Correlation between cardiac index (CI) and cardio ankle vascular index (CAVI) at different degrees of head up tilt table

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Abstract:
Background: Cardio Ankle Vascular Index (CAVI), a new index for arterial stiffness that can be measured by VaSera VS-1000 CAVI device. This is a new method for estimating the level of arteriosclerosis, which is relatively uninfluenced by changes of blood pressure. An association between some arterial fitness indices and cardiac function has been recently demonstrated.

CI: is Cardiodynamic measure based on the Cardiac output (CO) which is normalized according to body size ,this is gained by dividing CO on body surface area.

Aim: To establish if any significant interrelationship exists between indexed cardiac output (CI) and Cardio ankle vascular Index (CAVI). Further, to introduce a new index as a haemodynamic parameter, notably CI/CAVI.

Method: This study was carried out at Dr.Akeel Zwain private clinic, on 20 healthy male volunteers of a mean age of 30±5 year and BMI of 23.1±1 Kg/m². Measurement of cardiac output (CO) is accomplished by estimation of aortic diameter (D) and calculating the velocity time integral (VTI) of aortic flow by Doppler echocardiography, then utilizing the equation: CO=(VTI*D²*0.785)*heart rate. Measurement of arterial stiffness index (CAVI) can be generated by VaSeraVS-1000 device. A motorized tilting table of incremental degrees; at 0°, 30° and 60° of head up tilt (HUT), was used to bring about peripheral sympathetic outflow modifications, together with postural changes in stroke volume, hence CO and CI.

Results: This study demonstrated that there was a statistical significant negative correlation between CI and the degree of head up tilt. CI is significantly decreased relative to increase of HUT degree, in a stepwise manner; CI is significantly lower at 30 and 60 degrees than that at zero degree, (Pearson’s correlation coefficient: r=0.63 for 0°and 30°; r=0.81 for 0°and 60°, p<0.001 for both; r= 0.71for 30°and 60°; p<0.05).

On the other hand, CAVI showed a statistical significant positive correlation relative to the degree of HUT. CAVI was significantly increased, in a stepwise fashion, at 30 and 60 degrees, than that at supine zero degree (Pearson’s correlation coefficient: r =0.88 for 0° and 30°; r=0.83 for 0°and 60°; r=0.81 for 30° and 60°; p<0.001 for all).
Correlation between CI and CAVI at different degrees of HUT was studied, the results demonstrated a significant negative correlation exists between CI and CAVI \((r = -0.47; p<0.05)\). The result of dividing the two indexes, by each other, CI/CAVI, yielded significant inverse inter relationship with respect to degree of HUT; being lower at 30º and 60º than that obtained at 0º tilt. It was significantly lower, in a slope wise pattern, at 60º than that at 30º of tilt \((r =0.65\) for 0º and 30º; \(r =0.78\) for 0º and 60º; \(r =0.68\), for 30º and 60º; \(p<0.001\) for all).

**Conclusion:** the present investigation reveals an inverse interrelationship between CI and CAVI; a decrease of CI is consistently associated with an increase of CAVI. A new index CI/CAVI may be proposed; it can be employed to early detect subclinical atherosclerosis impact on cardiac muscle pump function. This new integrated parameter could possibly serve for fitness assessment, and for cardiovascular risk stratification.

Abbreviations: CAVI, cardio ankle vascular index; HUT: head up tilt; CI: cardiac index; CO: cardiac output; VTI: velocity time integral; D: aortic diameter; SV, stroke volume; HR, heart rate; Dd :change of diameter; PS, systolic pressure; Pd, diastolic pressure.

**Introduction**

**Cardiac index (CI):** is the volume of blood pumped from the heart per minute divided by body surface area (BSA); CO is normalized according to a patient body size \((\text{L/min/m}^2)\) as it increases proportional to the individual BSA. One commonly used formula for BSA, is the Mosteller formula \(^{(1)}\): BSA \((\text{m}^2) =\sqrt{\text{weight (Kg)}\times \text{height (cm)}}/3600).

CI can be determined by stroke volume \((\text{SV})\) and heart rate \((\text{HR})\) as illustrated from this equation \(^{(2)}\): \(\text{CO}=\text{SV}\times \text{HR}\). Another way for measuring CO noninvasively, is by Echo Doppler technique, according to Feigenbaum: \(\text{CO} =0.785(\text{D})^2 \times (\text{VTI}) \times \text{HR}\) (where D: aortic diameter, VTI: velocity time integral) \(^{(3)}\).

CI is considered the most important indicator for the function of cardiovascular system. The normal range of cardiac index at rest is 2.6 - 4.2 L/min per square meter \(^{(4)}\); an age wise decrease of indexed Cardiac Output has long been reported \(^{(5,6)}\). Unlike LV EF, CI offers a more precise estimate for the pumping action of the heart; it does not change with increase of heart rate and concomitant decrease of stroke volume, when pacing a normal size heart \(^{(7)}\). Additionally, maintenance of CI by IV administration of Ringer’s solution, has been implicated to improve postoperative outcome and decrease of in-hospital death of patients underwent major surgery \(^{(8)}\).

Reports on linking CI values with overt or subtle atherosclerotic process are scarce. There exist studies relating indices of cardiac function including CI to neuropsychological impairment \(^{(9,10)}\), dementia and cognitive dysfunction among patients with severe cardiomyopathies \(^{(11)}\). In another report, in the absence of end-stage heart disease, it is shown that subclinical cardiac dysfunction affects brain aging: In 1504 Framingham Offspring Cohort participants (age, 61±9 years) free of clinical stroke, transient ischemic attack, or dementia. Jefferson et al \(^{(12)}\) studied the association between Cardiac dysfunction and neuroanatomic/neuropsychological changes in aging adults with or without prevalent cardiovascular disease. It was found that cardiac index was positively related to total brain volume; CI values <2.54 had significantly lower brain volumes. It was hypothesized that adequate CI is essential for a stable brain health; subtle reduction of cardiac function may be associated with accelerated brain aging.
Considerable numbers of studies have investigated the impact of body weight on CI. Interestingly, both obese and non-obese individuals were shown to have similar cardiac indexes, despite the increased LV EF in obese individuals (13). Further, the increase of body weight (key determinant of CI) is not associated with the extent of coronary atherosclerosis and has no increased risk of total mortality (14, 15).

In the current investigation we sought to investigate if a meaningful correlation exists between CI and stiff arteries, using VaSera VS-1000 device to estimate CAVI, as a measurement of stiffness. Hereunder, some of the related literature reports on this device and arterial stiffness measurement:

**Cardio ankle vascular index (CAVI)**

In a population-based study, it is shown that arterial stiffness is strongly associated with atherosclerosis at various sites in the vascular tree (16). Arterial stiffness is a predictive of cardiovascular diseases (CVD) and mortality in lifestyle-related diseases (17,18,19), where it has been reported increasingly in cases of metabolic syndrome and other atherosclerotic diseases developing at different age groups (20-22). Methods used to estimate this stiffness include cardiac ultrasound and pulse wave velocity (PWV) (23, 24).

The cardio-ankle vascular index (CAVI), a new index of arterial stiffness, has been recently developed in Japan, by measuring of pulse wave velocity (PWV) and blood pressure (BP). CAVI is adjusted for BP based on stiffness parameter $\beta$ and alleged to be less influenced by BP (25, 26), suggesting its superiority over the frequently used brachial-ankle PWV (baPWV), which bears the problem with its clinical use, that it closely dependent on blood pressure (19, 25). However, the clinical usefulness of CAVI has not yet been fully clarified (26).

Hayashi, et al (27) proposed the stiffness parameter $\beta$. Kawasaki, et al. (28) defined $\beta$ as $\ln (P_s/P_d) * D/dD$. Where $P_s$: systolic pressure. $P_d$: diastolic pressure. $D$: diameter $dD$: change of diameter. The relation between PWV and reciprocal of radius percentage changes expressed as follow with $p$=blood density:

$$ \text{PWV}^2 = \frac{dP}{2p} \frac{D}{dD} \quad (\text{dP is pulse pressure}) $$

$$ D/dD = 2p * \text{PWV}^2 / dP $$

$$ \text{CAVI} = \frac{\text{Ln} (P_s/P_d)}{(D/dD)} = \frac{(\text{Ln} P_s/P_d) (2p * \text{PWV}^2 / P_s-PD)}{D/dD} $$

PWV is obtained by dividing the vascular length (L) by the time (T) taken for pulse wave to propagate from aortic valve to the ankle. L is obtained by measuring the length from aortic valve to the ankle (29).

$$ T = t'b + tba \quad (t'b: \text{the time between the aortic valve opening sound and the rise of the brachial pulse wave}; \quad tba: \text{the time between the rise of the brachial pulse wave and the rise of the ankle pulse wave. As the starting time of the blood stream from the aortic valve is difficult to identify from the valve opening sound, so T is obtained by summing tb and tba in place of t'b and tba, because t'b and tb are theoretically equal (tb: the time between the aortic valve closing sound and the notch of the brachial pulse wave}) $$

(Figure 1).
Figure 1 Adapted from Shiria et al. (29), with some modifications.

**VaSera VS-1000 device:**
CAVI is measured by VaSera VS-1000. The device VaSera VS-1000 assess the state of vessels with high accuracy. VaSera VS-1000 (Fukuda Denshi, Tokyo, Japan), Software Version 08-01, utilizes blood pressure cuffs with sensors for all four limbs to generate plethysmograms.

The cuffs were placed on the upper arms, the right knee, and both ankles, ECG leads were placed on the wrists, and a phonocardiogram (PCG) was placed at the right sternal border in the 2nd intercostal space (30). Validation of CAVI – VaSera VS-1000 has been established in our current investigation with respect to measurements of PEP/ET LV performance index, as these parameters can also be measured by Echo- Doppler equipment; a corollary study has been performed “in press”.

The main goal of this study is to assess the changes of CI in relation with CAVI values during incremental degrees of HUT (31). The concept that underlies the current investigation is that, to create variant levels of vasoconstriction that can be brought about by baroreceptor-sympathetic outflow activation, during graded HUT (32), to yield arteriolar vascular system stiffer, virtually simulating a clinical setting of variant degrees of atherosclerotic stiff arteries.

**Materials and method:**
Between 23rd of December 2010 to the 18th of May 2012, a twenty healthy male subjects of a mean age of 30±5SD were recruited, after having their informed signed consent upon arrival at the study venue (Dr. Akeel Zwain private clinic). All were in stable clinical condition, none was on any medication and they had normal blood pressure, CVS, renal, hepatic functions, blood sugar, serum cholesterol and uric acid levels. Also history of smoking should be ruled out.
All study subjects were reassured about the test beforehand, of being safe and noninvasive, to keep away from any emotional excitement.

Subjects were examined supine on a belt secured tilting table, in a quiet, temperature-controlled room. Measurements were carried out after at least 10-min supine rest to achieve a steady state which means that heart rate in the consecutive minute, changes by less than 3 beats/min \(^{(33)}\). The time needed to achieve steady state in our study, ranges between 7-10 min. Anthropometric data for each subject, along with measurements of distance from the aortic valve to the ankle were first installed in Vasera-1000\(^{(34)}\). Pulse oximeter was fixed on right index so as to follow up the changes in arterial pulse to gain a steady state. CAVI was measured by the use of a Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan) vascular screening device 20. This device generates, prints out and displays arterial BP waveform, ECG plus phonocardiogram (figure 3). Data obtained by automated measurement are analyzed by the VSS-15 software (Fukuda Denshi, Tokyo, Japan) and results are calculated separately for the left and the right side of the body. Final results are obtained by calculating the mean of 6 consecutive measurements. The expressed as parameter of stiffness \(\beta\), is obtained by the following equation: \(\beta = (\ln Ps/Pd)\cdot(D/dD)^{(28)}\); where \(\ln Ps/Pd\) is natural logarithm of systolic-diastolic pressure ratio, while \(D/dD\) is the ratio of wall extensibility.

Cardiac output can be calculated by using Echo-Doppler equipment Sonos 7500 Philips with a phase array 2.5 probe with PW Doppler facility and built-in ECG. To obtain left ventricular (LVOT) VTI, an optimal 4 or 5 chamber view image was acquired first, then Doppler sample volume was placed at the middle of LVOT, just below the aortic cups\(^{(35)}\). In our study, the highest VTI value was adopted in CO calculation, as depicted in figure 4. To obtain the LV outflow diameter (D), a parasternal long axis view was utilized.\(^{(36, 37)}\) as shown in Figure 5. Stroke volume can be calculated from this equation: \(SV=0.785(D)^2 \ast (VTI)^{(3)}\), where \(D\): Aortic diameter; VTI: velocity time integral. CO was calculated according to equation: \(CO=SV\ast HR^2\). Indexing the CO was made by dividing it on body surface area to yield CI. By Dividing CI on ČAVI yields a new index (CI/ČAVI).

The above cited measurements (VTI by Doppler echocardiography; CAVI by VaSeraVS-1000) were then carried out during 30° and 60° of tilting and after completing each maneuver of HUT, at pre-test supine position (figure 6). Evaluation of these indices was accomplished at incremental degrees of upright tilt.

Figure 3 Part of Vasera-1000 record that shows ECG, phonocardiogram and arterial pressure pulse waves.
Figure 4 Doppler echocardiogram shows VTI for measurement.

Figure 5 Left parasternal long axis view measurement of aortic diameter.

Figure 6 Subject at different degrees of HUT: A, 0°; B, 30°; C, 60°.

Results:
In all twenty participants, the following results obtained:

CI: at supine position, the baseline control was of a mean of 2.58 ± 0.25 SEM (range 2.55-3.2) L/min/m²; the respective value of CI at 30° and 60° were of a mean of 2.06 ± 0.42 SEM (range, 1.3-2.9) and 1.85 ± 0.45 SEM (range, 1.2-2.7) L/min/m². Significant correlation exists between CI at 0° and that at 30° and 60° of HUT (0° and 30° r = 0.63, y =1.0766X-0.7286; 0° and 60°: r =0.81, y =1.4819x-1.9841). Also, a significant correlation exists between CI at 30° and 60° (r=0.71, y= 0.7668X+0.2724). CI at 30° and 60° is significantly lower than that at 0° of HUT (p<0.001). CI at 60° is significantly lower than that at 30° tilt (p<0.05). As demonstrated in Figures 7 and 9, there were consistent and statistically significant (p < 0.0%) decrease of CI values upon increment of HUT degrees expressing a negative correlation.

CAVI: At supine position, the baseline control value of CAVI was of a mean of 7.1 ± 0.69 SEM (range, 5.6-8.05). The respective CAVI values at 30 and 60 degrees were of a mean of 8.6 ± 0.73 SEM (range,7.1-9.9) and 9.2±0.98 SEM (range,7.75-10.45). As shown in figure 8, There were statistically significant (p<0.001) and consistent increase of CAVI values upon increment of upright tilt degree in a step wise manner, expressing a positive correlation. At 0°and 30°: r =0.88 , y = 0.9135x + 2.1059; at 0° and 60°: r = 0.83, y =1.1831x + 0.7467). Likewise, significant correlation observed between CAVI at 30° and 60°: r = 0.81, y =1.0642x + 0.024.

Correlation between CI and CAVI at different degrees of tilt was studied. The results revealed a negative correlation between CI and CAVI (r = -0.47,p<0.05,y= -0.1976x+3.5866, as depicted in Figure 9. When dividing the two indexes by each other, CI/CAVI: at supine position a mean of 0.35±0.06 (range, 0.23-0.48) was obtained. The respective 30 and 60 degrees values were of a mean of 0.25±0.06 SEM (range, 0.14-0.37) and 0.19±0.05 SEM (range, 0.12-
A statistical significant correlation exists between CI/CAVI at 0° and that at 30° and 60° of upright tilt (r =0.65 for 0° and 30, y =0.6574X+0.0233; r =0.78, for 0° and 60°, y=0.6388X-0.0267). Also, significant correlation found between CI/CAVI at 30° and 60° (r = 0.68, for 30° and 60° y = 0.554X+0.0568). As demonstrated in figure 10, CI/CAVI at 30° and 60° is significantly lower than that at 0° of HUT (p<0.001). CI/CAVI at 60° is significantly lower than that at 30° (p<0.001).

Figure 7, A: Correlation between CI values at 0° and 30° of HUT.

Figure 7, B: Correlation between CI values at 0° and 60° of HUT.

Figure 7, C: Correlation between CI values at 30° and 60° of HUT.

Figure 7 Scatter diagrams show significant correlation between CI values at A: 0° and 30°; B: 0° and 60°; C: 30° and 60°.

-Dark lines represent line of regression, dotted lines: line of identity.
Figure 8, A: Correlation between CAVI values at 0º and 30º of HUT.

Figure 8, B: Correlation between CAVI values at 0º and 60º of HUT.

Figure 8, C: Correlation between CAVI values at 30º and 60º of HUT.

Figure 8 Scatter diagrams show significant correlation between CAVI values at A: 0º and 30º; B: 0º and 60º; C: 30º and 60º of HUT.

-Dark lines represent line of regression, dotted lines: line of identity.
Figure 9 Scatter diagram shows significant negative correlation between CAVI and CI at 0º, 30º and 60º of HUT.

A: Correlation between CI/CAVI values at 0º and 30º of HUT. Figure 10,

B: Correlation between CI/CAVI values at 0º and 60º of HUT. Figure 10,
Discussion

The cardiovascular responses to postural changes from supine to upright position have long been studied by several researchers. These responses reflect both changes mechanically induced by the influence of gravity on the circulatory system and those caused by the resulting nervous reflex responses (38). Our result regarding CI values which were significantly lower at 30º and 60º than those obtained at supine position, are primarily due to pooling of blood to the lower extremities by effect of gravity, where an increase in blood volume in the lower part of the body of around 700ml has been reported (39). This substantial decrease in central filling pressure would cause a significant fall in stroke volume and potentially a decrease in cardiac output, even in the presence of baroreflex-heart rate mechanism (40-44). Another well established baroreceptor mechanism, to keep arterial pressure from decreasing, is significant peripheral vasoconstriction taking place when body position changes from supine to standing position (38). It is apparent from previous investigations that reduction of stroke volume is the result of decrease venous return, thereby, reduction of preload, stroke volume and consequent decrease in CO. In the setting of HUT, it has been suggested, albeit in a minor magnitude, that a decrease in LV diameter (44), together with an increase in afterload, indicated by increase in peripheral vascular resistance, may also contribute in reduction of stroke volume and eventual decrease of CO and CI (45).

As mentioned earlier, CAVI estimation is dependent on pulse wave transmission between the aortic valve and peripheral blood vessels and can provide an expression on arterial diameter (27, 28). Such changes in arteriolar diameter evoked by baroreceptor-sympathetic nerves discharge, in response to incremental degrees of HUT, are superbly expressed by the estimated graded CAVI values to 30º and 60º of tilt, as compared to baseline supine value (Figure 8; A, B, and C). Thus, CAVI as an index of arterial stiffness, in view of strong association of vascular stiffness with atherosclerosis (16), can
be utilized as an estimate of the degree of vascular bed compliance that can be altered in various forms of related metabolic and/or cardiovascular disorders. Moreover, the graded alteration in arteriolar diameter in response to baroreceptor-sympathetic nerve activity induced by HUT, in normal individuals may furnish a novel technique in grading of an ongoing atherosclerotic process, i.e., CAVI value of a mean of 8.6 ± 0.73 (range, 7.1-9.9) obtained at 30 degree may represent a modest atherosclerotic process; CAVI value of a mean of 9.2±0.98 (range,7.75-10.45), Obtained at 60 degree may represent moderate to severe atherosclerotic process. Whereas, CAVI baseline value obtained at zero degree supine position of a mean of 7.1 ± 0.69 (range, 5.6-8.05) can be considered a normal value, with a cut off number of the index of 5.6, in this study population, though larger sample volume is needful to further certificate our findings. 

Another related issue of worth noting is that, a considerable body of evidence has established the implication of both vascular compliance and total peripheral resistance in determination of afterload, hence CO and CI (46, 47). In our study, we have noninvasively demonstrated an inverse correlation between variant degrees of peripheral resistance, modulated by change of arterial diameter (estimated by CAVI) and overall cardiac performance, expressed by cardiac index: a consistent and significant inverse interrelation ship revealed, at different angles of HUT (as shown in figure 9, A B, and C). We have to acknowledge that in this model, minor contribution of afterload in CO determination can be anticipated, and the decreased CO and CI to HUT is mainly a preload dependant. Thus, it could be argued that CI/CAVI correlation may hold true only with postural changes. Nevertheless, our results are identical with a recently published study to evaluate subclinical atherosclerotic process in 336 Finnish adults of age range 46-76 years (48) where highly significant inverse interrelation has been demonstrated to exist between increased arterial stiffness (indicated by a decrease of arterial tension time) and stroke volume. However, to further varify the impact of subclinical atherosclerosis on CI needs large sample size multicenter study population.

Further in this CAVI-HUT model we may introduce for the first time, a new haemodynamic parameter, notably CI/ CAVI, where CI and CAVI values are divided by each other. This new index would serve as a parameter for fitness assessment and cardiovascular risk stratification with respective normal and cut off values of 0.35±0.06 and 0.23. Moreover, CI/CAVI correlation may provide a non invasive technique to predict CI from peripheral circulation; peripheral estimation of CI can be expressed by the equation (Y=0.6574x+0.0233).

An important criticism that could be offered to our study is that, antigravity muscle contraction may contribute in the magnitude of increased CAVI measurement during HUT. This issue can be resolved by the following contention: we recorded change in CAVI values at 30 degree of HUT where the leg muscles are at its lowest tone. Furthermore, in paraplegics where no longer muscle tone exists, HUT at 30 degree was also found to increase in their leg vascular resistance to maintain blood pressure (49) Indeed, HUT at 60 degree is set to put the leg muscles at its modest tone. (50)

It is pertinent to point out that our study is not a one size that fits all. We do not advocate CAVI assessment or studying CI/CAVI correlation, in severe obliterative vascular disorders, since CAVI is dependant of generation of pressure waveform which is apparently impossible in this setting of vascular malady.
Conclusion
In this investigation, an inverse correlation between cardiac index (CI) and cardio ankle vascular index (CAVI) has been established. Further, a new parameter, CI/CAVI, has been proposed which may be employed to early detect subclinical atherosclerosis impact on cardiac muscle pump function. This new integrated parameter could possibly serve for fitness assessment, and for cardiovascular risk stratification. It has been postulated to further evaluate CI/CAVI index among hypertensive, diabetics and other related diseases associated with a possible derangement of CO and CI like obstructive sleep apnea (OSA), to gain more insight in to management strategy in contemporary cardiology.

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