

Letter

Pulse Wave Velocity in Systemic Sclerosis: Potential Beneficial Effects of Bosentan on Forearm Arterial Stiffness? An Exploratory Study

To the Editor:

Treatment of digital ischemia in systemic sclerosis (SSc) remains a challenge. Although vasculopathy is generally thought to occur on a microvascular level, some observations suggest the involvement of medium-sized arteries as well. In patients with advanced disease, obliteration of the ulnar artery is frequently observed, associated with an adverse outcome¹. A potential mechanism is arterial wall fibrosis. Arterial stiffness may be an easily identifiable sign of vasculopathy, early in the disease course, assessed noninvasively by pulse wave velocity (PWV). Although several studies have assessed aortic and upper extremity PWV in SSc, studies specifically on forearm PWV are limited²⁻⁸. Further, the effect of treatment on PWV has not been previously studied in SSc. Since endothelin-1 plays an important role in SSc vasculopathy and promotes arterial stiffness in animal models⁹, we hypothesize that the dual endothelin receptor antagonist bosentan may potentially improve arterial stiffness in SSc.

This exploratory study compared PWV in patients with limited cuta-

neous SSc (lcSSc) with age- and sex-matched healthy controls (HC) at baseline. Second, the effect of bosentan (62.5 mg twice daily, titrated to 125 mg twice daily after 1 mo if tolerated) was investigated on PWV after 3 months and 1 year in a randomized, prospective, 2-arm parallel group (usual care with bosentan vs usual care only), open-label, blinded endpoint intervention study. PWV of the aorta (carotid-femoral), upper arm (carotid-brachial), and forearm (brachial-radial) were measured, adjusted for mean arterial pressure.

Both parts of the study were approved by the Medical Ethical Institutional Review Board of the University Medical Center Groningen (2014/337) and carried out according to the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered on ClinicalTrials.gov (NCT02480335). All participants gave written informed consent.

Nineteen patients with lcSSc, classified according to the American College of Rheumatology/European League Against Rheumatism criteria¹⁰ and 19 HC completed baseline visits (Supplementary Table 1, available with the online version of this article). After the baseline visit, 3 patients discontinued because of non-SSc-related health complaints. No differences were observed in PWV (all sites) between HC and patients with SSc (Figure 1). In patients with SSc, no significant correlation of PWV (all sites) with age, sex, smoking pack-years, disease duration (Raynaud phenomenon and SSc), C-reactive protein, nailfold capillaroscopy patterns, or antihypertensive

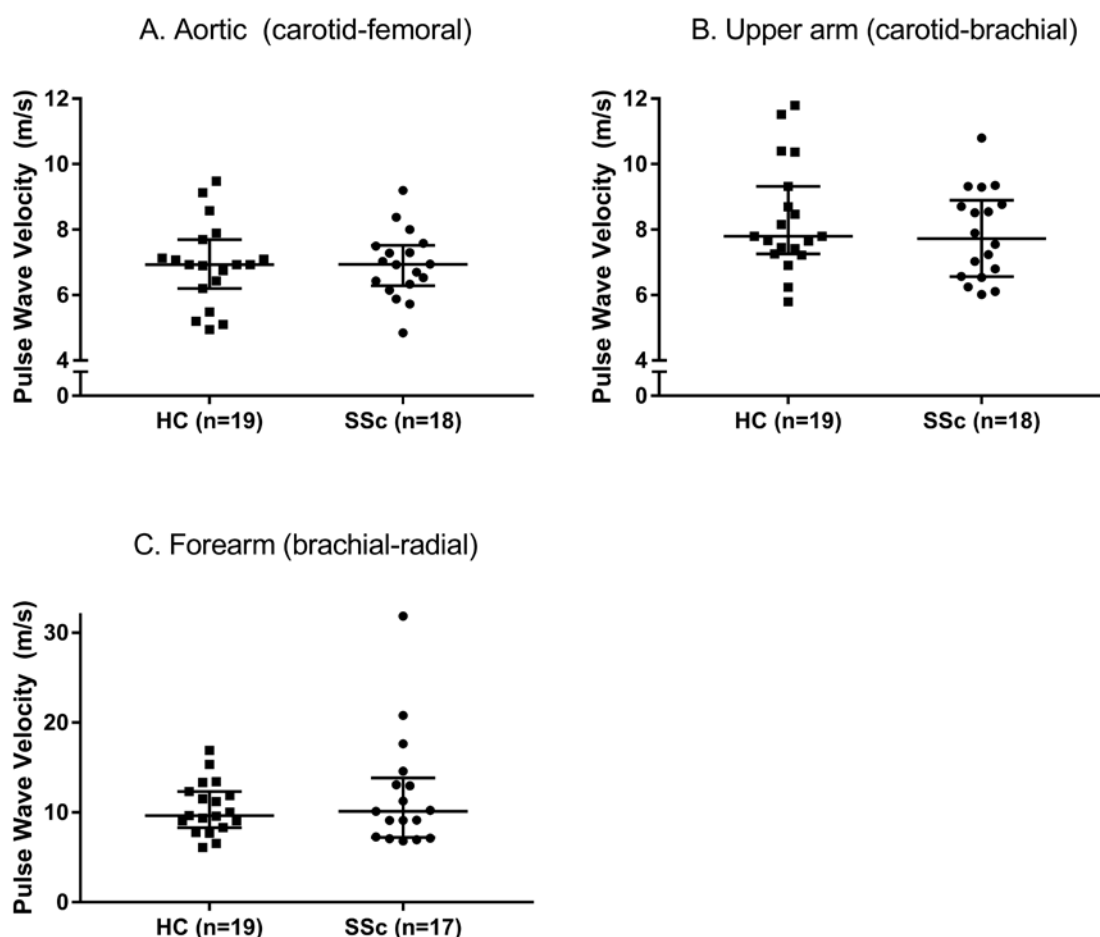


Figure 1. Median (IQR) of the (A) aortic, (B) upper arm, and (C) forearm pulse wave velocity. HC: healthy controls; SSc: systemic sclerosis.

medication was present. No difference was found between the bosentan and usual care only group in change in aortic PWV (Figure 2A). Although change in upper arm PWV differed between groups, PWV was already different at baseline (Figure 2B). Forearm PWV decreased significantly in the bosentan group compared to usual care only (Figure 2C).

Our preliminary results provide several relevant additions to the current knowledge on arterial stiffness in lcSSc. Contradictory to 2 previous reports^{2,4}, but in line with more recent studies^{6,7,8}, all using the same method, we found aortic PWV in our cohort of SSc patients not to be increased compared to HC. However, our exploratory analysis may suggest potential significant effects of bosentan on forearm PWV. Although smoking pack-years was higher in patients with SSc, we believe the confounding effect of smoking in our study is limited as smoking did not correlate with PWV, no patients changed smoking status during the study, and all patients refrained from smoking at least 10 h before study visits.


As atherosclerosis of the upper extremity is rare, changes found in arterial stiffness are more likely to result from SSc-related vasculopathy. Only 1 previous study investigated forearm arterial stiffness³. They reported higher forearm PWV in patients with SSc compared to HC; however, this increase was only present in patients with diffuse cutaneous SSc (dcSSc). In patients with lcSSc, PWV was similar compared to controls, in line with the results from our study. This suggests that increased arterial stiffness is mainly present in patients with dcSSc. Importantly, in our study and in that of Liu, *et al*³, forearm PWV was measured in the radial artery trajectory, whereas obliterations of the ulnar artery are frequently present in SSc¹. Although

higher forearm PWV is subtle, future studies investigating the ulnar artery should be performed.

In addition, we observed a reduction in forearm PWV in patients receiving bosentan. Given the small sample size, this part should be considered exploratory. This finding might indicate that bosentan has a beneficial effect on the stiffness of the medium-sized forearm arteries. Although we also found a difference in the change of upper arm PWV, this should be interpreted as a regression to the mean, as baseline levels were considerably different between both groups.

In conclusion, in this exploratory study, PWV of the aorta, upper arm, and forearm does not appear to be increased in patients with lcSSc, as compared to age- and sex-matched HC. These results are generally in line with previous observations in lcSSc, whereas in studies in subgroups with dcSSc, PWV was reported to be increased. Bosentan may potentially have a beneficial effect on the stiffness of the medium-sized arteries of the forearm, as PWV decreased in our exploratory study. We suggest future studies should be designed to focus on this effect in patients with dcSSc, in which arterial stiffness could be affected by bosentan, potentially reducing vascular complications.

Anniek Maaïke van Roon^{1,2} , MD, PhD

Amaal Eman Abdulle¹ , MD, PhD

Douwe Johannes Mulder¹ , MD, PhD

¹Department of Internal Medicine, Division of Vascular Medicine;

²Department of Rheumatology and Clinical Immunology, University

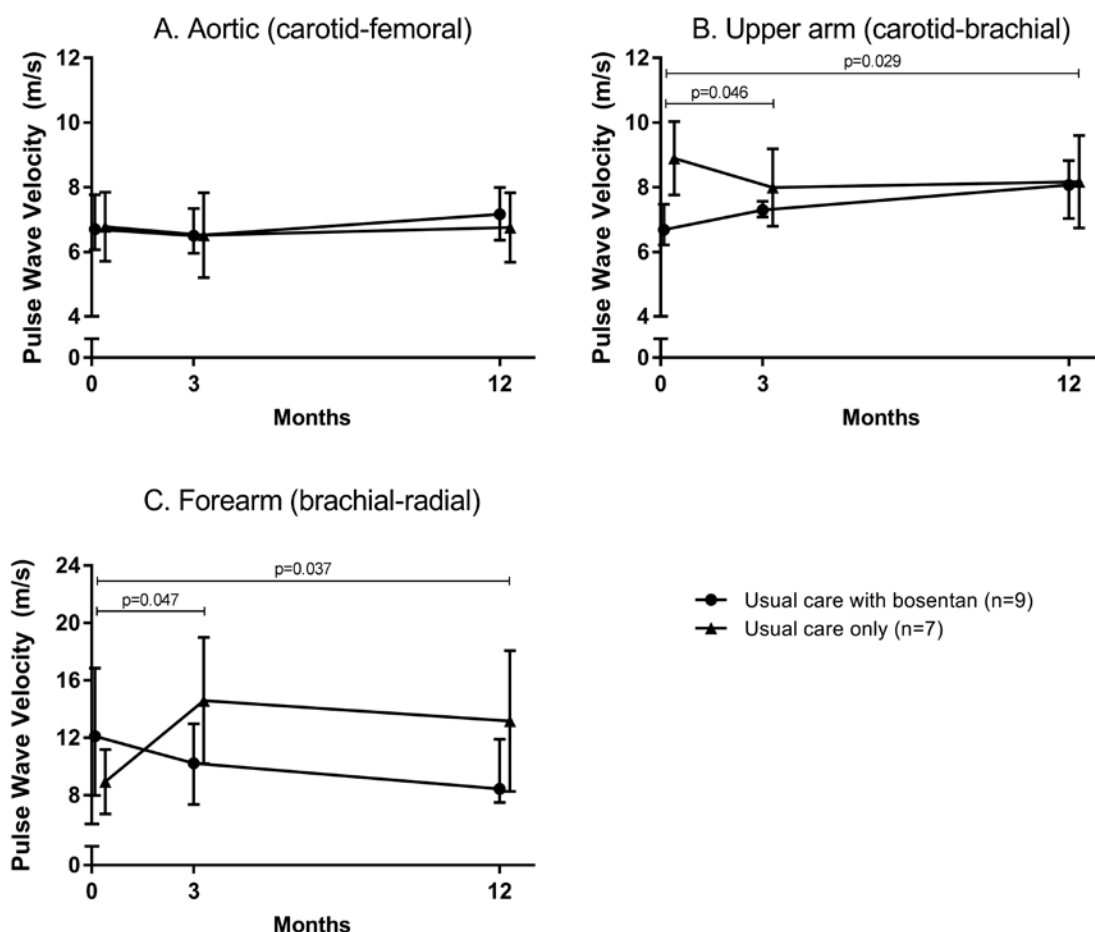


Figure 2. Change in arterial stiffness. The median (IQR) of the (A) aortic, (B) upper arm, and (C) forearm pulse wave velocity over time of the bosentan and usual care group. P values are of differences in change over time between groups.

of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

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Address correspondence to Dr. A.M. van Roon, University Medical Center Groningen, Huispostcode AA41, Hanzeplein 1, Postbus 30 001, Groningen, the Netherlands. Email: a.m.van.roon01@umcg.nl.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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