Reference range for brachial artery flow-mediated dilation in healthy Chinese children and adolescents

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KEY MESSAGES

1. This study establishes the local reference range for flow-mediated dilation in healthy Chinese children and adolescents (aged 8 to 18 years) in Hong Kong.
2. In females, flow-mediated dilation increased rapidly from 8.29% at age 8 years to reach a peak (8.80%) at age 13 years, then decreased to 8.38% at age 18 years.
3. In males, flow-mediated dilation increased gently from 8.34% at age 8 years to a peak (8.77%) at age 14 years, then decreased to 8.54% at age 18 years.

Hong Kong Med J 2018;24(Suppl 3):S36-8
HMRF project number: 01120406

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Introduction

The vascular endothelium was once considered an inert barrier that separates the vascular wall from the circulating blood. There is now evidence to suggest that this layer is active and functionally important in the maintenance of vascular homeostasis. Endothelial function can be assessed by measuring changes in the diameter of conduit arteries, commonly the brachial artery. Ultrasonography of flow-mediated dilation (FMD), also known as endothelium-dependent dilation, is the standard means to non-invasively evaluate vascular response. In adults, abnormal FMD of the brachial artery is an independent predictor of the development of cardiovascular adverse events.[1] In children, impaired FMD is associated with diabetes, low birthweight, dyslipidaemia, Henoch-Schönlein purpura, and sleep-disordered breathing.[2]

Few large-scale studies have been published on the reference range of FMD in children. The range of FMD differs between different ethnic and geographical populations. It is unknown if puberty has any effects on endothelial function. No such studies have been carried out in ethnic Chinese populations, and the use of a reference range for other ethnic groups may under- or over-diagnose endothelial dysfunction. We aimed to establish a reference range for FMD in Chinese children and adolescents in Hong Kong.

Methods

Ethnic Chinese children and adolescents (age, 8 to 18 years) were recruited from the community by the random selection of primary and secondary schools from four regions of Hong Kong (Hong Kong Island, Kowloon, New Territories East, and New Territories West) from May 2014 to July 2015. Anthropometric measurements included weight, height, body mass index, and waist circumference. After the participant had been laying in a recumbent position for 10 to 15 minutes, resting blood pressure was measured by oscillometry with the Datascope Accutorr Plus (Soma Technology, Bloomfield [CT], United States), which has been validated in local Chinese school children. For brachial artery FMD, a linear array transducer (L10-5 median frequency, 7.5 MHz) and MicroMaxx Ultrasound System (FUJIFILM SonoSite, Bothell [WA], United States) was used. B-mode ultrasonography was performed. Reactive hyperaemia was induced by inflation of a pneumatic tourniquet placed around the forearm (distal to the segment of the artery being scanned) to a pressure of 180 mm Hg for 4 to 5 minutes, followed by release to cause endothelium-dependent FMD. The artery was scanned for 30 seconds before and 90 seconds after deflation/release. FMD was defined as the percentage increase in baseline artery diameter after the corresponding stimulus, with reference to baseline. The absolute difference in artery diameter was recorded before and after stimulus. This is the most accepted and established method used in our unit, and the whole procedure results in minimal discomfort and is well tolerated.[3]

Results

Six primary schools and 14 secondary schools were recruited; two to three classes from each school were randomly assigned. Six participants were excluded because of self-reported hypertension; none had any chronic cardiovascular diseases. Of the students, 36 (7%) of the primary and 158 (12%) of the secondary school students declined to participate but reasons were not recorded. A total of 480 primary school students and 1157 secondary school students were recruited. Their anthropometric measurements, baseline artery diameter, blood pressure, and FMD by age and sex are presented in Tables 1 and 2.

Analysis of correlation coefficient confirmed significant correlations of FMD with age (r=0.060) and height (r=0.066) but not with weight, waist circumference, body mass index, or baseline artery diameter. The extent of FMD increased with age in both sexes, and the increase plateaued after about age 14 years; this trend was more obvious in females than in males. In females, FMD increased rapidly from 8.29% to reach the peak (8.80%) at age 13 years, then decreased to 8.38% at age 18 years. In males, FMD increased gently from 8.34% to the peak (8.77%) at age 14 years, then decreased to 8.54% at age 18 years. The mean FMD in Hong Kong children aged 14 years (males, 8.77%; females, 8.70%) was higher than that reported in the United Kingdom (males, 7.46%; females, 7.27%) [all P<0.01, Table 3], although the mean FMD of children aged 9 to 11 years in both studies was almost identical.[4]

Discussion

This study is the largest cross-sectional study of FMD in children and adolescents. It establishes the reference range for FMD in Chinese children and adolescents in Hong Kong. In our study, the FMD of participants was not related to baseline vessel

TABLE 1. Anthropometric characteristics by age and sex

Age, y	No. of males	No. of females	Height, cm*		Weight, kg*		Waist circumference, cm*		Body mass index, kg/m²*	
			Males	Females	Males	Females	Males	Females	Males	Females
8	58	58	129.50±6.00	128.90±5.30	27.30±4.87	27.27±4.68	73.93±124.01	58.48±7.46	16.17±1.96	16.35±2.14
9	58	57	134.10±5.80	132.90±5.30	28.05±3.47	26.47±3.24	56.93±4.27	55.76±8.72	15.55±1.26	14.93±1.18
10	58	58	138.60±5.30	139.80±6.30	31.64±4.82	31.76±4.36	60.30±5.72	59.55±5.06	16.39±1.69	16.22±1.51
11	58	58	145.80±6.20	148.80±6.80	35.71±5.51	37.05±5.33	61.40±5.66	61.59±6.08	16.71±1.70	16.68±1.71
12	99	99	154.20±7.30	154.20±5.40	47.79±11.71	46.83±9.05	69.22±10.55	67.70±7.19	19.91±3.79	19.64±3.33
13	101	99	160.50±8.30	157.00±4.90	48.65±8.26	47.00±6.10	66.97±6.57	68.49±6.52	18.79±2.23	19.02±2.02
14	100	96	166.40±6.40	158.90±5.80	54.94±7.45	51.42±8.85	79.07±93.17	68.91±8.17	19.83±2.43	20.33±3.06
15	88	80	168.90±7.70	159.10±6.20	56.32±8.58	55.36±11.70	80.29±99.33	70.87±10.30	19.68±2.38	21.91±4.78
16	88	89	170.30±6.50	159.60±5.50	61.43±11.84	49.17±5.60	72.48±12.79	68.61±6.68	21.16±3.69	19.29±1.93
17	74	81	170.70±5.80	160.00±5.90	63.42±13.56	52.92±8.70	75.63±11.99	70.99±7.99	21.74±4.39	20.65±2.88
18	47	33	170.60±6.20	159.20±5.50	64.81±15.17	51.98±7.07	75.91±14.34	68.07±7.56	22.21±4.71	20.49±2.32

* Data are presented as mean ± standard deviation

TABLE 2. Flow-mediated dilation, baseline artery diameter, and blood pressure by age and sex

Age, y	No. of males	No. of females	Flow-mediated dilation, %*		Baseline artery diameter, mm*		Systolic blood pressure, mm Hg*		Diastolic blood pressure, mm Hg*	
			Males	Females	Males	Females	Males	Females	Males	Females
8	58	58	8.34±0.87	8.29±0.82	2.25±0.23	2.14±0.2	103.11±9.58	103.05±9.8	60.95±8.4	60.64±7.59
9	58	57	8.65±0.67	8.64±0.79	2.30±0.25	2.11±0.25	104.40±9.3	104.37±9.72	62.67±7.3	62.40±6.93
10	58	58	8.44±0.96	8.37±0.7	2.42±0.25	2.26±0.21	103.94±9.48	104.99±10.28	61.46±7.38	62.90±8.62
11	58	58	8.50±0.74	8.33±0.99	2.48±0.3	2.30±0.27	103.64±9.26	107.25±9.75	62.30±7.86	61.17±7.3
12	99	99	8.32±1.07	8.64±0.76	2.69±0.28	2.46±0.24	110.72±9.23	107.54±9.87	63.97±7.07	61.82±6.83
13	101	99	8.53±1.11	8.80±0.81	2.83±0.41	2.46±0.26	108.73±10.15	105.65±8.25	62.33±8.32	62.06±5.98
14	100	96	8.77±0.89	8.70±0.91	2.93±0.32	2.52±0.24	115.27±9.26	108.30±8.21	65.29±6.99	62.34±7.18
15	88	80	8.65±0.98	8.64±0.68	2.97±0.29	2.56±0.29	114.95±10.63	107.95±8.77	65.41±7.83	62.85±8.16
16	88	89	8.63±0.99	8.63±0.7	2.95±0.31	2.47±0.23	118.32±11.59	106.63±10.58	68.55±9.05	63.38±7.49
17	74	81	8.37±1.22	8.64±0.72	3.03±0.52	2.49±0.3	118.23±10.51	109.65±9.55	69.69±6.68	65.15±7.66
18	47	33	8.54±1.09	8.38±0.97	3.08±0.37	2.48±0.23	119.99±8.57	110.13±9.19	70.23±8.22	67.77±6.83

* Data are presented as mean ± standard deviation

TABLE 3. Flow-mediated dilation by age in Hong Kong children versus United Kingdom children[4] (all P<0.01)

Age, y	Hong Kong children						United Kingdom children[4]					
	No. of males	No. of females	Flow-mediated dilation, %*		Adjusted flow-mediated dilation, %*		No. of males	No. of females	Flow-mediated dilation, %*		Adjusted flow-mediated dilation, %*	
			Males	Females	Males	Females			Males	Females	Males	Females
8	58	58	8.34±0.87	8.29±0.82	8.34±0.05	8.29±0.04	29	11	7.90±3.45	6.29±3.20	10.23±7.13	13.89±7.23
9	58	57	8.65±0.67	8.64±0.79	8.65±0.05	8.64±0.05	43	23	7.90±3.30	8.15±3.38	8.03±6.88	9.30±7.11
10	58	58	8.44±0.96	8.37±0.7	8.44±0.05	8.37±0.04	65	68	8.33±4.01	9.15±4.54	9.56±6.97	9.57±7.13
11	58	58	8.50±0.74	8.33±0.99	8.50±0.06	8.32±0.06	78	72	8.08±3.49	8.49±4.29	8.31±6.98	9.25±6.95
12	99	99	8.32±1.07	8.64±0.76	8.32±0.06	8.64±0.05	53	53	7.42±3.58	7.95±3.75	8.13±7.09	7.79±6.85
13	101	99	8.53±1.11	8.80±0.81	8.53±0.08	8.80±0.05	40	51	7.86±2.76	8.02±3.75	8.10±7.05	8.52±7.03
14	100	96	8.77±0.89	8.70±0.91	8.77±0.07	8.70±0.05	46	33	7.46±3.20	7.27±3.55	7.98±7.37	6.25±6.96
15	88	80	8.65±0.98	8.64±0.68	8.65±0.06	8.64±0.06	42	35	6.89±2.94	7.45±3.18	6.78±23.36	7.84±7.17
16	88	89	8.63±0.99	8.63±0.7	8.64±0.06	8.63±0.05	34	36	7.47±4.15	8.71±4.22	7.05±6.90	9.43±7.16
17	74	81	8.37±1.22	8.64±0.72	8.38±0.11	8.69±0.06	30	21	6.71±3.33	9.82±4.45	5.98±6.85	8.55±7.46
18	47	33	8.54±1.09	8.38±0.97	8.54±0.08	8.38±0.05	32	22	6.06±2.84	8.64±2.80	6.61±7.11	9.94±7.16

* Data are presented as mean ± standard deviation

size. Although the mean FMD was approximately 8%, it increased with age and was distinct between males and females, indicating age- and sex-specific endothelial function. Other studies have reported significantly higher FMD values in females than in males.[4,5] Our results showed that the FMD value was higher in females at the ages of 12 and 13 years only. This finding may be related to the earlier onset of puberty in females than in males; most females were at a post-pubertal stage after 14 years of age. As a higher oestrogen level is associated with enhanced vascular function, oestrogen production may account for the sudden improved endothelial function in girls during puberty.[4]

Strengths of the study include a large sample size, balance between males and females in each age-group, and the uniform approach and analysis of FMD. Limitations of the study include a lower-than-expected sample size for the 17- to 18-year age-group. After the citywide university admission reform in 2012, most of this age-group would have left secondary schooling to enter tertiary education. We did not examine vasodilatation independent of the endothelium with sublingual nitroglycerine, as this would have prolonged the testing time and may have caused discomfort to our participants. Further longitudinal studies are needed, as there is no scientific evidence to suggest that improvement in endothelial function during childhood will translate into decreased risk of future cardiovascular diseases.

Conclusion

Our study established the reference range for FMD in healthy Chinese children and adolescents in Hong Kong.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#01120406). The authors thank all participants and their parents who participated in the study.

Ethical Approval

This study was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (CREC-2012.456). Written informed consent was obtained from the parents of each participant.

Declaration

The authors have no conflicts of interest to disclose.

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