Measurement of Stiffness Index by Digital Volume Pulse Analysis Technique: Clinical Utility in Cardiovascular Disease Risk Stratification

Ashan Gunarathne[1], Jeetesh V. Patel[1], Elizabeth A. Hughes[1] and Gregory Y.H. Lip[1]

BACKGROUND
Indices of arterial stiffness are accepted as independent markers of cardiovascular disease (CVD), having both positive prognostic and diagnostic implications. The utility of stiffness index (SI) derived from digital volume pulse (DVP) analysis in CVD risk screening is not established.

METHODS
Using a representative sample of individuals from local communities (West Midlands, UK), we determined the performance of SI in the discrimination of increasing CVD risk. Arterial stiffness was measured by DVP photoplethysmography (PCA 2; Micro Medical) using a direct, standardized approach. CVD risk assessment was performed in accordance with the Joint British Society guidelines (JBS2).

RESULTS
Of our cohort of 247 individuals (51% male; mean age 55.2 (s.d. 10.3) years), 187 were apparently healthy and 60 had established CVD risk factors (diabetes mellitus: 33%, hypertension: 77.8%, hypercholesteremia: 61%). On univariate analysis, SI was strongly associated with CVD risk (the European Society of Cardiology (ESC) based HeartScore) (Pearson correlation coefficient (R): 0.56, $P \leq 0.001$) and increased in an ordinal fashion from "low risk" to "medium risk" to "high risk" to "very high risk" (pseudo $R^2 = 0.30$; $P < 0.001$). In receiver operator characteristic curve analysis, SI was the best discriminator between low to medium risk and high-risk categories (area under curve (AUC): 0.76 (95% CI 0.64–0.88), $P < 0.001$) when compared to total cholesterol, plasma glucose, systolic blood pressure, and waist-to-hip ratio and had the utility to discriminate the individuals with known CVD risk factors such as diabetes and hypertension.

CONCLUSION
Noninvasive measurements of arterial stiffness may aid the optimal stratification of CVD risk in an apparently healthy population.

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Messung von Steifigkeitsindex durch **Puls-Volumen-Analyse-Technik der Finger** : Klinische Nützlichkeit in der **Kardiovaskulären Risikostratifikation**

Ashan Gunarathne1, Jeetesh V. Patel1, Elizabeth A. Hughes1 and Gregory Y.H. Lip1

Schlussfolgerung : noninvasive Messung von **arterieller Gefäßsteifigkeit** vermag die **Unterstützung der optimalen Stratifikation des Kardio-Vaskulären Erkrankungsrisikos bei scheinbar gesund wirkender Bevölkerung**

[1]University Department of Medicine, City Hospital, Birmingham, UK.
Correspondence: Gregory Y.H. Lip (g.y.h.lip@bham.ac.uk)

by the DVP analysis method has been proven to be a validated and reproducible technique with minimal intraobserver variation.[16,17] The SI has been demonstrated to have a comparable sensitivity and specificity to the pulse wave velocity method in the identification of patients with latent CVD.[18] However, its utility in cardiovascular risk assessment process among an apparently healthy population has not been investigated.

We hypothesized that SIs measured by DVP technique are strongly associated with ESC based cardiovascular risk scores in an apparently healthy population and that the SI is a good discriminator of stratification of CVD risk categories among wider population that includes higher risk individuals. To test this hypothesis, we measured the indices of arterial stiffness in a representative population attending a CVD risk assessment clinic over a 1-year period.

METHODS

Using a representative sampling approach, volunteers who had similar socioeconomic[19] backgrounds based on the Townsend deprivation index were recruited from the Sandwell and West Birmingham Primary Health Care Trust (West Midlands, UK). The total cohort (aged 30–75 years) comprised apparently healthy people without any known established risk factors and people with a past medical history of hypertension, diabetes, and hyperlipidemia who were on treatment but had no history of established cardiovascular events (e.g., myocardial infarction or stroke) according to careful clinical history, examination, and hospital medical records. All healthy subjects were free from documented CVD or risk factors (hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, myocardial infarction, and atrial fibrillation), peripheral artery disease, or cerebrovascular disease (stroke or transient ischemic attack). None of the subjects was on any regularly prescribed cardiovascular medications at the time of the study. This was established by the elicitation of a full medical history and the completion of a comprehensive physical examination performed by a qualified medical practitioner. Any person with abnormal blood pressure measurements (>140/90 mm Hg), fasting blood sugar level (>7 mmol/l), or a total cholesterol level (>5 mmol/l) was excluded from the study. Demographic data including details of smoking habit and alcohol consumption were collected.

Using the ESC HeartScore risk calculator, the absolute CVD risk (%) of developing nonfatal coronary heart disease, coronary death, or stroke over the next 10 years was estimated.[20] This ESC HeartScore algorithm has been selected as the new standard in European CVD risk prediction and management by the Third Joint European Societies Task Force on CVD Prevention in Clinical Practice[4] and is based upon the risk factors, namely, age, gender, smoking status, systolic blood pressure, total cholesterol levels, and diabetes status. Each subject provided written and informed consent and the study was approved by the West Birmingham Local Research Ethics Committee.

Measurement of blood pressure. Systolic and diastolic brachial arterial blood pressure levels were measured in both arms at 1 min intervals in the first instance and repeated in the arm with the higher blood pressure reading with the validated semiautomatic Omron HEM-705CP (Omron Healthcare Europe, Mannheim, Germany) with appropriate cuff sizes after >5 min sitting.[21] The mean of the last two blood pressure levels were used in the analysis. The heart rate was recorded from the last recorded blood pressure reading. Mean arterial blood pressure was calculated by a formula: the mean pulse pressure added to one-third of the diastolic blood pressure.

Calculation of the SI using pulse wave form reflections. SI is a parameter derived from the analysis of the pulse wave forms which reflects the tone and arterial distensibility. Similar to other noninvasive measurements such as augmentation index, this is an indirect method of determining arterial stiffness peripherally. The digital pulse volume pulse waveform consists of a systolic peak and a second diastolic peak which is formed by the reflection of the pulse wave from the small arteries in the lower body distally. The time delay (peak-to-peak time (PPT), see **Figure 1**) between the systolic and diastolic peaks is related to the transit time of pressure waves from the root of the subclavian artery to the apparent site of reflection and back to the subclavian artery. In addition to large vessel wall stiffness, the degree of pulse wave reflection also depends on the impedance of the microvascular bed and the tone of the small to medium sized blood vessels. This path length can be assumed proportional to height (h). Therefore index of large artery stiffness can be calculated from: SI = h/PPT (ref. 15) (**Figure 1**).

Arterial stiffness measurement protocol. Arterial stiffness measurement was performed on the morning following an overnight fast (each subject was instructed to refrain from caffeine-containing beverages, alcohol, and smoking in the previous 12 h) after which the DVP was recorded in the person's right index finger. Subjects were laid supine resting for at least 20 min in a temperature controlled environment (24 ± 1 °C) before the measurements were taken. All the volunteers were advised to refrain from talking and sleeping while the measurements were done. Patients with risk factors who were on any antihypertensive or antianginal medications were asked to miss their morning dose.
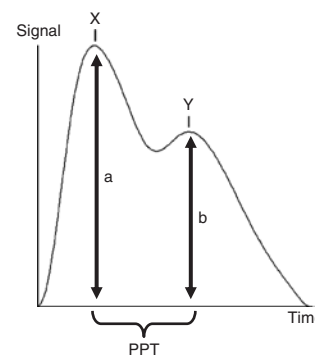

Figure 1 | Derivation of stiffness index from digital volume pulse analysis technique. X = forward wave/systolic peak; Y = reflected wave/diastolic peak; stiffness index = subject's height (m)/PPT. PPT, peak-to-peak time.

Recorded digital pulse wave forms using the photoplethysmography technique (PCA 2; Micro Medical) were used to generate indices of vessel reactivity and arterial stiffness as per a standard validated protocol.[20] Each person had at least three measurements (recorded for 30 s) taken 1 min apart and an average was calculated and used for the analysis. Volunteers whose pulse wave recordings could not be adequately assessed were excluded from the final analysis. In addition, volunteers who had an SI variation of >15% within measurements were also excluded. All of the measurements were performed by the same operator. Intraobserver variation (coefficient of variation) of the repeated measurements of SI in the same subject on the same day and 6 weeks later was 5.4% and 7.4%, respectively.

Statistical analysis. Data were analyzed using SPSS version v14 (SPSS, Chicago, IL). After being tested for normality using the Kolmogorov–Smirnov test, all the indices measured demonstrated a normal distribution. Data are presented as the mean ± s.d. Student's *t*-test and one-way analysis of variance tests were used to determine differences between groups with continuous variables, and the χ^2-test was used to compare the categorical variables. In univariate analysis, Pearson's correlation was used to observe the relationship between arterial stiffness and other cardiovascular risk indices. Linear regression models were used for multivariate analysis. For the correlation analysis of ordinal variables, Polytomous Universal Model ordinal regression analysis was used where the Cox and Snell pseudo R^2 values are reported to estimate the proportion of the total variation of an ordinal response that is explained by variables included in the model. Receiver operator characteristic curves were used to evaluate the performance of SI depicted by the mean area under the curve with 95% confidence interval. A two-tailed *P* value <0.05 was considered statistically significant for all comparisons. Data are reported to three significant figures.

Repeatability and reproducibility of SI measurements. SI was measured in a total of three times in each arm at 5-min intervals apart in 100 individuals at the same clinic visit. These measurements were repeated in a separate clinic visit in the same temperature controlled environment in 6 weeks time. Repeated measurements on the same visit (mean difference (s.d.): 0.09 (0.66)) as well as in the separate visit (0.12 (0.93)) demonstrated a good agreement (**Figure 2**).
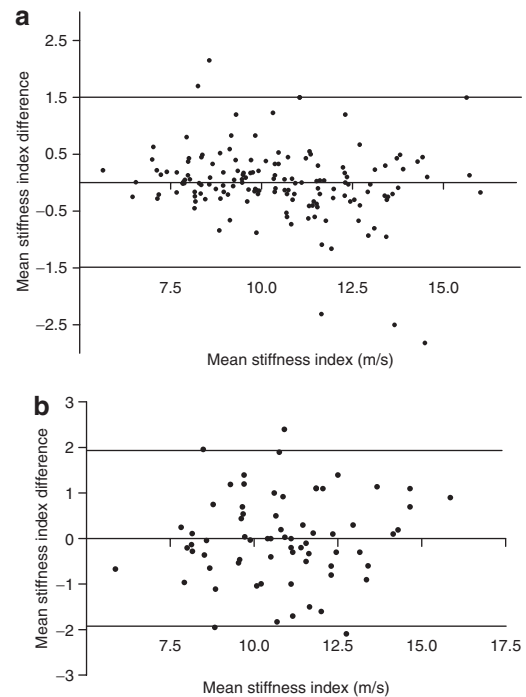

Figure 2 | Bland–Altman test demonstrating the agreement between repeated measurements of stiffness index (**a**) during a single-visit and (**b**) in follow-up visits.

Table 1 | Healthy volunteers vs. people with established cardiovascular risk indices

Cardiovascular risk factors Mean (s.d.)	Male			Female		
	Healthy volunteers	Risk controls	*P* value[a]	Healthy volunteers	Risk controls	*P* value[a]
Age (years)	45.6 (13.2)	65.8 (10.4)	<0.001	45.9 (12.5)	63.6 (10)	<0.001
Height (m)	1.69 (0.1)	1.69 (0.2)	0.97	1.59 (0.09)	1.58 (0.05)	0.12
Body mass index (kg/m^2)	25.5 (3.4)	27.9 (3.2)	0.02	26.5 (3.1)	26.9 (4.4)	0.49
Waist-to-hip ratio	1.01 (0.1)	0.99 (0.1)	0.27	0.98 (0.1)	0.93 (0.1)	0.28
Mean systolic BP (mm Hg)	137 (17)	145 (15)	<0.001	126 (16)	150 (15)	<0.001
Mean diastolic BP (mm Hg)	84 (11)	82 (13)	0.38	78.(10)	83 (10)	0.06
Mean arterial BP (mm Hg)	101 (12)	103 (13)	0.04	94 (11)	106 (10)	<0.001
Serum Cholesterol (mg/dl)	174 (34)	158 (15)	0.08	174 (36)	197 (42)	0.01
Fasting plasma glucose (mg/dl)	72 (28)	70 (22)	0.87	64.8 (25)	59 (27)	0.67
Smoking (%)	8.2	11.1	0.44	6.5	8.3	0.45
Alcohol (%)	9.8	15.6	0.42	8.2	12.8	0.41
ESC CVD risk score (%)	7.4 (6.1)	13.1 (5.9)	<0.001	4.58 (4.6)	11.3 (4.7)	<0.001
Stiffness index (m/s)	9.3 (2.2)	10.9 (2.4)	0.008	8.4 (2.1)	10.1 (2.4)	0.015

BP, blood pressure; CVD, cardiovascular disease; ESC, European Society of Cardiology.
[a]*P* value comparing healthy vs. risk controls; significance at 0.05 level.

RESULTS

A total of 187 healthy volunteers and 60 people with risk factors were recruited for the study (**Table 1**). Fifty-one percent of the subjects were between 30 and 41 years of age and 57.7% were male. As expected, patients with established CVD risk factors were older, had higher systolic blood pressure and CVD risk scores ($P < 0.001$; **Table 2**). Of the patients with established CVD risk factors, 33% had diabetes mellitus, 77.8% had a diagnosis of hypertension, and 61% had hypercholesteremia. Of these patients, 38.9% were on regular antihypertensive medications, 11.1% were on antidiabetes medications, 11.2% were on anticholesterol treatment, and 14.4% were on antiplatelet treatment.

SI was significantly higher in males ($P = 0.01$), as well as in people in the upper age tertile vs. lower tertile ($P < 0.001$), smokers ($P = 0.006$), those with a history of hypertension ($P = 0.007$), diabetes ($P = 0.02$), hypercholesteremia ($P = 0.002$), and those with a high waist-to-hip ratio ($P = 0.001$) but not with those

with a higher body mass index ($P = 0.49$). Subjects within the upper tertile of mean arterial pressure also had a higher SI compared to those in the lower tertile ($P < 0.001$).

Measurements of SI was also significantly higher in people with established risk CVD factors without any gender variation ($P < 0.01$). Subjects with higher SI (upper tertile) compared to lower tertile were older ($P < 0.001$), were smokers ($P = 0.04$), and had significantly higher mean systolic ($P < 0.001$) and diastolic ($P < 0.006$) blood pressure as well as CVD risk scores ($P < 0.001$) (**Table 3**).

Relationship to ESC based CVD risk stratification

On univariate analysis, there was a positive association between SI and CVD risk (Pearson correlation coefficient (R): 0.56, $P \leq 0.001$). On linear regression analysis, SI was associated with CVD risk scores (β (s.d.): 0.58 (1.3–2.0); $P < 0.001$). SI increased in an ordinal fashion across from low risk (<5%), medium (5–10%), high (11–19%), and highest risk (>20%) (Pseudo $R^2 = 0.30$; $P < 0.001$) (**Figure 3**).

Of the total population, 48.7% had lower-medium CVD risk (<15%) and correspondingly lower SI values (mean ± s.d.: 7.9 (1.5) m/s (**Figure 4**) compared to those at high risk ($P < 0.001$). In addition, male subjects had a higher CVD risk score ($P < 0.001$) and correspondingly higher SI compared to the females ($P = 0.01$). There was a significant difference in the mean risk score levels ($P < 0.001$) and SI between healthy volunteers and risk factor controls in both males ($P = 0.008$) and females ($P = 0.015$) (**Table 1**).

Correlations and multivariate regression

On univariate analysis (excluding people with established risk factors and medications), there was a significant positive association (R) between SI and age ($R = 0.41$; $P < 0.001$) mean systolic ($R = 0.24$; $P < 0.001$), diastolic blood pressure ($R = 0.29$; $P = 0.001$), pulse pressure ($R = 0.17$; $P = 0.03$), and mean arterial pressure ($R = 0.34$; $P = 0.003$). There was no significant association between SI and mean heart rate, body mass index, waist-to-hip ratio, fasting plasma glucose, and serum cholesterol. In multivariate regression analysis, β (95% CI) age (0.11 (0.04–0.17); $P < 0.002$), waist-to-hip ratio (0.33 (0.25–0.41); $P = 0.05$), and mean arterial pressure (0.06 (0.01–0.11); $P = 0.01$) independently associated with SI but not with serum cholesterol, fasting plasma glucose levels, or heart rate.

Receiver operator characteristic curve analysis

Receiver operator characteristic curve analysis of baseline characteristics to discriminate subjects with higher CVD risk found SI to be the most useful variable in this population (area under curve (AUC): 0.76 (s.e. 0.06), $P < 0.001$) compared to total cholesterol (AUC: 0.58 (0.07), $P = 0.17$), plasma glucose (AUC: 0.62 (0.07), $P = 0.07$), mean blood pressure (AUC: 0.60 (0.06), $P = 0.15$), and waist-to-hip ratio (AUC: 0.45 (0.04), $P = 0.35$). In addition, SI had the discriminatory utility to identify the patients with known diabetes (AUC: 0.68 (s.e. 0.04), $P < 0.001$), hypercholesteremia (AUC: 0.66 (s.e. 0.03), $P < 0.001$), hypertension (AUC: 0.66 (s.e. 0.03), $P < 0.001$), and higher

Table 2 | Indices of arterial stiffness (SIs) for the total cohort

Patient characteristics		% of all patients ($n = 247$)	Mean arterial stiffness m/s (s.d.)	P value[a]
Age (years)	I (<41)	51.0	8.3 (1.9)	<0.001
	II (41–55)	33.3	10.3 (2.3)	
	III (>56)	15.7	10.7 (2.5)	
Gender	Male	57.7	9.6 (2.3)	0.01[b]
	Female	42.3	8.8 (2.2)	
Waist-to-hip ratio	<0.9	40.1	7.9 (1.6)	0.001
	>1	59.9	9.4 (2.3)	
Body mass index (kg/m^2)	I (<25)	33.5	9.3 (2.5)	0.85
	II (25–28)	32.4	9.4 (2.2)	
	III (>28)	34.1	9.7 (2.3)	
Smoking	Yes	10.2	10.6 (2.5)	0.006[b]
	No	89.8	9.1 (2.2)	
Alcohol	Yes	9.6	10.1 (2.3)	0.5[b]
	No	90.4	9.6 (1.5)	
Diabetes	Yes	5.6	11.2 (2.4)	0.02[b]
	No	94.4	9.9 (2.3)	
Hypertension	Yes	18.3	10.4 (2.2)	0.007[b]
	No	81.7	9.1 (2.5)	
Hypercholesteremia	Yes	13.3	10.8 (2.8)	0.002[b]
	No	86.7	9.0 (2.2)	
Mean arterial pressure (mm Hg)	I (<94)	27.4	8.4 (2.1)	0.003
	II (94–104)	35.1	9.2 (2.1)	
	III (>105)	37.5	9.8 (2.4)	
CVD risk	I (0–5)	48.7	7.9 (1.5)	<0.001
	II (6–15)	22.8	9.4 (1.9)	
	III (>16)	28.5	11.2 (2.6)	

[a]P value using one-way analysis of variance across all groups and independent t-test; significance at 0.05 level. [b]P value using χ^2.

Table 3 | Cardiovascular risk profile according to stiffness index tertiles for the total population

Risk factors	Mean stiffness index tertiles			P value[a]
	I	II	III	
Mean stiffness index	6.8 (0.7)	8.6 (0.5)	11.6 (1.6)	<0.001
Age (years)	42.2 (11)	48.2 (14)	55 (12.2)	<0.001
Mean systolic BP (mm Hg)	128 (17)	136 (17.5)	139 (18)	<0.001
Mean diastolic BP (mm Hg)	79 (10)	81 (11)	84 (11)	0.006
Mean arterial BP (mm Hg)	95 (12)	99 (12)	103 (12)	<0.001
Body mass index (kg/m^2)	27 (4.3)	26.8 (4.4)	26.3 (3.3)	0.57
Waist-to-hip ratio	0.9 (0.1)	1.0 (0.12)	1.0 (0.09)	0.73
Fasting plasma glucose (mg/dl)	66 (21)	68 (27)	69 (30)	0.97
Serum Cholesterol (mg/dl)	169 (27)	173 (35)	181 (35)	0.1
ESC CVD risk	4.4 (4.3)	6.2 (5.1)	12.7 (7.9)	<0.001
Risk factor (%)				
Smoking status (%)	1.8	13.8	14.1	0.04[b]
Alcohol (%)	7.7	11.1	7.5	0.89[b]

Data are mean (s.d.).
BP, blood pressure; CVD, cardiovascular disease; ESC, European Society of Cardiology.
[a]P value using one-way analysis of variance across all groups; significance at <0.05 level. [b]P value using χ^2.
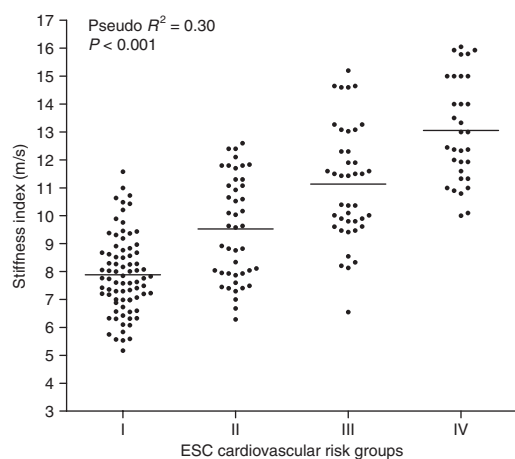

Figure 3 | Ordinal association between mean stiffness index and European Society of Cardiology (ESC) risk score groups in healthy volunteers and in patients with cardiovascular risk factors. ESC HeartScore–based cardiovascular disease (CVD) risk groups (%): Group I (<5%), Group II (6–15%), Group III (16–19%), Group IV (>20%). Line shows the mean CVD risk score.

waist-to-hip ratio (AUC: 0.69 (s.e. 0.05), $P = 0.001$) but not with higher body mass index (AUC: 0.50 (s.e. 0.06), $P = 0.92$).

DISCUSSION

In this study, we demonstrate the clinical utility of a marker of arterial stiffness to stratify CVD risk in individuals using the digital pulse wave form analysis technique. This study demonstrates a close association between SI and CVD risk score estimation using the ESC HeartScore model. More importantly, the discriminatory properties of the SI in identifying higher risk groups were significantly better than those of conventional cardiovascular risk indices such as total cholesterol level and fasting blood sugar measurements.
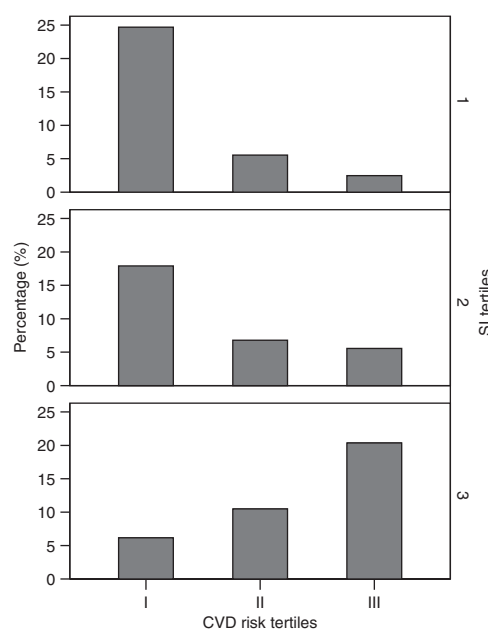

Figure 4 | Distribution of stiffness index (SI) and cardiovascular disease (CVD) risk groups according to tertiles for the healthy population. European Society of Cardiology HeartScore–based CVD risk tertiles (%): Tertile I = (<5%), Tertile II = (6–15%), Tertile III = (>16%). SI tertiles (m/s): Tertile 1 = SI <7.7; Tertile 2 = SI 7.8–9.7; Tertile 3 = SI >9.8.

Screening of the population with ESC HeartScore and Framingham-based risk score methods continue to be recommended in many current guidelines.[22] However, the absolute levels of cardiovascular risk factors are mathematically combined as a holistic approach during risk prediction with limited direct relationships to underlying pathophysiological changes. In this study, 16% of the people in the higher SI tertile still

had lower-medium CVD risk scores (**Figure 4**). This suggests that a significant proportion of the higher risk subjects may be missed in a traditional risk assessment process and highlights the importance of using potential new risk markers to aid more conventional cardiovascular risk stratification schemes.

The novel DVP technique used to asses the arterial distensibility of volunteers in this study is an easily performable, noninvasive technique with low intraobserver and interobserver variation. This method allows the indirect examination of the structural integrity of both large and small arteries simultaneously allowing the identification of apparently healthy individuals with subclinical atherogenesis and premature arteriosclerosis. Measurements of SI may therefore be more useful in the early identification of high-risk subjects without established risk indices such as high blood pressure or cholesterol levels. Such people are usually omitted in traditional CVD risk assessments.

As expected, subjects with established risk factors in our study also demonstrate higher SI when compared to healthy controls. Moreover, the SI was a better discriminator in identifying people with established CVD risk factors (such as hypertension, diabetes, and hypercholesteremia) where individual point measurements of theses risk indices are less useful, for example, where they are taking medications. While this study highlights the clinical utility and acceptability of DVP measurements in a wide spectrum of individuals with and without established risk factors, further studies are warranted to asses the utility of SI in clinical practice and to monitor treatment efficacy as well as disease progression.

In our study, the principal factors contributing to increased SI include age and mean arterial pressure but not body mass index. This is in keeping with the other published studies in which the pulse wave technique was used.[23–25] The independent association between waist-to-hip ratio with increased SI merits careful consideration. Indeed, several studies have reported an association between waist-to-hip ratio and cardiovascular risk factors such as hypertension and lipid and glucose concentrations.[26] People with a raised waist-to-hip ratio are also known to have varying degrees of insulin resistance[27] and have been shown to increase in patients with obesity.[28] The systemic effects of insulin resistance, such as increased adrenergic response, sympathetic tone, and vascular inflammation are some of other mechanisms that may be involved in increased arterial stiffness.

The limitations of this study include the cross-sectional nature of the design and use of indirect indices to measure arterial stiffness. However, other invasive complex measurements of arterial stiffness are not practical to use as a tool to screen larger populations in the clinical settings. In the current analysis, other metabolic, inflammatory biomarkers and the impact novel risk indices have on arterial stiffness in this population have not been examined. Diagnosis of diabetes mellitus was also made on the basis of fasting blood glucose measurements and available documented evidence. None of the volunteers had an oral glucose tolerance test for specific disease exclusion. In the current study, CVD risk calculation was based on a European risk score engine (ESC based Heart Score), which does not use high-density lipoprotein cholesterol for risk estimation compared with the Framingham (United States)-based risk calculation which allows finer risk stratification of higher CVD risk individuals with lower high-density lipoprotein values. In addition, the DVP method used to measure arterial stiffness in this study did not provide information on individual contributions that both large and small arteries make toward wave reflection and overall arterial stiffness. Furthermore, calculation of SI is based on the assumption that subject's height is proportional to the path length of the wave reflection. In addition, this study may not have the power to discriminate or compare the established risk factors such as smoking status between healthy and risk factor control groups. Moreover, this study doesn't provide the facility to determine the discriminatory utility of SI in different age categories. Using a larger prospective study design that used CVD outcomes with combined methods of measurement (pulse wave velocity and DVP, for example) would possibly have provided more comprehensive details thereby giving greater explanatory power to this study. However, the logistics for such a study are also limited by the need-to-treat individuals recognized to be at increased CVD risk.

In conclusion, SIs measured using the DVP technique is strongly associated with the ESC "HeartScore" cardiovascular risk score and demonstrates the discriminatory utility of the SI in identifying high-risk populations. Thus, noninvasive measurement of arterial stiffness may aid the identification of individuals with high cardiovascular risk. However, there is a need for future external validity studies of SI to demonstrate the ability to prospectively predict the clinical outcomes over and above those predicted by existing CVD risk score estimations.

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