Pulse Wave Analysis In Gujarati Type 1 Diabetics: A Case Control Study

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Abstracts: Introduction: Type 1 Diabetes is an early onset disease that imposes significant cardiovascular risk. Arterial stiffness and central haemodynamics are immediate and discrete parameters but studied scarcely. Pulse wave analysis (PWA) allows non-invasive measurement of them which we undertook in diabetics. Methodology: We performed a case control study on 36 treated type 1 diabetics and 36 non-diabetic, normotensive, matched controls. Oscillometric pulse wave analysis (PWA) was performed by Mobil-o-Graph (IEM, Germany). Parameters were compared between case and controls. Multiple linear regressions were accomplished to find significant predictors. $P < 0.05$ was taken as statistical significance. Results: - Cases showed significantly raised brachial haemodynamics (blood pressure, heart rate, rate pressure product); arterial stiffness (augmentation pressure, augmentation index, pulse wave velocity, total arterial stiffness, pulse pressure amplification) and central haemodynamics (central blood pressure, cardiac output, stroke work) than controls, with statistical significance for not all. Most outcome parameters were predicted by age, HR, BP to lesser extents. Genders, presence of hypertension, glycemic control, blood pressure control, physical activity were not significantly affecting study outcomes in case group. Conclusion: Gujarati type 1 diabetics had beyond brachial blood pressure, adverse profile of discrete cardiovascular parameters; independent of conventional confounders; suggesting vascular progeria. This baseline work hints further study of these PWA parameters. [Solanki J Natl J Integr Res Med, 2018; 9(6):-59-65]

Key Words: Arterial stiffness; blood pressure; haemodynamic; pulse wave analysis, type 1 diabetes

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Introduction: Type 1 Diabetes is lesser existent than type 2 diabetes [1] with scarcity of studies. Insulin deficiency imposes multiple functional abnormalities. Cardiovascular ageing is accelerated in type 1 diabetes. [2] This vascular progeria can be studied in terms of central blood pressure, central haemodynamics and arterial stiffness. [3] These parameters can be studied by pulse wave analysis (PWA) non-invasively and objectively. Our previous Mobil-o-graph based PWA studies[4-8] have reported utility of discrete and direct PWA parameters like augmentation index (AIx), aortic blood pressure (aBP), aortic pulse wave velocity (aPWV) and cardiac output (CO). These parameters were studied in normal individuals[4, 5], young individual with familial hypertension[6] or diabetes[7], type 2 diabetics, and hypertensives[8]. However, the study of same in type 1 diabetics is not available that we undertook by a cross-sectional design.

Materials and Methods: Study design and subjects : Our study protocol was first approved by institutional review board of our institute. We performed a case control study on patients of Medicine outdoor patient department of a tertiary care government hospital attached to a government medical college with collaboration of Physiology and Medicine departments from 27th January 2017 to 26th May 2018.

Inclusion and exclusion criteria: We included non-athletic, type 1 diabetics, on regular Insulin, aged > 15 years, of either sex, non-smoking, non-alcoholic, not known to have any acute or chronic systemic disease, ready for written informed consent. Apart from these criteria, we excluded participants using any alternative system of medicines or life style managements like Yoga, meditation.

Study groups :By convenience sampling, we screened and enrolled 44 diabetics meeting inclusion criteria from Medicine outdoor patient department. We excluded 6 subjects with irregular treatment, 1 with use of life style modification, 1 due to arm circumference beyond available cuff size. So, case group finally had 36 cases.

For comparison, we selected 36 apparently healthy, non-diabetic normotensive subjects from the available pool of healthy controls of

our previous studies. Controls were matched by number, age, gender and BMI.

Subject assessment and definitions : We interviewed participants personally regarding general features, demographic details, risk factors, moderate physical activity (self reported) and disease history. Detailed history of pharmacotherapy was elicited from each participant and regularity was confirmed by patient's case report chart. Systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP) ≥ 90 mm Hg or use of anti-hypertensive medication was defined as hypertension.SBP <140 mm of Hg and DBP <90 mm of Hg was taken as blood pressure control. Glycemic control was accepted as per guidelines of American Diabetes Association 2014[9] by fasting plasma glucose (FPG< 130 mg/dl) and 2 hour plasma glucose (2 hPG <180 mg/dl).

Instrument used : We used portable, personal computer attached, calibrated [10] and validated [11] instrument Mobil-o-Graph (IEM GMBH, Stolberg, Germany) of Physiology department to record brachial pulse wave. It undergoes oscillometric pressure pulse wave analysis as per protocol designed by European Society of Hypertension.

Pressure oscillations are generated by brachial arterial pulsation which are transmitted to brachial blood pressure cuff and measured by transducer to be fed into microprocessor. Computerized software records pulse wave of brachial artery and by validated a generalized transfer factor derives central aortic pulse wave. It further undergoes point based and area based analysis by computer software to derive various cardiovascular parameters.

Measurement protocol [10]: Based on measured mid arm circumference, a blood pressure cuff of appropriate size (mid arm circumference: 20-24 cm= small size, 24-32 cm= medium size, 32-38 cm=large size) was chosen and applied to left arm using standard protocol. All readings were taken after rest for 10 minutes, in post absorptive phase while subjects avoiding smoking or alcohol for 12 hours before measurement, in a calm room without external influences or avoiding arm movement.

Parameters measured [6, 7]:

1) Heart rate (HR), body mass index (BMI), body surface area (BSA)

2)Brachial blood pressure(bBP)-systolic(bSBP),diastolic(bDBP),pulse(bPP)and mean(bMBP)

3) Central blood pressure (cBP) - systolic (cSBP), diastolic (cDBP), pulse (cPP)

4) Central hemodynamics- cardiac output (CO), cardiac index (CI), peripheral resistance (PR)

5) Arterial stiffness- augmentation pressure (AP), augmentation index at heart rate 75 per minute (AIx@75), reflection magnitude percentage (Ref %), aortic pulse wave velocity (aPWV)

Parameters derived [6, 7]

1) Rate pressure product (RPP) – (heart rate per minute) x (systolic blood pressure) x 10^{-2}

2) Stroke volume (SV) - cardiac output / heart rate

3) Stroke volume index (SVI) - stroke volume/ body surface area

4) Stroke work (SW) - (pulse pressure) x (stroke volume) x 0.0144

5) Total arterial stiffness (TAS) - pulse pressure /stroke volume

6) Pulse pressure amplification (PPA) - brachial pulse pressure/aortic pulse pressure

Statistical analysis : The data was entered into and sorted out by Excel spreadsheet. Quantitative data was presented as mean ± standard deviation and qualitative data was presented as number (percentage). Statistical analysis were done by GraphPad InStat 3 software (demo version free software of GraphPad Software, Inc. California, USA).Quantitative data were compared by unpaired t test or Mann-Whitney test, based on outcome of Normality test for parametric distribution. We tested difference in distribution of qualitative data by Normality test or Chi

Square test. Multiple linear regression tests were applied to find major and significant predictors of study outcomes-central haemodynamics and arterial stiffness. Statistical significance level was kept at p value less than 0.05.

Results : Case group of diabetics (n=36) and control group of matched non-diabetic normotensive controls (n=36) had comparable age, sex distribution, anthropometry and prevalence of physical activity. Cases had mean diabetes duration 3.73 years, 28% prevalence of diabetics, 35% glycemic control and 65% blood pressure control. Most PWA cardiovascular parameters were significantly raised in cases than controls. Brachial and central blood pressures except pulse pressure were significantly higher in case group. Heart rate and rate pressure product were comparable between both groups. All arterial stiffness parameters were higher in cases with statistical significance only for aPWV. Central haemodynamics were accelerated in cases than controls but only cardiac output and stroke work exhibited statistically significant difference. [Table 1]

Table 1 Compassion of baseline and study parameters between cases and matched controls

Parameter, unit		Cases (n=36)	Controls (n=36)	P value
Age, years		30.14 ± 6.33	30.03 ±6.39	0.94
Male, no (%)		12(33%)	12(33%)	1.00
Height, cm		158.56 ± 6.78	155.88 ± 9.06	0.16
Weight, kg		59.61 ± 11.44	56.44 ± 9.07	0.28
BMI, kg/m^2		22.34± 4.49	23.39 ±4.65	0.99
P A no (%)		11(31%)	12(33%)	1.00
Duration, years		3.73± 3.98	-	-
HTN no(%)		10(28%)	-	-
BPC no (%)		23(64%)	35 (97%)	0.0006*
G C, no (%)		11(35%)	-	-
BP(mm Hg)	SBP	128.97 ± 13.47	118.77± 11.76	0.001*
	DBP	86.00 ± 10.75	78.00 ± 9.95	0.0016*
	MBP	105.72 ± 10.81	96.42± 9.58	0.0002*
	PP	42.97 ± 10.66	40.69±9.47	0.34
HR, bpm		95.75 ± 13.11	95.75 ± 14.03	>0.99
RPP, mm Hg.bpm		123.10 ± 18.90	113.91 ± 21.08	0.06
Art stiffness	AP, mm Hg	8.42 ±5.37	6.39 ±3.58	0.10
	Ref (%)	63.56 ±7.68	63.00 ±6.28	0.77
	AIx@75 (%)	34.44 ±9.26	39.25 ±8.85	0.31
	PWV, m/s	5.77 ±0.90	5.36 ±0.59	0.0238*
	TAS, ml/mmHg	0.81 ±0.19	0.82 ±0.16	0.88
	PPA	1.35 ±0.18	1.38 ±0.18	0.44
c BP(mm Hg)	cSBP	119.94 ± 13.64	109.75±10.62	0.0011*
	cDBP	88.06 ± 10.81	79.67 ± 9.91	0.001*
	cPP	32.44 ±9.24	30.08±8.37	0.33
Central Haemodynamics				
	CO,L/min	5.01 ±0.57	4.71 ±0.64	0.0356*
	PR,mm Hg/mL	1.30 ±0.19	1.25 ±0.13	0.62
	CI,L/min/m^2	3.12 ±0.45	3.03 ±0.40	0.53
	SV,ml/beat	53.37 ± 10.01	49.80 ±7.99	0.10
	SVI, ml/m^2/beat	33.42 ±7.30	32.23 ±5.23	0.43
	SW,g m/beat	100.33 ±26.93	85.90 ±20.12	0.012*

BMI= body mass index ,PA= physical activity, GC= glycemic control, BPC= blood pressure control, bBP- brachial blood pressure, SBP= Systolic blood pressure , DBP=diastolic blood pressure, MBP= mean blood

pressure, PP= pulse pressure, HR= heart rate, RPP= rate pressure product ,AP= augmentation pressure, Ref =reflection percentage, AIx@75=augmentation index at heart rate 75 beats per minute, PWV = pulse wave velocity , TAS= total arterial stiffness, PPA=pulse pressure amplification, cSBP= central systolic blood pressure , cDBP=central diastolic blood pressure, cPP= central pulse pressure, CO=cardiac output, PR=peripheral resistance, CI= cardiac index, SV=stroke volume, SVI= stroke volume index, SW=stroke work, '*' indicates statistical significance

Table 2 Calculation of predictors for dependant variables by multiple linear regression ($r_{partial}$ values) in case group

Parameters	AP	AIx@75	aPWV	TAS	cSBP	cDBP	cPP	CO	SW
Age	0.04	0.10	0.05**	0.01	0.11	0.05	0.12	0.01	0.11
Height	-0.14	-0.21	-0.04	0.02	-0.07	-0.08	0.10	0.01	0.16
Weight	0.05	0.06	-0.01	-0.05	0.04	-0.06	0.17	-0.01	-0.08
BMI	-0.15	0.03	-0.02	0.02	-0.07	0.07	-0.24	0.02	-0.13
SBP	2.55	3.50	0.27	0.10	1.89	1.39	0.13	-0.33	1.48
DBP	0.74	1.44	-0.11	-0.11	0.40	0.54	-0.02	-0.23	0.68
MBP	-3.20	-4.74	-0.13	-0.10*	-1.22	-0.95	0.01	0.59*	1.86*
HR	0.01	0.38*	0.01	0.01**	-0.04*	0.01	-0.01	0.62*	-1.00**
PP	-0.75	-1.07	-0.16	-0.04	-0.53	-0.94	0.65	0.10	0.59
Duration	0.14	0.35	0.01	0.01	0.17	-0.04	0.26	-0.01	-0.32
Gender	3.87	1.35	-0.29	-0.06	0.05	0.03	-0.09	0.37	6.89
P A	-1.94	0.99	0.07	0.03	-1.11	-0.01	-3.33	-0.14	-1.24
HTN	3.72	-0.58	1.87	-0.01	1.18	-1.30	7.02	-0.97	-6.38
GC	-1.14	1.03	-0.18	0.14	-0.03	4.28	-10.90	0.65	-2.43
BPC	-3.81	1.27	-2.74	0.03	-1.76	-1.50	4.29	-1.88	2.13

Abbreviations same as table 1, * indicates $p < 0.05$, ** indicates $p < 0.0001$

By multiple linear regressions, we tested predictors of major PWA parameters (as dependant parameters) from independent study parameters. Most arterial stiffness and central haemodynamics parameters were not significantly predicted by age, anthropometry, brachial blood pressure, heart rate and disease duration. Heart rate for AIx, age for aPWV, HR and MBP for TAS, MBP and HR for CO and SW were only significant predictor- outcome pairs. There was no significant predictor for central blood pressures out of studied independent parameters. Most brachial blood pressure parameters were not significant predictors of corresponding central blood pressures parameters. [Table 2] Linear regressions also gave association between PWA parameters and qualitative predictors. All arterial stiffness and central haemodynamics parameters were not significantly predicted by gender, physical activity, hypertension, glycemic control or blood pressure control. [Table 2]

Discussion : This is perhaps the first Mobil-o-graph based pulse wave analysis study on urban Gujarati type 1 diabetics. Oscillometric pulse wave analysis with generalised transfer factor provides details of cardiovascular health and ageing, beyond conventional brachial blood pressure.[12] Type 2 diabetes and cardiovascular health are studied by few researchers; but owing to lesser prevalence, similar studies for type 1 diabetes are lacking. We studied type 1 diabetics as compared to matched controls that allowed us to study effect of insulin dependent diabetes on cardiovascular ageing.

Cases showed augmented brachial haemodynamics, central haemodynamics and arterial stiffness parameters than controls despite anti-diabetic therapy. These results are supported by previous

(unpublished) studies done in type 2 diabetics (normotensives and hypertensives) from our set up but with middle aged study population. Abnormal results in diabetics can also be explained by poor glycemic control despite therapy which is a conspicuous feature of our diabetics.[14, 15, 16] Such results are in line with studies reported by other researchers.[17] It can also be due to 1) unavailability of HbA1c that gives better inference about glycemic control; 2) higher prevalence of physical inactivity; 3) poor blood pressure control; 4) ethnic predisposition; 5) delayed diagnosis and 6) lack of life style modification. There is a continuum of Insulin resistance, vascular and global ageing, arterial stiffness, diabetes, hypertension and cardiovascular risk [18] and same we found in treated diabetics in whom cardiovascular ageing is significantly higher despite mean young age. Pulse pressure was the only type of blood pressure that was not raised that highlights importance of SBP and DBP as a tool for early vascular progeria and PP to be better a predictor[19] in old age. Similarly, heart rate and rate pressure products were not significantly raised in type 1 diabetics indicating greater role of force than frequency of cardiac pumping in vascular progeria. Aortic PWV was the most significantly raised stiffness parameter while other parameters were small and insignificant. This indicates that aortic stiffness is earlier with type 1 diabetes and small arterial and systemic stiffness are late to be affected. It also hints towards importance of aPWV as a gold standard in young age group. Cardiac output and stroke work were significantly higher in case group despite comparable heart rate. This accelerated cardiovascular profile suggests increased work load on heart which can produce adversity to it as well as to other target organ damages.[20] Raised arterial stiffness also indicates future risk of incident hypertension[21] that is a frequent aftermath of diabetes, as we have previously reported in the form of co-existence of diabetes and hypertension in more than half cases[22].

We studied predictors of the PWA parameters by multiple linear regressions. The pattern of predictors was similar to our previous PWA studies.[4-8] Major highlights were : 1) most PWA parameters were not significantly predicted by age(except PWV), height, weight and BMI; 2) most parameters were independent of brachial blood pressures indicating their superiority to complement routine brachial blood pressure and heart rate measurement; 3) central blood pressures were not predicted significantly by corresponding brachial pressures values showing its importance beyond brachial blood pressure. Gender, BMI and physical activity are insignificant PWA predictors and in same age group it was found in our previous studies focusing various cardiovascular parameters.[4-7] Similarly, duration and glycemic control were not significant predictor for all parameters like our previous PWA based studies and other studies in our diabetics with reference to other cardiovascular investigations.[14,15,22-24] This can be in parts due to poor glycemic control, poor health literacy and lack of availability of HbA1c that could give better inference than blood glucose level. It suggests that early diagnosis and control of diabetes may be beneficial to reverse these changes, theoretically at least. Insulin related misconception, as we previously published[16], may hamper prompt glycemic control and with years to come aftermaths become adverse further. This cardiovascular progeria is found to exist in young healthy first degree relatives of type 2 diabetic and hypertensives as we previously published. These results and present study give evidence of utility of these parameters in young individuals over and above brachial blood pressure and heart rate.

Type 1 diabetes is a lesser growing concern but definitely inflicting cardiovascular health adversely. Evidences are more for type 2 than type 1 diabetes but for later studies are being published now. Hyperglycaemia accelerates cardiovascular ageing that manifests as raised stiffness, reduced

compliance and loss of elasticity. [25] And diagnosis and treatment of same is supposed to benefit these parameters. Our study suggests pulse wave analysis as a potential tool to discretely understand the disease that leads to vascular progeria- type 1 diabetes. Arterial stiffness and aortic haemodynamic parameters are more stable, reproducible, objective, reliable, direct, and discrete and with availability of Mobil-o-graph like devices it can be used on large scale. This baseline work calls for further interventional and cohort studies to consolidate our results and to understand role of other unstudied risk factors and predictors.

Our study had few limitations like cross-sectional nature, small sample size, lack of follow up and absence of biochemical markers of vascular progeria. Use of novel instrument Mobil-o-graph is more a strength than limitation of the study.

Conclusion : Oscillometric pulse wave analysis reveals beyond brachial blood pressure abnormality of direct and discrete cardiovascular parameters in Gujarati type 1 diabetics. This vascular progeria at the young age was independent of most conventional confounders. This baseline study suggests further work on these potential parameters.

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