Comparison of Invasive vs Noninvasive Pulse Wave Indices in Detection of Significant Coronary Artery Disease: Can We Use Noninvasive Pulse Wave Indices as Screening Test

Maddury Jyotsna[1], Alla Mahesh[1], Madhavapeddi Aditya[1], Pathapati Ram mohan[2] and Maddireddy Umameshwar Rao Naidu[2]

[1] Department of Cardiology, [2] Department of Clinical Pharmacology, Nizam's institute of medical sciences, Hyderabad, Andhra Pradesh, India.

Abstract: Various non-invasive techniques to assess the indices of arterial stiffness, such as augmentation Index were used previously to detect coronary artery disease (CAD). We studied two indices of arterial stiffness analyzed from pulse contour analysis—reflection (RI) and stiffness index (SI) both by noninvasively using plethesmography and invasively from radial artery along with ECG to detect CAD and its severity.

56 patients with a mean age of 52.62 ± 8.3 yrs undergoing coronary angiogram transradially either for the diagnosis or exclusion of CAD participated in this study. Significant coronary artery disease (CAD) is defined as greater than 50% stenosis in at least one epicardial coronary artery (ECA). Scores of 0, 1, 2, and 3 was given for normal (no CAD group), significant CAD in one ECA, two ECA and all three ECA respectively. 17 patients had normal ECA, 15 patients had score 1, 13 patients had score 2, and 11 patients had score 3. By noninvasive method, the mean value of RI for no-CAD group was $37.82\% \pm 7.3\%$ vs CAD group $73.09\% \pm 10.09\%$ ($p < 0.001$) and the mean value of SI is 8.00 ± 0.9 m/s for no-CAD group vs 9.52 ± 1.05 m/for CAD group ($P = 0.0055$). There was no correlation in predicting the degree of CAD by RI ($p > 0.05$) or SI ($p > 0.05$). By invasive method RI ($p = 0.0056$) and SI ($p = 0.0068$) showed statistically significant correlation in detection of CAD but not for the severity. In conclusion, reflection and stiffness index have a significant difference in patients with CAD and CAD patients receiving medication. However, the difference between these parameters in varying grades of CAD is not significant.

Keywords: reflection index, stiffness index, coronary artery disease

Introduction

Endothelial dysfunction is now recognized as an established cause of cardiovascular disease. The initial manifestation of endothelial dysfunction is an increase in arterial stiffness, which is due to an imbalance in the vasodilator-vasoconstrictor substances released from the endothelium. Increased arterial stiffness results in atherosclerosis and hypertension (1). As arterial stiffness increases, transmission velocity of both forward and reflected wave's increases and the reflected wave to arrives earlier in the central aorta and augments pressure in late systole. Therefore, augmentation of the central aortic pressure wave is a manifestation of early wave reflection and is the boost up of pressure from the first systolic shoulder to the systolic pressure peak.

Increased arterial stiffness, determined invasively, has been shown to predict a higher risk of coronary atherosclerosis (2). But these noninvasive methods are not yet standardized (3). Previous studies used augmented pressure- AP (the difference between the second and the first systolic peak) and augmentation index (AP expressed as a percentage of the pulse pressure) to detect coronary atherosclerosis (4). In this study we used different non-invasive indices to detect coronary artery disease and compared them with radial artery wave analysis obtained invasively.

Materials and Methods

Study population

We included 56 patients who were under going coronary angiogram transradially either for the diagnosis or exclusion of CAD. Patients with valvular heart disease were excluded. Demographic and clinical

history was noted. Blood pressure was recorded using sphygmomanometer, with radial artery kept at the level of heart. The average of three systolic pressure (SP) and diastolic pressure (DP) readings was used for final analysis. From these Pulses pressure (PP) and mean arterial pressure (MAP) was derived. All patients were studied while they taking regular medications (drugs were not withheld before measurement) as the patients were symptomatic.

MAP = diastolic pressure + 1/3 pulse pressure

Cardiac catheterization and coronary angiogram

For these 56 patients coronary angiogram (CAG) was performed transradially using 6F diagnostic Judkin's 3.5 curve catheters. Arterial pressure tracings were recorded from radial artery immediately after puncture. Simultaneously ECG was recorded to calculate exactly the time intervals and information about the dicrotic notch and wave. Repeat arterial pressure tracings were recorded immediately after giving the Nitroglycerine 200 micro grams in to the artery. Significant coronary artery disease (CAD) is defined as greater than 50% stenosis in at least one epicardial coronary artery (ECA). Scores of 0, 1, 2, and 3 was given for normal (no CAD group), significant CAD in one ECA, two ECA and all three ECA respectively.

Peripheral arterial wave recording

Arterial wave reflections were quantified noninvasively using Photoplethysmographic Pulse Wave Analysis system ("VasoWin" Genesis Medical, Hyderabad, India). This system acquires Digital Volume Pulse (DVP) waveform tracings from the forefinger of dominant hand of the subject. The waveforms were sampled at 200 Hz for a good resolution. VasoWin is designed according to IEC60601 patient safety guidelines for medical instruments. VasoWin System has in-built proprietary software to find the exact location of dicrotic notch from the second derivative of the PPG (Peripheral Pulse Graph) waveform and is accurate even when the dicrotic notch is invisible to human eyes. Electrocardiogram, blood pressure (BP) waveform and peripheral pulse graph (PPG) was acquired simultaneously. Ten sequential waveforms had been acquired; a validated generalized transfer function was used to generate average

waveform. To compare two or more waveforms of different amplitudes and time duration, one must normalize them to a standard amplitude as well as sample per pulse waveform. Otherwise such a comparison and the results obtained from the analysis will be on unequal scales. So as to get uniform values of results across these inequalities, one has to normalize the data over both the amplitude and the time scale. In the current scenario, all the PPG waveforms are transformed linearly to amplitude of 100(dimensionless)—i.e. Amplitude normalization and 100 samples per pulse- i.e. Time normalization (5, 6). The average of these 10 successive measurements, to cover a complete respiratory cycle, was used in the analyses.

All PWA measurements were taken in the supine position in a quiet, temperature controlled room (22 ± 1 °C) after a brief period (at least 5 minutes) of rest, one day prior to cardiac catheterization by research nurses who were not involved either in performance or interpretation of the angiograms.

Pulse wave analysis (for invasive and noninvasive)

By both invasive and noninvasive methods reflection index and stiffness index were calculated (Figs. 1 & 2).

RI is calculated as height of second systolic peak (B) to first systolic peak (A)

$$RI = \frac{height\ of\ second\ systolic\ peak\ (B)}{first\ systolic\ peak\ (A)}$$

Time interval between the two systolic peaks (A & B) is known as Digital Volume Pulse Transit time (ΔT_{DVP})

$$SI = \frac{height\ of\ the\ patients\ (meters)}{\Delta T_{DVP}}$$

h = height of patient.
ΔT_{DVP} = time interval between the two systolic peaks.

Statistical Analysis

Statistical analysis was carried out using "Graphpad InStat" version 3.06. Continuous data was presented as mean, standard deviation and the categorical data as percentages. Between group analysis was performed by using either unpaired
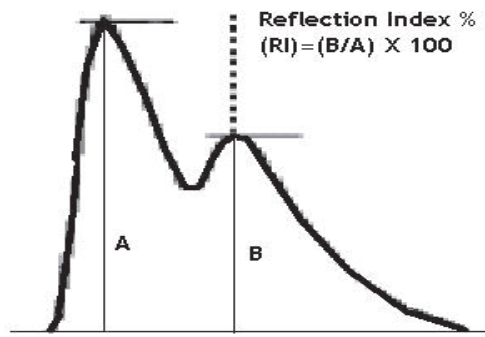
A = height of first systolic peak
B = height of second systolic peak

Figure 1. Reflection index calculation.

t tests or ANOVA. P value less than 0.05 was considered statistically significant.

Results

Baseline clinical characteristics

Fifty-six patients in the mean age group of 52.62 ± 8.3 yrs participated in this study; out of them 51 were males. Thirty patients (53.6%) had one or two risk factors and rest patients were without any risk factor (Table 1). Average SP, DP, MAP, MAPP, PP and HR in both group of patients (With CAD and without CAD) were given (Table 2).

Coronary angiogram findings

In 17 patients CAG revealed normal ECA or coronary stenosis less than 50%. 15 patients had score 1, 13 patients had score 2, and 11 patients had score 3.

Results of pulse wave analysis

Mean values of Reflection Index (RI) as assessed by noninvasive method in patients with significant coronary artery disease (score of 1, 2 and 3) were $74.51\% \pm 4.9\%$, $75.6\% \pm 4.5\%$ and $77.4\% \pm 6.4\%$ respectively. There was no significant difference ($p > 0.05$) in the values of RI between these
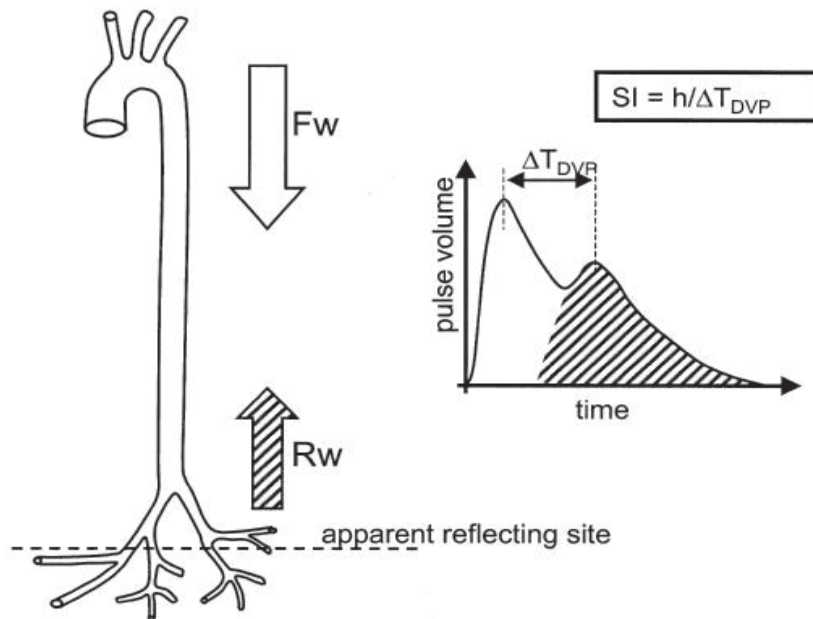

Figure 2. Stiffness index calculation.

Table 1. Demographic data.

Parameters	Values
Average age	52.62 ± 8.3 yrs
No. of patients	56
Females: Males	5:51
Risk factors	
Diabetes	15
Hypertension	20
Smoking	14
Family history of CAD	02
No risk factors	26

Column A: Grade 0 No-CAD   Column B: Grade 1 CAD

Column C: Grade 2 CAD   Column D: Grade 3 CAD

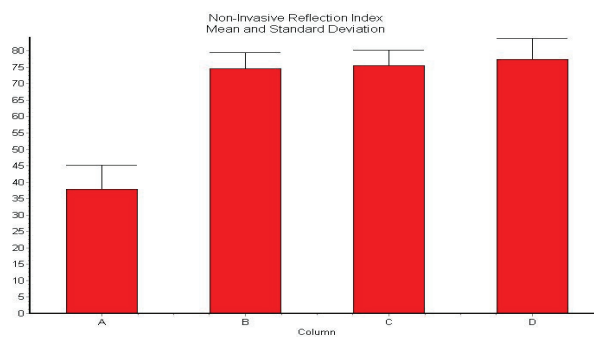**Figure 3.** Non invasive reflection index in different subgroup of CAD and No CAD patients.

groups. (B vs C, B vs D, C vs D) However, when we compared with the values of RI (37.82% ± 7.3%) in patients without coronary disease (score of 0); we observed that these values are significantly higher than the value of RI in patients without coronary disease (score of 0) 37.82% ± 7.3%. (P = 0.01) (A vs B, A vs C or A vs D) (Fig. 3). When the three CAD groups are put together and compared with No-CAD group, the observed difference was extremely significant (P < 0.001). RI for No-CAD group is 37.82% ± 7.3% which is considerably lower than that of combined CAD group 73.098% ± 10.093% (Fig. 4).These observations suggests that RI may useful in predicting CAD and not the severity.

Mean values of Reflection Index (RI) by invasive method in patients with significant coronary artery disease (score of 1, 2 or 3) was 45.85% ± 12.9%, 47.7% ± 9.5% and 48.7% ± 4.05% respectively. These values are significant higher than RI in patients without coronary disease (score of 0) 29.61% ± 9.29%. (P = 0.0056) (Fig. 5). RI for No-CAD group is 29.61% ± 9.29% which is significantly lower than that of combined CAD group 47.42% ± 8.82% (Fig. 6).

Mean value of Stiffness Index (SI) by noninvasive method in patients with significant coronary artery disease (score of 1, 2 or 3) was 8.34 ± 1.9, 8.54 ± 1.8 and 9.05 ± 1.8 meters/sec respectively. These values are higher than SI in patients without coronary disease (score of 0) 8.28 ± 1.06 (Fig. 7). In non-invasive method, the mean value of SI is 8.00 ± 0.9 m/s for No-CAD patients whereas for all CAD patients it is 9.52 ± 1.05 m/s (P = 0.0055)(Fig. 8).

Mean value of Stiffness Index (SI) by invasive method in patients with significant coronary artery

Table 2. Arterial pressure parameters in CAD and without CAD patients.

Parameter	No CAD group	CAD group
Systolic pressure (SP) (mm of hg)	139.5 ± 19.32	131.44 ± 22.97
Diastolic pressure (DP) (mm of hg)	98 ± 10.46	78.1 ± 13.22
Mean arterial pressure (MAP) (mm of hg)	112 ± 13.33	97.34 ± 17.91
Pulse pressure (PP) (mm of hg)	41.5 ± 10.65	63.82114 ± 9.87
Heart rate (HR)	78 ± 7.6	78.78 ± 8.9

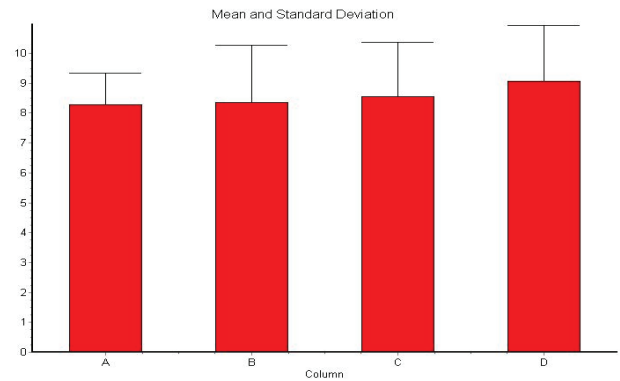Column A: No-CAD   Column B: All CAD groups put tougher
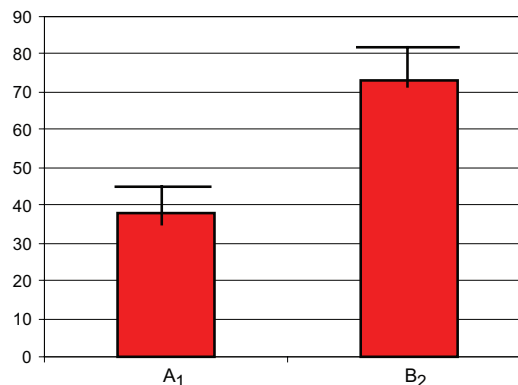
Figure 4. Noninvasive reflection index in all CAD and No-CAD patients.
Column A: No-CAD; Column B: All CAD groups put tougher.

Column A: Grade 0 No-CAD   Column B: Grade 1 CAD

Column C: Grade 2 CAD   Column D: Grade 3 CAD
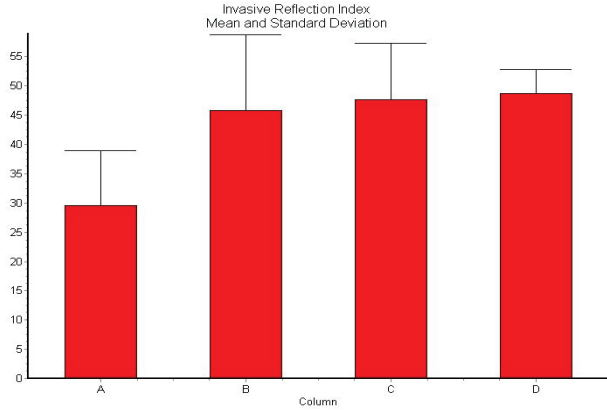
Figure 5. Invasive RI in No CAD and all subgroup of CAD patients.

Figure 7. Non invasive SI in different subgroup of CAD and No CAD patients.

disease (score of 1, 2 or 3) was 7.81 ± 2.6, 8.22 ± 4.4 and 7.35 ± 1.1 meters/sec respectively. These values are higher than SI in patients without coronary disease (score of 0) 6.94 ± 1.9 (Fig. 9) In Invasive method, the mean value of SI is 6.15 ± 1.00 m/s for No-CAD patients whereas for CAD patients it is 8.36 ± 2.82 m/s (P = 0.0068) (Fig. 10). Invasive and non-invasive Stiffness Index correlated well with a slope of 0.7331 (P < 0.0001)(Fig. 11).

Discussion

Previously Pulse wave monitoring was used in postoperative cases for the measurement of beat-to-beat changes in stroke volume or to analyze the interaction of ventilation and circulation which tests general circulatory performance (7). As the

pathophysiology of pulse wave pattern is better understood different indications are emerged to analyze the pulse wave pattern.

Large artery stiffness is an independent predictor of cardiovascular mortality and a major determinant of pulse pressure. When arteries are relatively compliant arterial wave forms travels relatively slow, reflected waves return to the central aorta in diastole, augments diastolic blood pressure and preserves coronary blood flow, which occurs predominantly during diastole. When arteries are stiffer, reflected waves arrives faster, augments central systolic rather than diastolic blood pressure, increases left ventricular workload and compromise coronary blood flow. Arterial stiffening reflects the degenerative changes of arterial wall. Arterial stiffness is dependent on drugs, age,

Column 1: Grade 0 No-CAD   Column 2: All CAD
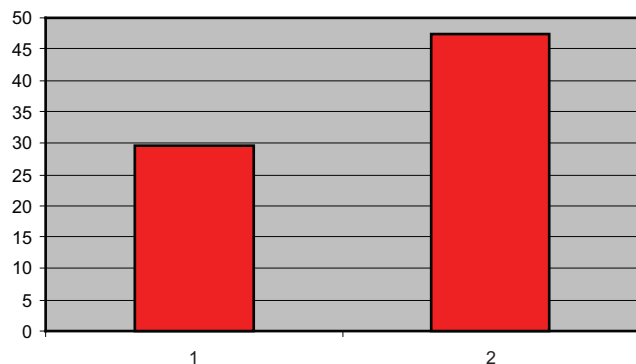
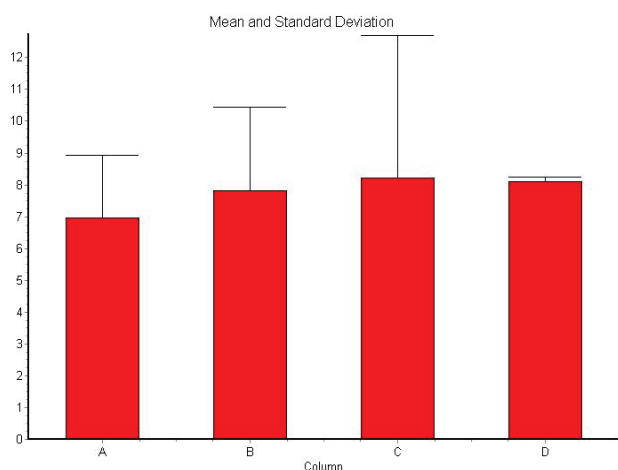**Figure 6.** Invasive RI in No CAD and all CAD patients.

Column A: No-CAD   Column B: CAD
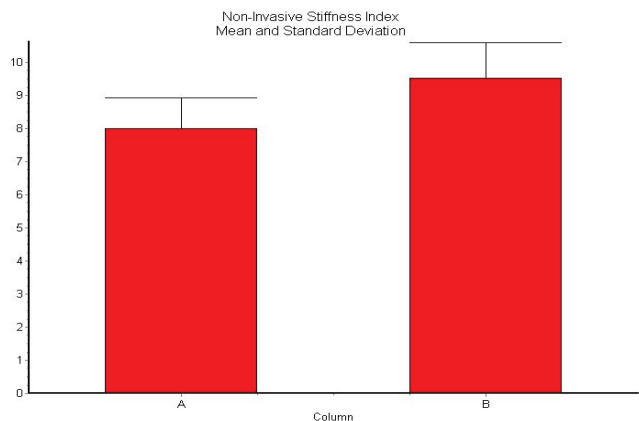
Figure 8. Non invasive SI in CAD vs No CAD patients.

Column A: Grade 0 No-CAD   Column B: Grade 1 CAD

Column C: Grade 2 CAD   Column D: Grade 3 CAD

Figure 9. Invasive SI in different subgroup of CAD and No CAD patients.

different risk factors duration and site used to record (8, 9, and 10). Thomas Weber et al. studied systemic arterial compliance, distensibility index, aortic pulse wave velocity, and carotid augmentation index using carotid applanation tonometry and Doppler velocitometry (4). They demonstrated that the indices of large artery stiffness/compliance correlated with time to ischemia (P = 0.01 to 0.009). In patients with moderate CAD, large artery stiffness is a major determinant of myocardial ischemic threshold. In our study also stiffness index is useful in detecting the severity of coronary artery disease.

Even though there is correlation in knowing the severity of CAD with pulse wave analysis, few studies demonstrated such correlation with only central pulse but not with peripheral pulse. Waddell TK demonstrated that patients with severe coronary stenosis (>90% stenosis) had low compliance and high mean pressure (11). Pulse wave velocity was higher in patients with severe stenosis than in those with moderate stenosis (50%–89% stenosis) (P < 0.01) and those in the control group (P < 0.001). Brachial pulse pressure was higher in patients than in controls (P < 0.05), but there was no difference between the 2 disease groups. In this study, we concentrated more on noninvasive method of pulse wave analysis even though central aortic pressure tracing also analyzed (which was recorded during CAG). As this is a noninvasive method large number of general population can be screened to detect CAD.

Most of studies that compared invasive vs noninvasive pulse wave analysis have used femoral site for recording central aortic pressures. At this site the systolic and pulse pressures will be greater and the dicrotic wave will be more prominent. The changes that occurred in transmission waves increased during vasoconstriction and decreased during vasodilatation Greater pulse pressure results in greater amplitude pressure waves. How ever, according to Carter et al. amplification did not differ significantly between control subjects and patients with hypertension or ischemic heart disease. In the absence of pronounced vasodilatation or luminal obstruction by atherosclerotic plaques, systolic and pulse pressures at the femoral site will be higher than in proximal pulses. To come over these problems we used transradial arterial wave form analysis.

Idia et al. used finger pulse for noninvasive wave analysis and femoral artery pressure for invasive wave analysis; they found that the derived values were different (12). In a study conducted on medical students, the ratio of time delay for the rise of toe pulse to that of finger pulse (t) was almost halved when there was postural change from the supine position to the sitting position. This was mainly due to an increase in the pulse wave velocity in the aorta, which was thought to be induced by the increase in hydrostatic pressure in the aorta. A distinct dicrotic wave was observed in both finger and toe pulse waves. The interval between the main and dicrotic wave (T) was shorter for finger pulse than toe pulse also seems to be ascribable to the influence of the intra aortic

Column A: No-CAD   Column B: CAD
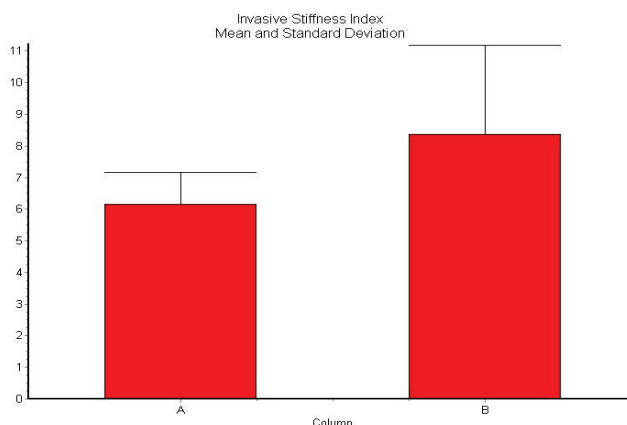
Figure 10. Invasive SI in CAD and No CAD patients.
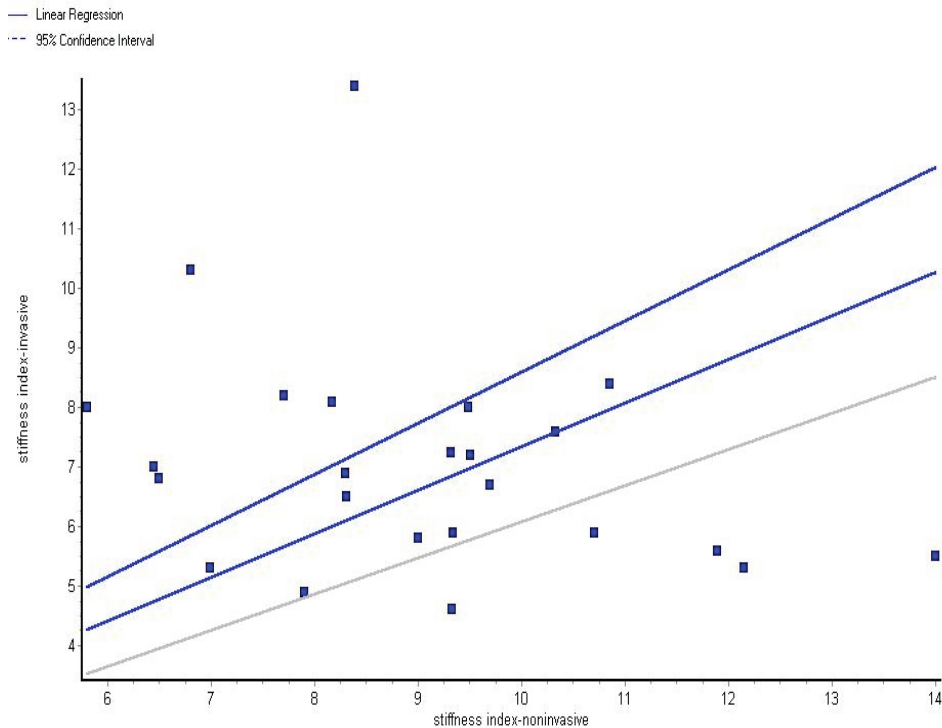
Figure 11. Correlation of SI invasively and noninvasively.

pressure: pulse was transmitted faster in the systolic phase than in the diastolic phase. The features of pulse waves of hypertensive patients were that time delay for the rise of pulse (t) was short even in the supine position, and the dicrotic wave was small or absent especially for toe pulse. In present study we used finger pulse and radial arterial pulse and observed that the non invasive pulse wave indices may useful in predicting CAD and not the severity. McLeod AL intravascular ultrasound guided study also did not demonstrate the good correlation with these indices derived from the noninvasive pulse wave analysis with the severity of CAD (13).

One potential limitation of our study is the confinement to symptomatic patients referred for coronary angiography. Many of them had athero-sclerotic obstructive CAD and very few had normal luminogram. However, the incidence of normal epicardial vessels varies between 10%–25% of total number of angiograms. To get significant number of cases with normal epicardial vessels, we have to screen large number of patients. Getting asymp-tomatic subjects for invasive studies is not practi-cal. However, it seems very much possible that our findings may be reproduced in large scale studies of this milieu. Another limitation of the study was

that the patients were continued medications pre-scribed for CAD, which will have effect on these indices (14, 15).

Conclusion

The values of noninvasive pulse wave indices, reflection index and stiffness index, were signifi-cantly different in patients without CAD and CAD patients under medication. This difference may be higher if the patients were not under medication. However, the difference between these parameters in varying grades of CAD is not significant. This may indicate that though these parameters may be used for differentiation between patients without CAD and CAD patients, their potential to indicate the degree of CAD may be limited.

References
[1]   O'Rourke, M.F. and Mancia, G. 1999. Arterial stiffness. *J. Hypertens*, 17:1–4.
[2]   Kingwell, B.A., Waddell, T.K., Medley, T.L., Cameron, J.D. and Dart, A.M. 2002. Large artery stiffness predicts ischemic threshold in patients with coronary artery disease. *J. Am. Coll. Cardiol.*, 40(4):773–9.
[3]   Kuvin, J.T., Patel, A.R., Sliney, K.A., Pandian, N.G., Sheffy, J., Schnall, R.P., Karas, R.H. and Udelson, J.E. 2003. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am. Heart J.*, 146(1):168–74.

[4] Thomas Weber, M.D., Johann Auer, M.D., Michael, F., O' Rourke, M.D., Erich Kvas, ScD., Elisabeth Lassing, M.D., Robert Berent, M.D. and Bernd Eber, M.D. 2004. Arterial Stiffness, Wave reflections, and the risk of coronary artery disease. *Circulation*, 109:184–9.

[5] Applied functional data analysis: methods and case studies, Ramsay, J.O. and Silverman, B.W. 2002. Springer series in statistics, New York, London: SpringerISBN:0–387–95414–7.

[6] Functional Data Analysis, Ramsay, J.O. and Silverman, B.W. Copyright# 2001 Elsevier Science Ltd. International Encyclopedia of the Social and Behavioral Sciences ISBN:0–08–043076–7.

[7] Murray, W.B. and Foster, P.A. 1996. The peripheral pulse wave: information overlooked. *Clin. Monit.*, 12:365–77.

[8] Mitchell, G.F., Parise, H., Benjamin, E.J., Larson, M.G., Keyes, M.J., Vita, J.A. and Levy, D. 2004. Changes in arterial stiffness andwave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension*, 43:1239–45.

[9] Millasseau, S.C., Kelly, R.P., Ritter, J.M. and Chowienczyk, P.J. 2002. Determination of age-related increases in large artery stiffness by digital pulse contour analysis. *Clinical Science*, 103:371–7.

[10] Pierre Boutouyrie, Anne Isabelle Tropeano, Roland Asmar, Isabelle Gautier, Athanase Benetos, Patrick Lacolley and Stephane Laurent. 2002. Aortic Stiffness Is an Independent Predictor of Primary Coronary Events in Hypertensive Patients. A Longitudinal Study. *Hypertension*, 39:10–15.

[11] Waddell, T.K., Dart, A.M., Medley, T.L., Cameron, J.D. and Kingwell, B.A. 2001. Carotid pressure is a better predictor of coronary artery disease severity than brachial pressure. *Hypertension*, 38(4):927–31.

[12] Iida, N. and Iriuchijima, J. 1992. Postural changes in finger and toe pulse waves. *Kokyu To Junkan*, 40:981–6.

[13] McLeod, A.L., Uren, N.G., Wilkinson, I.B., Webb, D.J., Maxwell, S.R. and Northridge newby, DE. 2004. Non-invasive measures of pulse wave velocity correlate with coronary arterial plaque load in humans. *J. Hypertens.*, 22:363–8.

[14] Hope, S.A. and Hughes, A.D. 2007. Drug effects on the mechanical properties of large arteries in humans. *Clin. Exp. Pharmacol. Physiol.*, 34(7):688–93.

[15] Ting, C.T., Chen, C.H., Chang, M.S. et al. 1995. Short and long term effects of antihypertensive drugs on arterial reflections, compliance and impedance. *Hypertension*, 26:524–30.