Pathophysiologic Arterial Alterations to the Systemic Circulation Following Traumatic Lower Limb Amputation

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Clinical Question: Are there pathophysiologic arterial alterations to the systemic circulation following traumatic amputation compared to people without amputation?

Background: People with traumatic lower limb amputation have been shown to have 1.58-3.50 greater odds of mortality due to cardiovascular disease (CVD) compared to the general population, with higher odds linked to higher level of amputation or increased number of amputations.[1,2] Although the pathophysiological mechanisms for this increase in CVD is not well understood, available literature has demonstrated higher blood coaguability,[2] hyperlipidemia,[2] hyperinsulinemia and increased insulin resistance,[3,4] and increased sympathetic activity,[3] in people with amputation compared to people without amputation. Ejtahed et al. found 62.1% of male veterans with bilateral traumatic amputation presented with metabolic syndrome, compared to 27% of the population.[5] Although lifestyle factors may be involved in decreasing cardiovascular health, relationships between CVD and amputation remain significant after adjusting for other known lifestyle or risk factors. Naschitz and Lenger reviewed potential mechanisms responsible for increased CVD and suggested that endothelial dysfunction and abnormalities in arterial flow create pathophysiological systemic and hemodynamic changes. For example, they proposed that reduced vascular wall shear stress and increased insulin resistance may chronically increase arterial stiffness and the build-up of fatty deposits due to vasoconstriction or occlusion sites.[6] The goal of this CAT is to review pathophysiological alterations of the vascular system following traumatic lower limb amputation that may increase risk for CVD.

Search Strategy:
Databases Searched: Pubmed, CINAHL, Web of Science, pearling
Search Terms: (Amputation, Traumatic OR Amputation/adverse effects OR Amputation/physiopathology OR Amputees) AND (vascular resistance OR systemic system OR circulatory system OR arteriosclerosis OR arterial stiffness OR vascular remodeling OR hemodynamic) AND (change OR alter OR alteration OR difference OR pathophysiolog* OR physiopathology* OR control OR nonamputee)

Synthesis of Results: Four original research studies[7-10] were reviewed that investigated alterations to the arterial system in people with traumatic lower limb amputation compared to people without amputation. None of the studies measured the same primary outcome, but all evaluated aspects of the systemic vascular system relevant to the clinical question. In total, 1,318 participants were assessed, 427 of whom had traumatic lower limb amputation (studies ranged from 16-1031 participants). All reported participants were males, although one study did not describe the gender of the participants;[8] in the group with amputation, 389 were veterans,[7,9] and 30 were athletes on a national sports team.[8] Three studies[8-10] were cross-sectional in design and one[7] was a prospective cohort study. Causation cannot be determined in the cross-sectional studies and the prospective cohort study from 1989 lacked descriptive information about the methodology and statistical analyses. Overall, this appraisal found that people with traumatic lower limb amputation had increased vascular resistance;[10] increased arterial stiffness;[9] higher incidence of abdominal aortic aneurysms;[7] and decreased common femoral inner arterial diameter, volumetric blood flow, and stroke flow to the amputated limb.[8] Results remained significant after adjusting for confounders, although the effect of physical activity was not well described. Increased arterial stiffness has been shown to be an independent predictor of cardiovascular mortality.[11] Participants with transfemoral amputation showed significantly higher evidence of abdominal aortic aneurysms, 5.8% vs. 1.1%.[7] National athletes with unilateral transtibial amputation showed increased common femoral arterial diameter and trends towards increased common femoral stroke flow in the non-amputated limb, suggesting that chronic vascular remodeling occurs dependent on metabolic need.[8] Available evidence suggests that arteriosclerotic changes occur following traumatic amputation and may increase future risk for CVD.

Clinical Message: People with traumatic limb amputation demonstrated arterial alterations compared to people without amputation. Most of these results are predictors of future adverse cardiovascular events and possibly highlight the importance of preventative assessment of cardiovascular health, independent of other known risk factors. Suggestions that arterial adaptations occur through training warrants further investigation of the effect of physical activity and the extent to which these negative alterations are modifiable. Future research is needed to understand vascular pathophysiology in people with amputation, determine causation for these vascular differences, and understand how prosthesis-related factors affect the circulatory system.

Evidence Table

	Vollmar, 1989[7]	Huonker, 2003[8]	Magalhães, 2011[9]	Paula-Ribeiro, 2015[10]
Purpose	Investigate the relationship between above-knee amputation and future risk of abdominal aortic aneurysm.	Examine arterial adaptations in response to training, disproportionate, or disuse of extremities.	Compare arterial stiffness by assessment of carotid-femoral pulse wave velocity between men with and without amputation.	Assess if people with lower limb amputation have increased resting peripheral vascular resistance compared to controls without amputation.
Population	Number of participants: 1031 War veterans with above-knee amputation (329). Time since amputation: average of 43.8 years War veteran controls without amputation (702) Age: 67.2 years ± 7.9 group with amputation Age: 68.1 years ± 5.3 control group Gender: males (1031)	Number of participants: 125 Athletes with transtibial amputation (30) Able-bodied elite road cyclists (34); able-bodied professional tennis players (18); athletes with paraplegia (26); able-bodied untrained participants (30) Age: 34.3 ± 11.5 group with transtibial amputation Age: 25.3 ± 3.4 untrained, able-bodied controls; 23.5 ± 3.4 able-bodied road cyclists; 22.3 ± 9.1 able-bodied tennis players; 32.7 ± 7.6 athletes with paraplegia Gender: not reported	Number of participants: 146 Unilateral traumatic lower limb amputation (60); transtibial amputation (41), transfemoral amputation (19). Time since amputation: at least 8 years prior Age-matched control (86) Age: 48.1 ± 6.3 (ages 36-62) Gender: male (146)	Number of subjects: 16 Unilateral traumatic lower limb amputation (8) Control group (8) Age: 45 years ± 16.2 group with amputation Age: 39 years ± 19.3 control group Gender: male (16)
Inclusion and Exclusion Criteria	Male veterans with above-knee amputation or without amputation	Not reported; however, purposive sampling used to recruit specifically trained athletes with asymmetrical extremity training; unilateral transtibial amputation but the etiology was not specified	In the group with amputation: unilateral lower limb amputation due to trauma Both groups: no obesity, diabetes, stroke, arrhythmia, peripheral arterial disease, end-stage renal failure, medication for diabetes, hypertension, hypercholesterolemia	18-65 years old; sedentary for at least 6 months; non-smoker; no neuromuscular or cardiovascular diagnosis; no history of altered biochemical variables in the last year; no medications

Setting	Laboratory	Laboratory	Orthopedic Center (Luanda, Angola) and University (Angola)	Cardiovascular and Exercise Physiology Research Unit of University Hospital (Minas Gerais, Brazil)
Study Design	Prospective Cohort Study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Exposure	Lower limb amputation	Lower limb amputation	Lower limb amputation	Lower limb amputation
Comparison	Male veterans without amputation	Controls without amputation or exercise training	Males without amputation	Males without amputation
Outcomes	Ultrasound of infrarenal aorta and iliofemoral arteries. Arteriography performed when the infrarenal aorta exceeded 3.5 cm in diameter.	Size and blood flow of central and peripheral arteries. Both volumetric blood flow and stroke flow assessed for total regional blood perfusion.	Arterial stiffness measured by pulse wave velocity.	Vascular resistance calculated from mean blood pressure and forearm blood flow.
Key Findings	Group with transfemoral amputation had significantly higher evidence of abdominal aortic aneurysms compared to male veterans without amputation, 5.8% vs. 1.1%. All abdominal aortic aneurysms in the group with amputation showed convexity towards the amputated limb and relative dilation of the common iliac artery on the contralateral side. Groups had similar risk factors for arterial damage, such as hypertension, hyperlipidaemia, smoking, diabetes, and obesity.	Athletes with unilateral transtibial amputation exhibited significantly decreased vessel diameter, volumetric blood flow, and stroke flow in the common femoral artery to the amputated limb compared with the contralateral side and compared to untrained, able-bodied individuals. The contralateral common femoral artery showed significantly larger vessel diameter compared to the amputated side and the untrained, able-bodied individuals. Resting heart rate was similar between athletes with unilateral transtibial amputation and untrained, able-bodied individuals. Central arteries showed no significant differences in size or	Group with amputation had significantly higher pulse wave velocity (10.8 ± 1.9 vs. 9.9 ± 1.8) and systolic blood pressure (146 ± 23 vs. 137 ± 24). The significance remained after adjustment for confounders. Group with amputation found to have a pulse wave velocity increase of 0.9 ± 0.1 m/s; an increase of 1.0 m/sec is clinically important for 10-40% increased future cardiovascular risk. No significant difference in diastolic or mean blood pressure, pulse pressure, or heart rate but mean blood pressure and pulse pressure tended to be higher in the group with amputation.	Group with amputation showed significantly higher forearm vascular resistance. Group with amputation had significantly higher heart rate, systolic pressure, diastolic pressure, and mean blood pressure and similar forearm blood flow compared to control group.

		blood flow between groups.		
Study Limitations	Lack of information reported for methodology and statistical analysis.	There can be a 10-15% variability in volumetric blood flow and 2.7% ± 0.7% variability in the interior vessel diameter as measured by ultrasound; causation cannot be determined due to cross-sectional design; participants were matched by training expertise but could not be matched by age; cause of amputation not specified.	Causation cannot be determined due to cross-sectional design; results limited to males with traumatic amputation; although the significance remained after adjustment for confounders, factors that are damaging to arterial wall structure tended to be higher in group with amputation, such as uric acid and systolic blood pressure.	Small sample size; causation cannot be determined due to cross-sectional design; presence of cardiovascular disease inquired through self-report; results limited to males with unilateral traumatic amputation
Conclusions	People with transfemoral traumatic amputation showed higher incidence of abdominal aortic aneurysm, even with similar arteriosclerotic risk factors. Structural arterial changes of blood flow magnitude and direction may have long-term effects explaining these results.	Blood vessel lumen diameter, volumetric blood flow, and stroke flow in the peripheral arteries seem to adapt to chronic changes in size and magnitude depending on metabolic need and muscular demand.	Relationship found between unilateral lower limb amputation and increased large central arterial stiffness, independent of other known pathological risk factors. Arterial stiffness is an independent predictor of all cause and cardiovascular mortality. Routine assessment of arterial health may be important for people with amputation, regardless of other known risks.	Increased peripheral vascular resistance may contribute to increased blood pressure in populations with traumatic lower limb amputation and increase cardiovascular risk factors.

References

1. Hrubec Z, Ryder RA. Traumatic limb amputations and subsequent mortality from cardiovascular disease and other causes. *Journal of Clinical Epidemiology*. 1980;33(4):239–250.

1. Modan M, Peles E, Halkin H, et al. Increased cardiovascular disease mortality rates in traumatic lower limb amputees. *American Journal of Cardiology*. 1998;82:1242-1247.

2. Peles E, Akselrod S, Goldstein DS, et al. Insulin resistance and autonomic function in traumatic lower limb amputees. *Clinical Autonomic Research*. 1995;5(5):279–288.

1. Rose HG, Yalow RS, Schweitzer P, Schwartz E. Insulin as a potential factor influencing blood pressure in amputees. *Hypertension*. 1986;8(9):793-800.

1. Ejtahed H-S, Soroush M-R, Hasani-Ranjbar S, et al. Prevalence of metabolic syndrome and health-related quality of life in war-related bilateral lower limb amputees. *Journal of Diabetes & Metabolic Disorders*. 2017;16:17. doi:10.1186/s40200-017-0298-2

1. Naschitz JE, Lenger R. Why traumatic leg amputees are at increased risk for cardiovascular diseases. *QJM*. 2008;101(4):251-259. doi:10.1093/qjmed/hcm131

2. Vollmar JF, Pauschinger P, Paes E, Henze E, Friesch A. Aortic aneurysms as late sequelae of above-knee amputation. *The Lancet*. 1989;334(8667):834–835.

3. Huonker M, Schmid A, Schmidt-Trucksäß A, Grathwohl D, Keul J. Size and blood flow of central and peripheral arteries in highly trained able-bodied and disabled athletes. *Journal of Applied Physiology*. 2003;95(2):685-691. doi:10.1152/japplphysiol.00710.2001

4. Magalhães P, Capingana DP, Silva ABT, Capunge IR, Gonçalves MAA. Arterial Stiffness in Lower Limb Amputees. *Clin Med Insights Circ Respir Pulm Med*. 2011;5:49-56. doi:10.4137/CCRPM.S7757

5. Paula-Ribeiro M, Garcia MMN, Martinez DG, Lima JRP, Laterza MC. Increased peripheral vascular resistance in male patients with traumatic lower limb amputation: one piece of the cardiovascular risk puzzle. *Blood Pressure Monitoring*. 2015;20(6):341-345. doi:10.1097/MBP.0000000000000148

6. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of Cardiovascular Events and All-Cause Mortality With Arterial Stiffness. *Journal of the American College of Cardiology*. 2010;55(13):1318-1327. doi:10.1016/j.jacc.2009.10.061