Arterial Stiffness in Lower Limb Amputees

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Abstract

Background: A high carotid-femoral pulse wave velocity (PWV) has been related to increased cardiovascular morbidity and mortality, but has not been previously evaluated in amputees. The aim of this study was to compare PWV between amputees and nonamputees.

Methods: In this cross-sectional study, data were collected from 60 male lower limb amputees and 86 male age-matched nonamputees. PWV was measured noninvasively using a Complior® device. All participants underwent laboratory investigations and anthropometry. The difference in PWV between amputee and nonamputees was estimated. Multivariate regression was used to adjust for differences between the groups as a result of potential confounders.

Results: PWV was higher in amputees than in nonamputees (10.8 ± 1.9 m/sec versus 9.9 ± 1.8 m/sec, P = 0.008, respectively). This difference remained even after adjusting for confounding factors.

Conclusion: A higher PWV was demonstrated in lower limb amputees. Routine assessment of PWV may contribute to cardiovascular risk stratification in amputees.

Keywords: arterial stiffness, hypertension, lower limb amputees, cardiovascular risk
Introduction

Post-traumatic amputation of limbs is a common phenomenon, particularly in war survivors. Survival following lower limb amputation in the amputee population is decreased by advancing age, proximal amputation level, and comorbid conditions, including cardiovascular disease. Previous studies have demonstrated that subjects with post-traumatic amputation of the lower limbs are at increased risk of cardiovascular mortality and morbidity. Results of the larger controlled studies have demonstrated that the relative risk of death due to cardiovascular causes is higher in bilateral than in unilateral lower limb amputees. In addition, it has been reported that the mortality rate is higher in subjects with transfemoral amputation than in those with transtibial amputation.

Although the causes of this excessive cardiovascular morbidity and mortality are still not well understood, it is known that post-traumatic amputees show various features which may have adverse consequences for the arterial system, such as high blood coagulability, sympathetic hyperactivity, insulin resistance, smoking, obesity, low levels of physical activity, and excessive consumption of alcohol.

Arterial stiffness, characterized by high values of carotid-femoral pulse wave velocity (PWV), has been recognized as an independent predictor of cardiovascular events and mortality in addition to known classical risk factors, even in healthy subjects. Measurement of carotid-femoral PWV has been considered as a surrogate endpoint for cardiovascular disease, and used for risk stratification in several populations. Indeed, in the past few years, the European Society of Hypertension/European Society of Cardiology guidelines have recommended measurement of PWV as a gold standard method for routine evaluation of aortic stiffness in individual patients, clinical studies, and for assessment of target organ damage in the management of hypertension. However, arterial stiffness has not been previously evaluated in subjects with post-traumatic amputation of the lower limbs. Therefore, the aim of the present study was to compare arterial stiffness assessed by carotid-femoral PWV measurements between men with single lower limb amputations and nonamputees.

Materials and Methods

Study design and population

This was a cross-sectional study involving 60 men with unilateral traumatic lower limb amputation and 86 age-matched control men without amputation. Amputees were veterans recruited from the Orthopedic Center at Viana, Luanda, Angola, and were included in the study if they had trauma-related unilateral lower limb amputation. Amputees were excluded if they had amputations due to diabetes, cancer, or other degenerative diseases, and if they had upper limb or bilateral lower limb amputations. Controls were selected from men without amputation who participated in a larger parallel project involving screening for cardiovascular risk factors in workers at the University in Luanda, which was conducted in April–December 2010 by the Department of Physiology, Faculty of Medicine, Agostinho Neto University, Angola. Exclusion criteria in both groups were obesity, a history of diabetes, stroke, arrhythmia, peripheral arterial disease, or end-stage renal failure, and being on medication for diabetes, hypertension, or hypercholesterolemia. The study was conducted according to the tenets of the Declaration of Helsinki, and all subjects signed an informed consent form approved by the ethics committee of the Faculty of Medicine, Agostinho Neto University.

Study protocol

Participants attended to participate in the study after 12 hours of fasting and refrained from smoking, physical exercise, and caffeinated beverages for at least three hours before the visit. Clinical and laboratory investigations were performed between 8 am and noon in a room with controlled temperature (22 °C–23 °C). Fast blood samples were obtained for determination of triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low density lipoprotein cholesterol, blood
glucose, creatinine, and uric acid. The triglyceride to high-density lipoprotein cholesterol ratio was calculated to test for insulin resistance.  

**Data collection**

After blood sample collection, each participant completed a questionnaire about demographic and clinical history, use of drugs, diet, and family medical history. Smoking and alcohol consumption were also assessed as part of the questionnaire, according to an international standardized protocol. The participants were classified as nonsmokers (never and exsmokers) or smokers (daily and occasional smokers), and as alcohol consumers or nonconsumers according to their answer to the question about alcoholic beverage consumption.

**Anthropometry**

Weight, height, waist circumference, and hip circumference were measured, and the waist/hip ratio was calculated for all participants. In the amputees, body weight was measured in the standing position after prosthesis removal. To achieve this, amputees were asked to stand as still as possible by applying plantar pressure on the remaining lower limb. To avoid underestimation of nutritional status, body weight was corrected as described elsewhere in detail. Estimated body weight was then used to estimate body mass index reliably in subjects with limb amputation. In the whole sample, body mass index was calculated as weight (kg) divided by square of height (m).

**Hemodynamic measurements**

Basal blood pressure (BP) and heart rate were measured three times in the dominant arm after five minutes of resting in the sitting position with the arm at the level of heart, using a validated automated digital oscillometric sphygmomanometer (Omron 705CP, Tokyo, Japan) with an appropriately sized cuff. Readings were repeated at intervals of three minutes. The mean of the two last readings was recorded. Pulse pressure was computed as systolic BP—diastolic BP, and mean BP was computed as diastolic BP + (pulse pressure/3). Hypertension was defined as systolic BP $\geq 140$ mmHg, diastolic BP $\geq 90$ mmHg, or use of antihypertensive drugs.

To assess arterial stiffness, PWV was measured automatically using a Complior SP® device (Artech Medical, Pantin, France) after each participant had been resting for 10–11 minutes in a supine position. In amputees, PWV was measured after prosthesis removal. Common carotid artery and femoral artery pressure waveforms were recorded noninvasively in all participants by simultaneous assessment of pulse waves in the right common carotid artery (at the neck) and in the right femoral artery (at the anterior side of the hip bone). The technical characteristics of the Complior device have been described in detail in a previous validation study. In brief, the PWV is calculated from measurement of pulse transit time and the distance travelled by the pulse between two recording sites, according to the following formula: PWV (m/s) = distance (m)/transit time (sec). Carotid-femoral PWV is calculated from the time delay between the recorded proximal (carotid) and distal (femoral) feet of the wave, and the superficially measured distance separating the respective transducers.

To evaluate the intraobserver reproducibility of PWV measurement in our laboratory, the same experienced observer performed the assessment of PWV on two occasions in 10 healthy young students from the Faculty of Medicine (five females, five males, mean age 23.4 ± 5.4 years, all nonsmokers) and found good reproducibility ($r = 0.914$).

**Statistical analysis**

The normality of the data was examined using the Kolmogorov-Smirnov test. Logarithmic transformation was performed for glucose and triglycerides because they were not normally distributed. Continuous variable data were expressed as means and standard deviations, and categorical variables were expressed as proportions. The independent-samples $t$-test was used to perform the comparative analysis between nonamputees and amputees in terms of age, systolic BP, diastolic BP, pulse pressure, mean BP, heart rate, body mass index, creatinine, uric acid, waist and hip circumference, waist-to-hip circumference, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, log-triglycerides, triglyceride to high-density lipoprotein cholesterol ratio, and log-glucose. The difference in PWV between amputees and nonamputees was estimated using the independent-samples $t$-test.
Multivariable linear regression analysis was used to adjust the differences between amputees and controls for potential confounding factors (age, mean BP, body mass index, hypertension, smoking, alcohol consumption, total cholesterol, log-triglycerides, log-glucose, uric acid, low-density lipoprotein cholesterol, heart rate, waist circumference, log triglyceride to high-density lipoprotein cholesterol ratio). Groups were coded as nonamputees = 0 and amputees = 1. Statistical significance was set at $P < 0.05$. The data analysis was performed using SPSS software, version 13.0 (SPSS Inc, Chicago, IL).

**Results**

**General characteristics of study sample**

A total of 146 male subjects aged 36–62 (mean 48.1 ± 6.3) years participated in the study. Table 1 shows that the control group at baseline was not significantly different from the amputees in terms of age, smoking status, alcohol consumption, weight, height, body mass index, waist circumference, hip circumference, waist-to-hip ratio, glucose, triglycerides, total cholesterol, triglyceride to high-density lipoprotein cholesterol ratio, and very low-density lipoprotein cholesterol ($P > 0.05$). However, amputees had significantly higher levels of uric acid, low-density lipoprotein cholesterol, and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, whereas controls had significantly higher levels of creatinine and high-density lipoprotein cholesterol ($P < 0.01$). The frequency of hypertension, smoking, and alcohol consumption was 52.1%, 17.1%, and 60.3%, respectively; and stratification of hypertension by group showed that the amputees had a higher proportion of hypertensive individuals ($P < 0.05$), whereas the distribution of smokers and alcohol consumers in each group was similar in nonamputees and amputees ($P > 0.05$). With regard to smoking status, 55 (37.8%) of subjects were never smokers and 66 (45.2%) were ex-smokers. Amputees had a significant higher proportion of ex-smokers than controls (53.3% [32/60] versus 39.5% [34/86], $P = 0.023$).

Of a total of 60 amputees, 41 (68.3%) had transtibial and 19 (31.7%) had transfemoral amputations. All limbs had been amputated more than eight years before

**Table 1. Baseline characteristics of nonamputee controls and amputee subjects.**

| Variables                        | Controls (n = 86) | Amputees (n = 60) | $P$ value |
|----------------------------------|------------------|-------------------|-----------|
| Age, years                       | 47.5 ± 7.1       | 48.9 ± 5.0        | 0.191     |
| Smokers, n (%)                   | 11 (12.8)        | 14 (23.3)         | 0.119     |
| Alcohol consumers, n (%)         | 57 (66.3)        | 31 (51.7)         | 0.087     |
| Hypertension, n (%)              | 37 (43.0)        | 39 (65.0)         | 0.012     |
| Weight, kg                       | 66.1 ± 13.6      | 68.8 ± 14.1       | 0.243     |
| Height, cm                       | 167.5 ± 7.2      | 169.3 ± 7.7       | 0.143     |
| Body mass index, kg/m²           | 23.4 ± 3.8       | 23.9 ± 4.3        | 0.492     |
| Waist circumference, cm          | 78.4 ± 11.5      | 78.6 ± 12.3       | 0.898     |
| Hip circumference, cm            | 89.6 ± 8.6       | 90.8 ± 14.2       | 0.578     |
| Waist-to-hip ratio               | 0.87 ± 0.1       | 0.87 ± 0.1        | 0.970     |
| Glucose, mg/dL                   | 95.0 ± 25.5      | 94.8 ± 13.5       | 0.958     |
| Creatinine, mg/dL                | 1.14 ± 0.18      | 1.03 ± 0.21       | 0.001     |
| Uric acid, mg/dL                 | 6.2 ± 1.8        | 7.1 ± 2.0         | 0.006     |
| Total cholesterol, mg/dL         | 183.8 ± 42.5     | 195.6 ± 32.6      | 0.073     |
| LDL, mg/dL                       | 117.2 ± 42.8     | 136.1 ± 31.0      | 0.002     |
| HDL, mg/dL                       | 45.7 ± 11.3      | 40.0 ± 11.9       | 0.004     |
| LDL/HDL ratio                    | 2.8 ± 1.5        | 3.9 ± 1.6         | 0.001     |
| VLDL, mg/dL                      | 20.8 ± 8.0       | 19.4 ± 7.0        | 0.250     |
| TG, mg/dL                        | 104.2 ± 49.1     | 97.0 ± 35.0       | 0.263     |
| TG/HDL ratio                     | 2.5 ± 1.4        | 2.7 ± 1.5         | 0.303     |

**Note:** Values are mean ± SD or percentages.

**Abbreviations:** HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; VLDL, very-low density lipoprotein cholesterol; TG, triglycerides; TG/HDL, triglyceride to high-density lipoprotein cholesterol ratio.
the study. A large proportion (96.7%) of the subjects had undergone amputation due to landmine injuries, and the causes were artillery bullets (1.7%) and road traffic accidents (1.7%) in the remaining patients.

BP, heart rate, and PWV in amputees versus nonamputees
Table 2 shows the hemodynamic parameters of amputees versus nonamputees. Amputees had a higher PWV and systolic BP than nonamputees \((P < 0.05)\), but no statistically significant differences were found for diastolic BP, mean BP, pulse pressure, or heart rate \((P > 0.05)\), although the mean BP and pulse pressure tended to be higher in amputees. Table 3 shows that the difference in PWV remained significant in the amputee group on multivariate linear regression, even after adjustment for confounding factors such as age, mean BP, body mass index, smoking, alcohol consumption, hypertension status, total cholesterol, log-triglycerides, log-glucose, uric acid, low-density lipoprotein cholesterol, heart rate, waist circumference, and triglyceride to high-density lipoprotein cholesterol ratio \((P = 0.047)\).

Discussion
The main finding of this study was a higher arterial stiffness in amputees, even after adjustment for potential confounders. Arterial stiffness was determined by noninvasive measurement of carotid-femoral PWV using a robust and reproducible method for direct assessment of aortic stiffness.\(^{18}\) An increased PWV is a factor influencing prognosis and is an early index of hypertension-related target vascular (large artery) damage.\(^{16}\) Our findings suggest an association between lower limb amputation and increased stiffness of the large central arteries. Thus, independent of the potential underlying mechanism, this increase in PWV represents an important hemodynamic alteration causing amputees to be prone to morbidity. Although the difference in PWV that we found between amputees and nonamputees was only \(0.9 \pm 0.1\) m/sec, this may be of clinical importance for future cardiovascular risk. Evidence from a recent meta-analysis shows that for an increase in aortic PWV of 1 m/sec or one standard deviation, the risk of cardiovascular events, ie, cardiovascular mortality, and all-cause mortality, increases by more than 10% and 40%, respectively.\(^{15}\)

To our knowledge, this is the first study demonstrating increased arterial stiffness in subjects with traumatic amputation of lower limb.

The underlying mechanisms for cardiovascular morbidity in amputees are still not well understood. It has been suggested that systemic influences and regional hemodynamic effects occurring after amputation could explain the excessive morbidity and mortality in amputees.\(^{13}\) A unilateral flow reduction after amputation has been considered as the cause of late damage to the aorta in subjects with unilateral lower limb amputation.\(^{4}\) Regarding hemodynamic factors, it has been suggested that subjects who had traumatic amputation of the lower limb could have enhanced aortic stiffness due to a high prevalence of insulin resistance and changes in local hemodynamics.\(^{13}\) In addition to genetic causes, several factors may contribute to a change in arterial stiffness, including body mass index,\(^{14}\) high BP, age, gender,\(^{23}\) increased cholesterol,\(^{26-28}\) elevated insulin, increased triglycerides, smoking,\(^{24,25}\) elevated low-density lipoprotein cholesterol,\(^{24,26,27}\) and elevated glucose levels.\(^{28}\)

It is known that comparisons of cardiovascular function and structure among individuals or groups of individuals are often difficult when differences in body dimensions exist. Thus, it has been recommended to adjust cardiovascular parameters for differences in body size.\(^{29}\) In the present study, this difference was corrected by estimating the body weight for amputees before calculation of body mass index. Moreover, by using multivariate analyses, we were able to adjust
for any effects of major confounders, including the body mass index, but significantly higher values of PWV remained even after this statistical correction. Even so, we are not completely able to exclude the influence of these variables on the observed results. The coexistence of higher PWV and systolic BP in amputees may reflect the impact of multiple risk factors on the central arterial tree because we found that amputees had more factors which may have a negative impact on arterial wall structure and function, such as higher systolic BP, serum levels of uric acid, low-density lipoprotein cholesterol, and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, and a lower level of high-density lipoprotein cholesterol, regardless of the lack of statistical significance. This nonsignificance may be just due to the small sample size we studied. Also, it is likely that any effect of these variables was confounded by factors not assessed in the present study.

High BP in amputees has been demonstrated in previous studies, and are thus consistent with our findings. The relationship between arterial stiffness and hypertension is more complex, mainly for mean BP, which is an important confounder of measurements of arterial stiffness, although this is not a linear relationship because mean BP is not influenced to a large extent by arterial stiffness. In contrast, there is some evidence of a higher degree of correlation between arterial stiffness and systolic BP. In this regard, a longitudinal study demonstrated that PWV was an independent predictor of the increase in systolic BP and of incident hypertension, whereas others reported an increased PWV with the presence of systolic hypertension. It is believed that a chronic increase in BP may accelerate central arterial stiffening, thereby contributing to rapid structural and functional alterations in the walls of these arteries, and thus may create a vicious cycle of arterial stiffness. Stiffness of the arteries causes an increase in wave reflection, which leads to increased systolic BP in the central arteries, ie, the aorta and carotid. Hence, we may assume that lower limb amputees have increased wave reflection, independently of other known pathological factors. Experimental studies in humans have demonstrated that external compression of the femoral arteries causes a substantial increase in aortic systolic BP and wave reflection. Thus, the hemodynamic conditions induced by these experimental studies are similar to those seen in subjects with lower limb amputations.

There are limitations to this study. Its cross-sectional design does not allow causality to be established when examining the relationship between arterial stiffness and multiple covariates in amputees. Also, the small sample size may limit the relevance of

### Table 3. Multiple linear regression model for pulse wave velocity.

| Variable        | Unstandardized coefficients B (95% CI) | Standardized coefficients B | P value |
|-----------------|----------------------------------------|----------------------------|---------|
| Groups          | 0.653 (0.009–1.297)                    | 0.169                     | 0.047   |
| Age             | 0.080 (0.032–0.128)                    | 0.264                     | 0.001   |
| Mean blood pressure | 0.017 (−0.014–0.048)                 | 0.149                     | 0.270   |
| Heart rate      | 0.036 (0.003–0.068)                    | 0.179                     | 0.033   |
| Smoking         | −0.252 (−1.157–0.652)                  | −0.050                    | 0.582   |
| Alcohol consumption | 0.289 (−0.318–0.897)                 | 0.074                     | 0.348   |
| Hypertension    | 0.683 (−0.288–1.655)                   | 0.179                     | 0.166   |
| Total cholesterol | −0.044 (−0.133–0.045)                | −0.905                    | 0.326   |
| LDL             | 0.040 (−0.047–0.127)                   | 0.826                     | 0.365   |
| Triglycerides   | 2.280 (−3.208–7.769)                   | 0.426                     | 0.413   |
| Uric acid       | −0.050 (−0.206–0.106)                  | −0.051                    | 0.526   |
| Glucose         | 0.003 (0.017–0.011)                    | 0.028                     | 0.722   |
| TG/HDL ratio    | −1.595 (−5.181–1.991)                  | −0.402                    | 0.380   |
| BMI             | −0.059 (−0.203–0.085)                  | −0.123                    | 0.420   |
| WC              | 0.023 (−0.026–0.071)                   | 0.139                     | 0.363   |

**Abbreviations:** CI, confidence interval; LDL, low-density lipoprotein cholesterol; TG/HDL-c, triglyceride to high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference.
our finding to all amputees. A final limitation is that the present findings only apply to male subjects.

To conclude, we found an association between unilateral traumatic lower limb amputation and arterial stiffness in males, independently of traditional risk factors. This finding supports the importance of routine assessment of arterial stiffness for cardiovascular risk stratification in amputees, independent of the presence of known risk factors for cardiovascular disease.

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Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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