Pulse wave analyzed cardiovascular parameters in young first degree relatives of hypertensives

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Background: First-degree relatives (FDRs) of hypertensive (HT) are predisposed to hypertension (HTN) which accelerates cardiovascular aging. Same can be studied noninvasively by pulse wave analysis (PWA), encompassing central hemodynamics such as central blood pressure (cBP), cardiac output, and stroke work (SW) and vascular stiffness parameters such as pulse wave velocity (PWV) and augmentation index at heart rate 75 (AIx@75). We studied PWA-derived cardiovascular parameters in FDRs of HT compared to controls. Materials and Methods: We conducted a case–control study in 119 FDRs of HT and 119 matched controls. Oscillometric PWA was performed by Mobil-o-Graph (IEM, Germany) and cardiovascular parameters were compared. \( P < 0.05 \) was considered statistically significant. Results: Groups were comparable with gender, age, height, weight, body mass index, and physical activity. FDRs of HT had significantly higher brachial and cBPs, SW (101.41 ± 25.44 vs. 88.31 ± 20.25, \( P = 0.001 \)), rate pressure product-119.40 ± 25.34 vs. 108.34 ± 18.17, \( P < 0.0001 \), PWV (5.22 ± 0.46, \( P < 0.0001 \)), and AIx@75 (31.48 ± 9.01 vs. 27.95 ± 9.4, \( P = 0.002 \)) than control. Dependent study variables correlated with brachial blood pressure more in magnitude and significance level than age or anthropometric variables. PWA results of FDR with maternal inheritance did not differ significantly from those with paternal inheritance. Conclusion: PWA reveals early cardiovascular aging in young FDRs of HTs. It clues to future cardiovascular disease including HTN itself, need for primary prevention, and further study for consolidation of these results.

Key words: Cardiovascular, first degree relative, hypertensive, oscillometric, pulse wave analysis

INTRODUCTION

Hypertension (HTN) is a serious public health issue in India,[1] known to occur at relatively younger age. This submerged iceberg population is large as recently revealed that one out of every third Indian is hypertensive (HT) or pre-HT.[2] Family history of HTN, a major nonmodifiable risk factor, puts first-degree relatives (FDRs) at a risk for incident HTN,[3,4] a disease leading to accelerated cardiovascular aging[5] (progeria). Targeting same can have a great preventive potential,[6] more so in individuals living sedentary stressful life. It is difficult to separate degenerative vascular process from ongoing age-related disorders such as atherosclerosis.[7] Conventional clinical measures of cardiovascular functioning may underestimate aging effect.[7]

Brachial blood pressure is a simple tool to assess HTN, but it does not infer about more discrete cardiovascular parameters[8] affecting heart directly such as vascular stiffness parameters (pulse wave velocity [PWV] and augmentation index at heart rate [HR] 75-AIx@75) and central hemodynamics (cardiac output [CO], central blood pressure [cBP], stroke work [SW]). All these parameters are supposed to be increased with family history of HTN. Pulse wave analysis (PWA) offers beyond brachial blood pressure assessment of arterial stiffness and central hemodynamic parameters.[9] These are gold standards in known HTs,[10] but their role in young and adolescents is studied less with no data from our region. FDRs of HT are known to have higher brachial blood pressure,[3] but PWA-derived parameters are not extensively studied. We compared PWA-derived cardiovascular parameters in young FDRs compared to controls.
apparently healthy adults with or without family history of HTN.

MATERIALS AND METHODS

We conducted a case–control study at Clinical Research Laboratory of Physiology Department of a government medical college attached to tertiary care teaching government hospital from June 18, 2015 to June 3, 2016. Study protocol was approved by the Institutional Review Board (no 527/GMCB/28th IRB HEC/2015 of Government Medical College, Bhavnagar, Gujarat; dated 24/06/2015). Sample size was calculated by Raosoft software (Raosoft, Inc., free online software, Seattle, WA, USA). We intended 95% confidence level and 5% precision for population our city 6 lakhs having 7.3% prevalence of HTN. A sample size of 103 (Considering either parent diabetic for each subject, size is halved to 52) was adequate for it. We used convenience sampling method and enrolled 486 apparently healthy subjects from our institute with known parental history of HTN and type 2 diabetes. After scrutiny in terms of inclusion and exclusion criteria, we finally had 119 subjects as FDRs (FDR, subject having either a parent or a grandparent having known HTN) of HTs (defined as systolic blood pressure [SBP] ≥140 mmHg and diastolic blood pressure [DBP] ≥90 mmHg or use of anti-HT medication) taken as case group. We further subgrouped cases of FDR of HT based on maternal versus paternal heritance of disease, excluding 13 subjects having both paternal and maternal heritance of HTN. We excluded subjects with a family history of type 2 diabetes from the current study. Of remaining participants, we made a control group of 119 subjects matched to case group by age, gender, body mass index (BMI), and physical activity but with negative family history of HTN [Figure 1].

We included FDRs of HTs, aged 15–35 years, of either sex, not known for any disease, not taking any medical treatment, living sedentary lifestyle, ready to give written consent. Apart from noncompliance with these inclusion criteria, we excluded current or ex-smokers or tobacco chewers, subjects using of any alternative system of medicines/lifestyle managements such as yoga and mediation. We excluded one subject from analysis after pulse wave recording owing to irregular pulse rhythm. Criteria for the control group were similar as above except family history of HTN.

All subjects were interviewed personally in the form of questionnaires including general features, demographic characteristics; self-reported physical activity and family history of HTN.

We used portable, personal computer attached calibrated[11] and validated[12] instrument Mobil-o-Graph (IEM Gmbh, Stolberg, Germany) owned by Physiology Department of our institute to record brachial pulse wave. It performs PWA based on oscillometric principle. Arterial pulsation generates the pressure oscillations which are transmitted to blood pressure cuff and measured by transducer to be fed into microprocessor. Computerized software records pulse wave of brachial artery and by a generalized transfer factor derives central aortic pulse wave, and based on this, central hemodynamics and arterial stiffness parameters are calculated.[13]

It further undergoes point-based and area-based analysis by computer to derive various cardiovascular parameters.

A blood pressure cuff of appropriate size was chosen based on mid-arm circumference and applied to left arm using standard protocol. All readings were taken after 10 min of rest, in postabsorptive phase with subjects avoiding smoking or alcohol for 12 h before the test, in a calm room avoiding external influences or arm movement.[13]

Parameters measured by PWA of brachial pulse wave with units

- Heart rate/HR (beats/min)
- Brachial blood pressure/bBP (mm of Hg) = systolic (brachialSBP), diastolic (brachialDBP), pulse (brachial pulse pressure), and mean (brachial mean blood pressure)
- Central blood pressure/cBP (mm of Hg) = systolic (central SBP), diastolic (central DBP) and pulse (central PP)
- Central hemodynamics = Cardiac output/CO (L/min), cardiac index/CI (L/min/m²), systemic vascular resistance/SVR (mmHg/ml/min)
- Arterial stiffness-augmentation pressure/AP (mmHg), augmentation index at HR 75/min/AIx@75 (%), reflection magnitude %/Ref % (%), PWV/PWV (m/s)
- Parameters derived from PWA parameters
• Rate pressure product/RPP (mmHg. beats/min) = HR/min (beats/min) × SBP (mmHg) × 10⁻²
• Stroke volume/SV (ml/beat) = CO (L/min)/HR (beats/min)
• Stroke volume index/SVI (ml/m²) = stroke volume (ml)/body surface area (m²)
• Stroke work/SW (gm. m/beat) = pulse pressure (mmHg) × stroke volume (ml) × 0.0144
• Total arterial stiffness/TAS (mm Hg/ml) = pulse pressure (mm Hg)/stroke volume (ml).

Statistical analysis
The data were transferred on Excel spreadsheet and continuous data were expressed as mean ± standard deviation, while categorical data were presented as number (%). All calculations were done by GraphPad InStat 3 software (demo version free software of GraphPad Software, Inc, La Jolla, California, USA). Each datum was checked for parametric or nonparametric distribution by normality test before applying a test. Continuous data were compared by Mann–Whitney test (for nonparametric data) or unpaired Student’s t-test (for parametric data). Normality test or Chi-Square test was used for comparing categorical data between groups. Pearson’s correlation test was used for correlation between parameters. Statistical significance level was set at $P < 0.05$.

RESULTS
Case and control groups were matched by age, gender with comparable height, weight, BMI, body surface area, and self-reported physical activity status [Table 1]. Case group had higher brachial blood pressure, vascular stiffness, cBP, and central hemodynamics as compared to control group, with statistical significance for all except five results. Case group had significantly higher percentage of pre-HTs and HTs than control group [Table 1]. Subgroups of cases with paternal or maternal inheritance of HTN did not have significantly different study parameters [Table 1].

Pearson correlation of vascular stiffness parameters was tested with other independent variables. In either group, PWV correlated positively with most independent variables (except height and HR) with statistical significance. AP showed weak and mostly insignificant correlations except height, SBP, and PP in either group. AIx@75 correlated with most parameters except height and HR but without statistical significance [Table 2].

Simple linear correlation of central hemodynamic parameters revealed that age and BMI had a weak insignificant correlation with cPP, CO, and SW in either group. Height (only in case group) and weight (in both groups) correlated significantly with cPP, CO, and SW. These three central hemodynamic parameters correlated with all brachial blood pressure parameters (SBP, DBP, MBP, and PP), positively and significantly with most (except negative correlation of DBP and cPP) in either group. BMI correlated significantly with cPP, CO, and SW, in both groups, more consistently in case than control. In both groups, there was a significant correlation of HR negatively with cPP and SW and positively with CO [Table 3].

DISCUSSION
In our sample population, young FDRs of HT had higher values of blood pressure (brachial and central), central hemodynamics (CO, SW, and RPP), and vascular stiffness (PWV and AIx@75) than controls. This abnormal profile of cardiovascular parameters is known and supported by other studies[14,17] done elsewhere. This result looks even significant by the fact that subjects were matched by most confounding factors[18,19] such as age, gender, BMI, height, weight, ethnicity, physical activity, environment, and level of stress. Such difference at age <35 years also underscores onset of early cardiovascular aging in individual with positive family history of HTN. Aging produces reduced compliance and elasticity of aorta that increase impedance and with early wave reflection increased workload on heart[20] which in our case was evident as significantly higher SW and RPP.

A study has showed that individual with stiffer carotid arteries at 36 years of age had raised BP and PWV during adolescence.[21] Such functional and structural changes define vascular phenotype of HTN,[22] and we highlighted the same as indirectly measured aortic parameters.

We did not find any difference due to maternal or paternal family history of HTN in test parameters as opposed to one[4] indicating former to affect significantly higher than later. Both central hemodynamic and vascular stiffness were dependent on blood pressure and HR. We found that PWV was dependent on age, while AIx@75 was not in young individuals which is in line with other studies.[18,19] Similarly, PWV was correlating strongly with brachial blood pressure than AIx@75. These two facts support the concept that, in young individuals (like our study subjects), AIx@75 is more sensitive marker of arterial alteration and cardiovascular risk.[23,24] Central hemodynamics fluctuate overtime and sporadic measurement by PWA may not reflect their long-term effect on arterial wall, yet they indicate increased workload on heart.[22] PWV has high prognostic value as it is a stable parameter which reflects cumulative damage due to cardiovascular risk factors on arterial wall over long periods.[23] cBP, AIx@75, and PWV, despite aforementioned differences, reflect different characteristic of structural or functional change in vessel wall and PWA provides an objective, noninvasive, cost-effective mean to assess all these simultaneously.[22]

Population is aging around the globe and HTN is the most common chronic disease[25] with many vascular...
Table 1: Comparison of baseline data and study parameters between case and control group (n=119 each) and between individuals with paternal history and maternal history of hypertension in case group

| Parameter (unit) | Case (n=119) | Control (n=119) | P | FDR maternal FH+ (n=39) | FDR paternal FH+ (n=67) | P |
|-----------------|--------------|----------------|---|------------------------|------------------------|---|
| Age (years)     | 22.07±5.12   | 21.88±5.30     | 0.591 | 0.44±2.80            | 22.45±5.61            | 0.425 |
| Male/female (n) | 74/45        | 74/45          | 1.000 | 15/24                 | 21/46                  | 1.000 |
| Height (cm)     | 164.59±14.29 | 162.41±9.82    | 0.149 | 165.50±10.26          | 164.53±16.70          | 0.237 |
| Weight (kg)     | 62.79±14.61  | 60.64±12.99    | 0.393 | 63.10±15.97           | 62.52±13.85           | 0.845 |
| BMI (kg/m²)     | 23.13±4.51   | 23.02±4.46     | 0.853 | 22.88±4.90            | 23.14±4.38            | 0.778 |
| BSA (m²)        | 1.68±0.22    | 1.64±0.21      | 0.161 | 1.68±0.22             | 1.64±0.21             | 0.785 |
| Physical activity (n) | 6/119 | 5/119 | 1.000 | 2/39                 | 3/67                   | 1.000 |
| bBP (mmHg)      | 127.56±12.61 | 118.09±10.27   | <0.0001* | 126.41±11.96        | 128.46±12.59        | 0.412 |
| DBP             | 82.82±9.86   | 76.23±10.30    | <0.0001* | 82.00±10.06        | 83.16±9.39           | 0.550 |
| MBP             | 103.33±9.71  | 95.51±7.79     | <0.0001* | 102.41±9.50        | 103.90±9.44          | 0.438 |
| PP              | 45.00±11.78  | 41.31±9.79     | 0.035* | 43.90±11.18          | 45.17±11.04          | 0.573 |
| HTN strata, n (%)^† |                     |                 |     |                       |                       |     |
| NT              | 79 (66)      | 115 (97)       | <0.0001* | -                | -                      | -   |
| PHT             | 32 (27)      | 3 (2)          | -     | -                     | -                      | -   |
| HT              | 8 (7)        | 1 (1)          | -     | -                     | -                      | -   |
| HR (bpm)        | 93.29±16.15  | 91.66±12.40    | 0.873 | 92.62±17.85           | 94.30±13.40           | 0.583 |
| RPP (mmHg/bpm)  | 119.40±25.34 | 108.34±18.17   | <0.0001* | 121.50±22.90       | 117.07±24.99         | 0.356 |
| Vascular stiffness |                     |                 |     |                       |                       |     |
| AP (mmHg)       | 6.90±3.02    | 5.55±2.89      | 0.001* | 6.62±3.16            | 6.94±2.83            | 0.437 |
| Ref (%)         | 60.73±7.32   | 59.50±8.61     | 0.331 | 60.41±7.68           | 60.43±7.43           | 0.958 |
| AIx@75 (%)      | 31.48±9.01   | 27.95±9.40     | 0.002* | 30.33±10.30          | 31.67±7.86           | 0.212 |
| PWV (m/s)       | 5.22±0.46    | 4.90±0.41      | <0.0001* | 5.10±0.41          | 5.27±0.48            | 0.072 |
| TAS (ml/mmHg)   | 0.83±0.19    | 0.81±0.17      | 0.352 | 0.83±0.21            | 0.84±0.20           | 0.881 |
| cSBP (mmHg)     | 115.62±11.03 | 105.76±12.26   | <0.0001* | 114.15±10.39       | 116.24±10.80         | 0.333 |
| cDBP            | 84.81±9.82   | 78.34±8.42     | <0.0001* | 84.05±9.82        | 85.07±9.33           | 0.597 |
| cPP             | 30.83±7.60   | 27.84±7.39     | 0.003* | 30.10±8.03           | 31.19±7.46           | 0.378 |
| Central haemodynamics |                     |                 |     |                       |                       |     |
| CO (L/min)      | 4.98±0.63    | 4.65±0.57      | <0.0001* | 4.99±0.53            | 5.00±0.69            | 0.987 |
| PR (mmHg/mL)    | 1.25±0.11    | 1.25±0.15      | 0.777 | 1.24±0.10            | 1.25±0.12            | 0.532 |
| CL (L/min/m²)   | 3.01±0.43    | 2.86±0.35      | 0.008* | 3.00±0.47           | 3.03±0.39           | 0.788 |
| SV (ml/beat)    | 54.91±11.84  | 57.78±8.92     | 0.031* | 55.62±11.10          | 53.69±8.58          | 0.319 |
| SVI (ml/m²/beat)| 32.92±7.13   | 31.54±5.25     | 0.137 | 32.92±7.13          | 31.54±5.25          | 0.137 |
| SW (g/m²/beat)  | 101.41±25.44 | 88.31±20.25    | 0.001* | 102.08±26.28        | 100.02±22.28         | 0.668 |

^Statistical significance, χ^2=340.60 with df=2. BMI=Body mass index; BSA=Body surface area; bBP=Brachial blood pressure; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; MBP=Mean blood pressure; PP=Pressure pulse; NT=Normotensive; PHT=Prehypertensive; HT=Hypertensive; HR=Heart rate; AP=Augmentation pressure; Ref=Reflection percentage; AIx@75=Augmentation index at heart rate 75 beats per min; PWV=Pulse wave velocity; TAS=Total arterial stiffness; FDR=First degree relative; HTN=Hypertension; RPP=Rate pressure product; cBP=Central blood pressure; cSBP=Central SBP; cDBP=Central DBP; cPP=Central PP; CO=Cardiac output; SV=Stroke volume; CI=Cardiac index; SVI=Stroke volume index; SW=Stroke work; PR=Peripheral resistance; FH+=Familial history

Changes of aging precede the inception of disease itself,[3] It occurs at relatively younger age group,[2] leading to various cardiovascular complications which are preventable by lifestyle modifications. This becomes even significant with the concept that cardiovascular aging determines lifespan of an individual. [26] Cardiovascular diseases and its correlates have enormous economic and health burden to the society and strategies are needed to prevent and repair damaged arteries to decrease HTN and related targeted end-organ damage. [3] Urban Asian adults have known to have escalation of cardiovascular risk factors by the age 30–39 years and intervention should focus on these individuals.[27] Positive family history for chronic diseases is amenable to direct therapeutic intervention yet it remains important for risk stratification as evidenced by our study highlighting early cardiovascular aging with risk of positive family history. There is complex interaction between genetic, environmental, and abnormal behavioral factors [28] in FDRs of HT which can be targeted for prevention. A recent study [29] has shown that cardiovascular risk factors are significantly higher in prediabetic than normal FDRs of diabetics with age group same as our study. This and our results further hint to a potential of research in this direction for possible preventive measures such as lifestyle modifications. Early identification of cardiovascular aging and arterial dysfunction provides a window for early intervention.
Along with blood pressure screening, one may also measure central hemodynamics and arterial stiffness parameter by PWA to further consolidate prognosis in HTs and risk stratification in those at risk like individuals belonging to a family with HTN.

There were few limitations of the study. First, the cross-sectional nature requires a follow-up study for further consolidation of results over time which we intend after 5 years. Second, sample size was not too large and larger sized studies are needed, but considering the targeted small age group, it may be fairly sufficient. Third,
simple inquiry about family history and recall bias might ensue[^53] but chance is lesser as most participants were medical, paramedical staff, being aware about parental history and HTN. Fourth, results derived by PWA depend on generalized transfer function where brachial blood pressure is not measured invasively and directly. This is of lesser significance as this method is validated against intraoperatively, inversely measured blood pressure.[^51]

**CONCLUSION**

Young, nonobese, sedentary FDRs of HTs have an early abnormal cardiovascular profile as compared to matched controls, suggesting progeria, dependent on blood pressure. This suggests risk for incident HTN itself, calls for follow-up study and implementation of primary prevention to retard, if not to cease, its aftermaths likely to come relatively early in future.

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**Conflicts of interest**

There are no conflicts of interest.

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