

Assessing the Relationship between Digit Ratio as a Marker for Prenatal Androgen Exposure and Different Blood Pressure Components among North Indian Males: A Pilot Study

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ABSTRACT

Introduction: Digit ratio (2D:4D) has been associated with cardiovascular diseases using association with surrogate markers. Studies showing an association of digit ratio with cardiovascular parameters within normal limits are scarce.

Aim: To explore the relation between different blood pressure components and digit ratio in normal young males within physiological range.

Materials and Methods: In this cross-sectional pilot study, 25 apparently healthy male volunteers were included. Digit ratio (2D:4D) was measured. Body Mass Index (BMI) was estimated. Peripheral blood pressure, central aortic blood pressure and all four limb blood pressures were measured using periscope arterial health and cardiovascular analysis system. Blood pressure was measured using oscillometric method from all peripheral sites and estimated central aortic pressure by a validated transfer function. Pearson's correlation studies were performed to assess any preliminary association. Two groups were formed of low and high digit ratio and

Student's t-test was performed to assess any significant difference between the groups.

Results: Digit ratio of both hands correlated best with peripheral Diastolic Blood Pressure (DBP) (Right 2D:4D $r=0.43$, $p<0.05$ /Left 2D:4D $r=0.40$, $p<0.05$). No significant association observed for peripheral systolic pressure ($p>0.05$) and digit ratio of both hands. Significant association observed for all four limb blood pressure components and digit ratio. Pulse pressure components did not show any association with digit ratio. Significant difference of blood pressure components was observed when low and high digit ratio groups were compared. It was observed that blood pressure components were on higher side within the normal limits among the subjects with high digit ratio.

Conclusion: Preliminary observations from this pilot study suggests that in normal young adult males digit ratio associate positively with different blood pressure components in normotensive males and has the potential to be used as a potent marker for early changes in cardiovascular diseases.

Keywords: Ankle blood pressure, Aortic blood pressure, Cardiovascular disease, Finger length ratio

INTRODUCTION

Digit ratio (2D:4D) research is continuing its journey from early till date. Initially, it was speculated to be a marker for prenatal androgen exposure [1] and later confirmed by empirical research [2]. Digit ratio or Finger length ratio or 2D:4D ratio is the ratio of length of the index finger (2D) and Ring finger (4D) from the proximal ridge to the tip of the finger measured from palmar aspect [3]. This anthropometric measurement is not fixed and varies across the ethnicity [4]. The common observation throughout the ethnicity reveals it is sexually dimorphic and males tend to have lower ratio than the females [5,6]. Digit ratio has been found to have association with many physiological and psychological parameters [1]. Masculinity [7], Running ability, Soccer ability [8], Running speed [1], Myocardial infarction [1,9], Hypertension [10], Coronary artery disease [11,12]. Studies observing relationship with hypertension and body composition indicators are also reported from India [10,13]. Association with different surrogate anthropological markers for cardiovascular diseases such as neck circumference [14], waist to hip ratio [13], BMI [15] and digit ratio was also reported. Several observations reported that digit ratio has a positive association with hypertension [10,16] and thus may be used as a possible marker for predisposition to coronary heart disease. Data regarding the association of digit ratio in relation to four limb blood pressure and aortic pressure in normotensive population is not available. Hence, the present study explores the relation between different blood pressure components and digit ratio in normal young males within physiological range.

MATERIALS AND METHODS

This cross-sectional pilot study was conducted in the Department of Physiology, Mayo Institute of Medical Sciences, Barabanki, Uttar Pradesh, India. Study was planned during May 2019 and conducted between December 2019 to March 2020, for four months as a pilot study. Study was approved by the Institutional Ethics Committee vide approval letter no. MIMS/Ex/2019/198 dated 19/11/19 and written informed consent was obtained from all participants.

Sample size calculation: For the calculation of sample size, the formula based on prevalence was used for the original study,

$$n = \frac{t^2 \times p(1-p)}{m^2}$$

where, n =Sample Size, t =confidence level at 95%, p =estimated prevalence 14% [17], m =margin of error. For the actual study, the sample size was found to be 230 including the margin of dropouts and incomplete investigations. Twenty five male subjects aged between 18-40 years were included, which was not less than 10% of the actual sample size fulfilling the criteria for sample size of pilot study [18].

Volunteered subjects were screened at Out Patient Department (OPD) of Department of General Medicine, Mayo Institute of Medical Sciences as per study protocol. During the period of the study no female candidate reported and left authors devoid of any choice but to report the data exclusive to males.

Inclusion criteria: Subjects between the age 18-40 years who were clinically normal and not suffering from hypertension, diabetes, any endocrine disorder, any cardiovascular diseases any kind of restrictive or obstructive disease of lung, present history of liver disease, viral myositis, and other muscular diseases were included in the study.

Exclusion criteria: Subjects aged <18 years and aged >40 years, any kind of arthropathy, history of cardiac disease, Hyper/hypothyroidism, diabetes, hypertension, tuberculosis, any kind of restrictive or obstructive disease of lung, present history of liver disease, viral myositis, and other muscular diseases. Female subjects with hormonal disorders including polycystic ovarian disease and adrenal hyperplasia and subjects, who were smoker or using tobacco in any form, were excluded from the study.

BMI Estimation

Height and weight were measured for each subject using standard calibrated stadiometer and BMI was calculated using formula

$$BMI = \frac{m}{h^2}$$

where m is mass in kgs and h is height in meters.

Digit Ratio Measurement

Length of the 2nd digit (index finger) and 4th digit (ring finger) was measured from the palmer surface. The distance from proximal crease to distal tip was measured to get the length of the digits. Digit ratio was calculated as the ratio of length of index finger to ring finger (2D:4D).

Four limb blood pressure recording, central blood pressure and Ankle Brachial Index (ABI) estimation: Subjects were allowed rest for five minutes in supine condition in ambient room temperature before the recording of different blood pressure components. Dedicated pressure cuffs were tied around both arms (brachium) and both ankles. Electrocardiogram (ECG) standard limb leads were placed as per the manufacturer's guideline. Demographic details were fed to the software before initiation of the measurement. Simultaneous four limb blood pressure was recorded using periscope arterial health and cardiovascular analysis system by Genesis Medical System Pvt., Ltd., India [19]. The instrument calibrates itself before initiating the recording procedure. Central aortic pressures and ABI were measured with dedicated Periscope™ software (Ver.3.0). Ankle to brachial index is the ratio of ankle systolic pressure to brachial systolic pressure. Subjects were instructed to restrict themselves from use of caffeine products for 24 hours prior to participate in the study.

STATISTICAL ANALYSIS

Data was analysed using Microsoft excel 365 statistical plugin software. Results were expressed as mean and Standard Deviation (SD). Correlation studies (Pearson's) were performed with data obtained and the significant correlation was considered whenever $p < 0.05$. Independent t-test was performed to analyse any significant difference observed for the high and low digit ratio groups (categorised using a median split). The difference was considered statistically significant whenever $p < 0.05$.

RESULTS

Descriptive statistics for baseline data is described in [Table/Fig-1].

Systolic blood pressure: Correlation studies between right hand digit ratio and Systolic Blood Pressure (SBP) component showed moderate degree of correlation with Peripheral SBP, Aortic SBP and four limbs SBP. Correlations were significant for Left arm SBP ($r=0.43$, $p=0.031$), Right Ankle SBP ($r=0.40$, $p=0.044$) and Aortic SBP ($r=0.42$, $p=0.035$) [Table/Fig-2].

| Variables (Unit) | Mean±SD (n=25) | Confidence interval (95%) |
|--------------------------|----------------|---------------------------|
| Age (years) | 29.60±5.22 | (27.4419, 31.7581) |
| Height (cm) | 167.00±6.44 | (164.3409, 169.6591) |
| Weight (kg) | 70.52±11.87 | (65.6198, 75.4202) |
| BMI (kg/m ²) | 25.21±3.55 | (23.7496, 26.6848) |
| PERI SYS (mmHg) | 121.36±9.95 | (117.2514, 125.4686) |
| PERI DIA (mmHg) | 79.36±7.12 | (76.4197, 82.3003) |
| RA SYS (mmHg) | 121.12±9.91 | (117.0262, 125.2138) |
| RA DIA (mmHg) | 79.960±7.26 | (76.9609, 82.9591) |
| LA SYS (mmHg) | 120.16±11.56 | (115.3852, 124.9348) |
| LA DIA (mmHg) | 78.16±9.24 | (74.3438, 81.9762) |
| RF SYS (mmHg) | 131.60±15.50 | (125.1997, 138.0003) |
| RF DIA (mmHg) | 79.08±7.49 | (75.9843, 82.1757) |
| LF SYS (mmHg) | 130.88±11.96 | (125.9391, 135.8209) |
| LF DIA (mmHg) | 78.68±7.33 | (75.652, 81.708) |
| AO SYS (mmHg) | 105.36±9.83 | (101.2983, 109.4217) |
| AO DIA (mmHg) | 77.32±7.50 | (74.2202, 80.4198) |
| RA PP (mmHg) | 41.16±6.95 | (38.2886, 44.0314) |
| LA PP (mmHg) | 42.00±6.49 | (39.3196, 44.6804) |
| RF PP (mmHg) | 52.52±10.80 | (48.0597, 56.9803) |
| LF PP (mmHg) | 52.20±8.91 | (48.5215, 55.8785) |
| AO PP (mmHg) | 28.04±5.65 | (25.7065, 30.3735) |
| RA MAP (mmHg) | 93.68±7.56 | (90.5574, 96.8026) |
| LA MAP (mmHg) | 92.16±9.60 | (88.1961, 96.1239) |
| RF MAP (mmHg) | 96.58±9.57 | (92.6341, 100.5392) |
| LF MAP (mmHg) | 96.08±8.12 | (92.727, 99.433) |

[Table/Fig-1]: Showing the baseline demographic data (n=25).

Values are expressed as mean±SD; PERI: Peripheral; AO: Aortic; RA: Right arm; LA: Left arm; RF: Right ankle; LF: Left ankle; SYS: Systolic blood pressure; DIA: Diastolic blood pressure; PP: Pulse pressure; MAP: Mean arterial pressure

Diastolic blood pressure: Diastolic component of Peripheral, Aortic, and all four limbs blood pressure correlated with Right and Left hand digit ratio except the correlation between Left hand digit ratio and right arm DBP was non significant ($r=0.34$, $p=0.0933$). Correlation between ankle DBP components with both hands digit ratio was the strongest among all [Table/Fig-2].

Pulse pressure: No significant association was observed for peripheral, aortic, and all four limbs pulse pressure when correlated with digit ratio of both hands [Table/Fig-2].

Mean arterial pressure: Mean Arterial Pressures (MAP) of all four limb pressure was only studied and found to be correlated significantly with both hands digit ratio except the correlation between left hand digit ratio and right arm MAP ($r=0.35$, $p=0.0860$) [Table/Fig-2].

Two groups of low and high digit ratio were made by median split method using the Right Hand Digit Ratio (median=0.963). The t-test results are described in [Table/Fig-3]. It was observed that Peripheral SBP was significantly ($p=0.02$, $p<0.05$) less in low digit ratio group. Aortic systolic pressure ($100.25±7.21$ mm Hg) was significantly less ($p=0.009$, $p<0.05$) in low digit ratio group compared to aortic systolic pressure ($110.07±9.78$ mmHg) among high digit ratio group. All four limb SBP were found to be significantly low ($p<0.05$) in low digit ratio group. Peripheral systolic and diastolic pressure was found to significantly low ($p<0.05$) in the low digit ratio group. Aortic systolic and diastolic pressure found to significantly low ($p<0.05$) in the low digit ratio group. The same observations were noted for all four limb SBP and DBP. There was no significant difference observed for peripheral, aortic and all four limb pulse pressure between the groups. MAP of all four limbs was found to be significantly low [Table/Fig-3] in low digit ratio group.

| Variables | Right hand digit ratio (2D:4D) | | Left hand Digit ratio (2D:4D) | |
|-----------|--------------------------------|----------|-------------------------------|-----------|
| | Pearson's coefficient (r) | p-value | Pearson's coefficient (r) | p-value |
| Age | 0.34 | 0.088549 | 0.38 | 0.058293 |
| BMI | 0.04 | 0.836059 | 0.04 | 0.819029 |
| PERI SYS | 0.35 | 0.0824 | 0.30 | 0.1387 |
| PERI DIA | 0.40 | 0.0463* | 0.43 | 0.0281* |
| RA SYS | 0.35 | 0.0828 | 0.29 | 0.1461 |
| RA DIA | 0.42 | 0.0348* | 0.34 | 0.0933 |
| LA SYS | 0.43 | 0.0313* | 0.43 | 0.0301* |
| LA DIA | 0.44 | 0.0263* | 0.46 | 0.0180* |
| RF SYS | 0.40 | 0.0448* | 0.39 | 0.0483* |
| RF DIA | 0.60 | 0.0014** | 0.69 | 0.0001*** |
| LF SYS | 0.36 | 0.0753 | 0.44 | 0.0277* |
| LF DIA | 0.52 | 0.0068** | 0.68 | 0.0001*** |
| AO SYS | 0.42 | 0.0351* | 0.41 | 0.0405* |
| AO DIA | 0.41 | 0.0376* | 0.49 | 0.0113* |
| RA Pulse | 0.07 | 0.7077 | 0.06 | 0.7449 |
| LA Pulse | 0.13 | 0.5140 | 0.10 | 0.6164 |
| RF Pulse | 0.16 | 0.4362 | 0.09 | 0.6607 |
| LF Pulse | 0.29 | 0.1586 | 0.02 | 0.8935 |
| AO Pulse | 0.10 | 0.6177 | 0.05 | 0.7885 |
| RA Mean | 0.41 | 0.0389* | 0.35 | 0.0860 |
| LA Mean | 0.45 | 0.0213* | 0.47 | 0.0163* |
| RF Mean | 0.53 | 0.0061** | 0.57 | 0.0025** |
| LF Mean | 0.49 | 0.0119* | 0.62 | 0.0007*** |

[Table/Fig-2]: Table showing correlations of different blood pressure parameters and right and left hand digit ratio (n=25).

Significance of correlation *p<0.05, **p<0.01, ***p<0.001. PERI: Peripheral; AO: Aortic; RA: Right arm; LA: Left arm; RF: Right ankle; LF: Left ankle; SYS: Systolic blood pressure; DIA: Diastolic blood pressure; PP: Pulse pressure; MAP: Mean arterial pressure

| Variables (Unit) | Low digit ratio (n=12) | High digit ratio (n=13) | t value | p-value |
|------------------|------------------------|-------------------------|----------|-----------|
| Age | 29.08±4.12 | 30.07±6.21 | 0.4746 | 0.6412 |
| BMI | 24.07±2.82 | 25.76±3.82 | -1.24515 | 0.22 |
| PERI SYS | 116.83±9.06 | 125.53±9.13 | -2.38944 | 0.0254* |
| PERI DIA | 75.5±3.58 | 82.92±7.81 | -3.00818 | 0.0062** |
| RA SYS | 116.66±9.19 | 125.23±9.00 | -2.35192 | 0.0276* |
| RA DIA | 76.41±4.71 | 83.23±7.81 | -2.61137 | 0.0156* |
| LA SYS | 113.08±6.41 | 126.69±11.55 | -3.59586 | 0.0015** |
| LA DIA | 72.58±4.98 | 83.30±9.40 | -3.51804 | 0.0015** |
| RF SYS | 123.33±10.79 | 139.23±15.75 | -2.94118 | 0.0073** |
| RF DIA | 74.5±6.23 | 83.30±6.04 | -3.58606 | 0.0015** |
| LF SYS | 124.58±8.52 | 136.69±11.98 | -2.88766 | 0.0083** |
| LF DIA | 74.58±7.12 | 82.46±5.36 | -3.1388 | 0.0046** |
| AO SYS | 100.25±7.21 | 110.07±9.78 | -2.83767 | 0.0093** |
| AO DIA | 72.58±3.36 | 81.69±7.69 | -3.77489 | 0.0009*** |
| RA Pulse | 40.25±9.46 | 42.00±3.60 | -0.62032 | 0.541147 |
| LA Pulse | 40.5±8.57 | 43.38±3.54 | -1.1153 | 0.276241 |
| RF Pulse | 48.83±9.34 | 55.92±11.28 | -1.70259 | 0.102124 |
| LF Pulse | 50.0±6.94 | 54.23±10.26 | -1.19654 | 0.243675 |
| AO Pulse | 27.66±6.49 | 28.38±4.99 | -0.31123 | 0.758432 |
| RA Mean | 89.83±4.80 | 97.23±8.05 | -2.75869 | 0.0111* |
| LA Mean | 86.08±3.73 | 97.76±10.03 | -3.7948 | 0.0004*** |
| RF Mean | 90.77±6.73 | 101.94±8.77 | -3.54915 | 0.0017** |
| LF Mean | 91.25±6.88 | 100.53±6.60 | -3.44182 | 0.0022** |

[Table/Fig-3]: Table showing the mean values obtained for the anthropometric and blood pressure parameters in low and high digit ratio group and independent t-test results for comparison of mean.

Significance *p<0.05, **p<0.01, ***p<0.001; PERI: Peripheral; AO: Aortic; RA: Right arm; LA: Left arm; RF: Right ankle; LF: Left ankle; SYS: Systolic blood pressure; DIA: Diastolic blood pressure; PP: Pulse pressure; MAP: Mean arterial pressure

DISCUSSION

Hypertension is one of the leading causes of death worldwide and major reason for numerous life-threatening disease conditions. The digit ratio has been associated with cardiovascular diseases by several authors. After conducting an exhaustive search for literature authors declare that in our best knowledge this study probably is the first attempt to observe the relation between digit ratio, aortic blood pressure and all four limbs blood pressure. Present study revealed that systolic pressure component of peripheral blood pressure does not correlate with either hand digit ratio but aortic systolic pressure does correlate significantly with both right and left hand digit ratio.

In 1985, a study by Beevers D reported that systolic and diastolic pressures both can predict mortality in patients but predictive capacity of SBP is more than DBP [20]. The present study also observed significant difference in SBP and DBP between the low and high digit ratio groups. Both SBP and DBP were observed to be low in the low digit ratio group. Previous Indian study reported that high digit ratio of both hands is associated with hypertension. Study also showed significant difference of digit ratio between stage-1 and stage-2 hypertension [10]. Aortic systolic and diastolic pressures both correlated significantly with the digit ratio of both hands. Aortic systolic pressure and aortic diastolic pressure differed significantly between the groups. It has been observed in several studies that the central aortic blood pressures exhibit higher predictive risk for cardiovascular disease than peripheral brachial artery blood pressure [21,22]. Central aortic SBP is lower than the corresponding Peripheral (Brachial) SBP [21] and a same phenomenon is observable from present study also. The difference was mainly due to the stiffness of arterial tree and pressure wave reflection from peripheral impedance mismatch points [21]. Left ventricular pump works against the afterload in the central large arteries [23]. Aortic and peripheral pressures differ significantly, and pressure wave amplification is more prominent in young non hypertensive subjects [24]. Central aortic BP has been found to be independently associated with subclinical cardiovascular disease in general and disease population [25]. So brachial pressure though have a better predicting power to predict cardiovascular outcome, the central pressure reflects the cardiac loading, vascular damage and prognosis [24].

Interesting observation of the present study was no significant correlation was observed between pulse pressure from all the above mentioned recording sites and the digit ratio of both hands. Neither any significant difference of pulse pressure observed between low and high digit ratio groups. Independent predictive power of pulse pressure towards, arterial stiffness or cardiovascular and cerebrovascular events is controversial [26].

Systolic and diastolic pressure is considered as pulsatile component of blood pressure curve whereas MAP is considered as the static component [27]. MAP and pulse pressure both are considered to be a useful marker cardiovascular risk. A study showed that MAP is a better predictor of ischemic stroke in a continuous scale than pulse pressure [28]. In present study, it was observed that the difference of all four limb MAP was significant for the groups. All four limb mean pressure correlated significantly with right hand digit ratio. Left hand digit ratio did not correlate with right arm mean pressure.

Digit ratio is considered to be the marker for prenatal androgen exposure and found to remain stable throughout the life [29]. Digit ratio has been implicated several times with different markers of cardiovascular diseases. Studies have suggested digit ratio as a predictor of metabolic syndrome [15]. In North Indian population, hypertension was found to be positively associated with digit

ratio [10]. It has been observed that right hand digit ratio and the difference of both hand digit ratio (R-L) negatively correlated with age of myocardial infarction but there was no differences observed for finger length ratio in myocardial infarction groups and control group [30]. A study suggested that higher 2D:4D ratio is associated with coronary heart disease and breast cancer in female Chinese population [11,12] and in males though the age of onset correlated with left hand digit ratio [31]. Most of the studies have shown relationship with anthropometric variables to link digit ratio and cardiovascular risk disposition.

Digit ratio studies are not without contradiction. Studies have observed that it may not be a correct biomarker for prenatal androgen exposure [32]. A recent study found no association between digit ratio and cardiovascular disease in post menopausal women [33]. Authors did not use any surrogate markers and tried to explore the physiological relation between normal adult cardiovascular physiology and digit ratio. It has been reported that at least in animal model, exposure to prenatal androgen increase the haemodynamic parameters of heart in male Wistar rats [34]. The present pilot study showed a positive association between digit ratio and different blood pressure components of peripheral and aortic blood pressures. It was also observed that within a small population there was a significant difference in different blood pressure components between low and high digit ratio groups where blood pressure components were statistically lower in the low digit ratio group.

Limitation(s)

These observations are made from a very small population and basically to check any possible existence and trends of the association between digit ratio and blood pressure components in normal population. Though the subjects were screened for confounding factors before incorporation in this study, authors admit that the effect of dietary habits on blood pressure was not taken into care. The risk of the cardiovascular disease varies among the ethnicity a multicentric study with different ethnicity will help to generalise the relation across the population. To explore the pathophysiological relation between prenatal androgen and adult cardiac function study of molecular dimension must be undertaken which was not done.

CONCLUSION(S)

Initial observation from the pilot study suggests a significant positive association digit ratio and blood pressure components within normotensive males. Digit ratio of both hands correlated with systolic and diastolic aortic blood pressure. For systolic component left hand digit ratio had shown significant correlation with right and left ankle, left arm and aortic SBP. For diastolic components right hand digit ratio had shown significant association with all four limbs and aortic DBP. Pulse pressure components did not correlate with either hand digit ratio. MAP of all four limbs correlated with right hand digit ratio. High digit ratio group had significantly more blood pressure for all the pressure components. Thus, it may be assumed that not only in hypertension, but blood pressure in normotensive young adult males also associate positively with the digit ratio and may be considered as a useful tool to study the cardiovascular function and early changes associated with blood pressure beside the commonly present markers.

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PLAGIARISM CHECKING METHODS: [\[Jain Het al.\]](#)

- Plagiarism X-checker: May 28, 2021
- Manual Googling: May 28, 2021
- iThenticate Software: Jul 08, 2021 (7%)

ETYMOLOGY: Author Origin**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **May 27, 2021**Date of Peer Review: **Jul 08, 2021**Date of Acceptance: **Jul 20, 2021**Date of Publishing: **Aug 01, 2021**