery patients is also to be studied, which might improve the long term outcome of these patients.

Study limitations:

Sample size was small size, which could have influenced the results. During vascular analysis continuous video recording was not done, which could have resulted in inaccurate assessment of the brachial artery diameter Steriotactic probe holder was not used during the study which could have resulted in inaccurate assessment of the vascular diameter.

VII. Conclusion

Patients with repaired aortic coarctation have impaired vascular function in the upper part of the body, with abnormal responses to flow and NTG when compared to the age and sex matched control subjects. Impaired endothelial function may also contribute to the vascular dysfunction. Early repair is associated with improved reactivity .

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Legands

Table 1: Showing the baseline parameters among cases and controls
Table 2: Showing the echocardiographic parameters of patients
Table 3: Showing the vascular study parameters in cases and controls
Figure 1 : Showing the timing of peak flow mediated dilatation among cases after cuff release
Figure 2 : Showing the timing of peak flow mediated dilatation among control subjects after cuff release
Figure 3 : Showing the timing of post NTG mediated dilatation among cases after cuff release
Figure 4 : Showing the timing of post NTG mediated dilatation among control subjects
Figure 5 : Showing an ultrasound image of the brachial artery of a case at basal condition. The diameter measured to be 3 mm.
Figure 6 : Showing an ultrasound image of the brachial artery of a case during peak flow mediated dilatation at 60 sec after cuff release. The diameter was measured to be 3.3 mm.
Figure 7 : Showing an ultrasound image of the brachial artery of a case during peak post NTG dilatation mediated dilatation at 4 min. The diameter was measured to be 3.5 mm.

Table 1

	Min	**Max**	**Mean**	**SD**	**Significance** (p value)

AGE (in yrs)	*Case*	4	35	17.12	10.04	.07
	Control	7	40	18.40	11.47	
BMI (kg / m2)	*Case*	17.3	29	22.16	2.98	
	Control	12.8	26.1	20.56	2.83	.68
Total cholesterol (in mg /dl)	*Case*	169	202	183.63	9.01	
	Control	180	208	191.00	11.38	.69
FBS (in mg /dl)	*Case*	76	110	89.18	8.19	.11
	Control	77	110	87.50	12.89	

Table 2

Echocardiography parameters	Number of patients
Coarctation gradient >20 mmHg	-
Bicuspid aortic valve	13
Aortic regurgitation	5 (trivial)
Aortic stenosis	-
Morphologically abnormal mitral valve	2
Mitral stenosis / mitral regurgitation	-
VSD	1 (small)
PDA	-
Coarct site aneurysm	-

Table 3 : Vascular study parameters

		Mean	SD	Significance (p value)
Basal brachial artery diameter (in mm)	*Cases*	3.05	0.61	0.94
	Controls	3.04	0.64	
Absolute FMD(in mm)	*Cases*	0.22	0.07	
	Controls	0.30	0.07	0.001
Percentage FMD	*Cases*	7.72	2.97	
	Controls	10.38	3.51	0.008
Absolute NTG mediated dilatation (in mm)	*Cases*	0.36	0.05	0.002
	Controls	0.42	0.08	
Percentage NTG mediated dilatation	*Cases*	12.18	2.43	
	Controls	14.63	4.26	0.020

Fig1

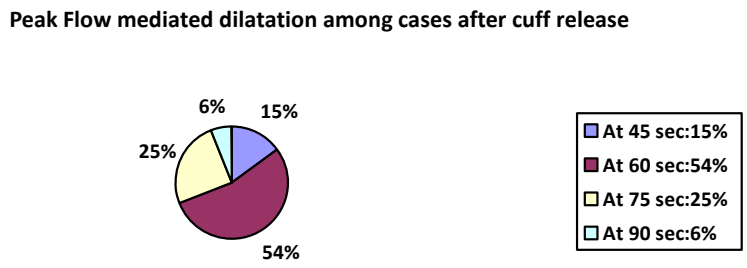


Fig 2

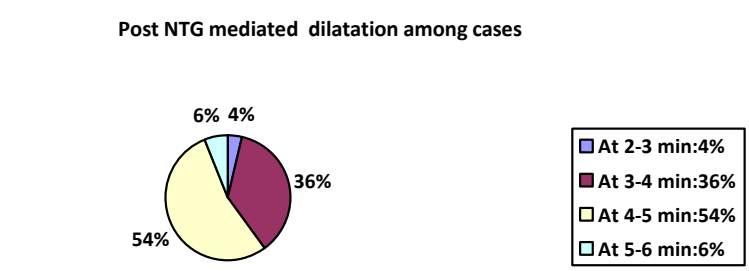
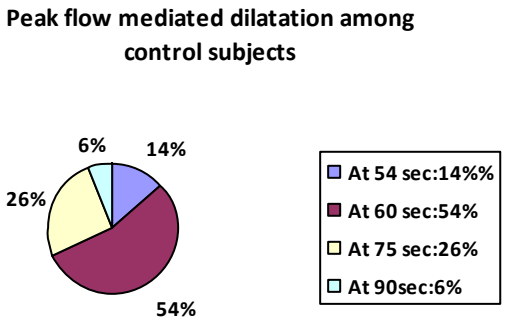


Fig 3
Fig 4



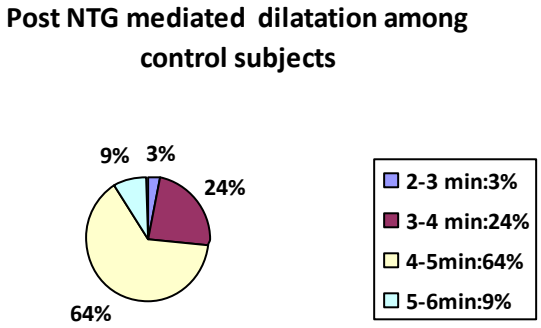


Fig 5

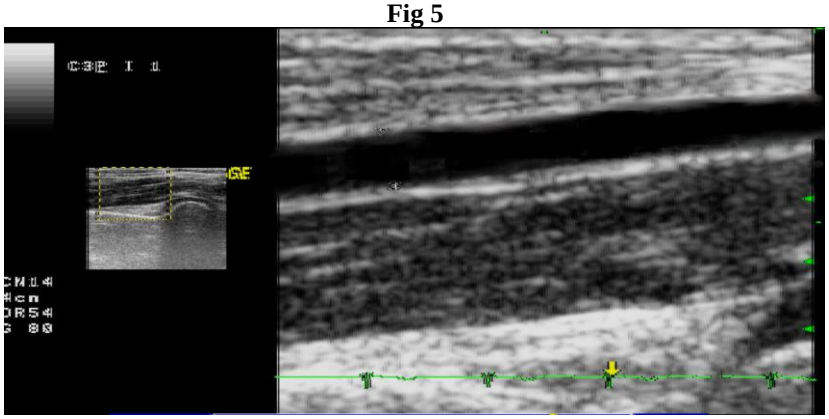


Fig 6

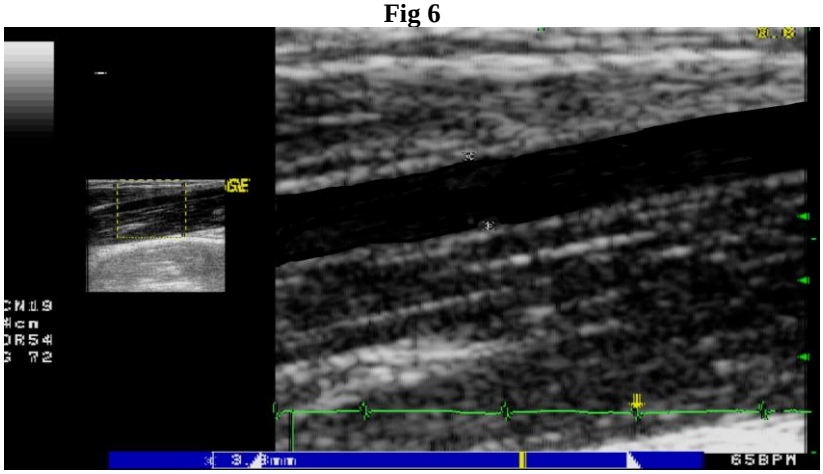


Fig 7