Arterial Stiffness and Wave Reflections in Patients With Sickle Cell Disease

Daniel Lemogoum, Luc Van Bortel, Boutaina Najem, Anasthase Dzudie, Charles Teutcha, Ernest Madu, Marc Leeman, Jean-Paul Degaute, Philippe van de Borne

Abstract—We tested the hypothesis that lower blood pressure and increased vasodilatation reported in sickle cell disease (SCD) patients with hemoglobin SS genotype (SS) are translated by lower arterial stiffness determined by pulse wave velocity (PWV) and wave reflections assessed by augmentation index (AI). We enrolled 20 SS (8 females; 12 male) patients closely matched for age, gender, height, and body mass index to 20 subjects with hemoglobin AA genotype (AA). Carotid–femoral PWV (PWVCF) and carotid–radial PWV (PWVCR) were recorded with the Complior device. Aortic AI was derived from pressure wave analysis (Sphygmocor). PWVCF and PWVCR were lower in SS than in AA (4.5±0.7 m/s versus 6.9±0.9 m/s, P<0.0001 and 6.6±1.2 m/s versus 9.5±1.4 m/s, P<0.0001, respectively). AI was lower in SS than in AA (2±14% versus 11±8%, P<0.02). Multivariate analysis revealed that both PWVCF and PWVCR were negatively associated with hemoglobin SS type and positively related to mean arterial pressure (MAP), whereas AI was positively associated with MAP and total cholesterol (all P<0.0001). Multivariate analysis restricted to SS indicated a positive association between PWVCF and PWVCR with age but a negative association with MAP (R²=0.57 and 0.51, respectively, both P<0.001); whereas MAP and heart rate were independently associated with AI (R²=0.65, P<0.001). This study provides the first evidence that SCD is associated with both lower arterial stiffness and wave reflections. SS patients have a paradoxical negative association between PWV and MAP, suggesting that low MAP does not protect them against arterial stiffness impairment. (Hypertension. 2004;44:924-929.)

Key Words: arteries ■ wave reflections

Sickle cell disease (SCD) patients with homozygote hemoglobin SS genotype (SS) have considerably lower blood pressure (BP) than published normal values. Moreover, black SS patients have less hypertension than black subjects with homozygote hemoglobin AA genotype (AA). The mechanism of this low BP in SS patients is not clear. Altered vascular reactivity to angiotensin II has been evoked as a possible protective factor from hypertension in the SS population. Moreover, whereas patients with SCD have impaired vasodilatation during vaso-occlusive crises, the opposite is observed in steady-state SS patients. Increased basal nitric oxide (NO) bioavailability has been reported in patients with SCD in the steady-state. Anemia and increased shear-stress, as well as compensatory responses to chronic vascular injury, increase endothelial NO production. Despite this elevated NO bioavailability and the relative low BP, SCD is associated with increased risk of cardiovascular disease. Increased arterial stiffness is an independent determinant of cardiovascular mortality. Pulse wave velocity (PWV) is a measure of arterial stiffness. Increased arterial stiffness leads to elevated pulse pressure, the dynamic component of BP. Furthermore, arterial stiffness is influenced by mean arterial pressure (MAP), which reflects the steady component of BP. Because BP is a major determinant of arterial stiffness, we tested the hypothesis that lower BP and peripheral vasodilatation are translated by lower arterial stiffness as determined by PWV in stable SS patients. Moreover, we anticipated that lower brachial BP and increased vasodilatation in SS patients would modify timing of wave reflection and result in a lower aortic augmentation index (AI) derived from the central pressure wave analysis.

Methods

Subjects and Design

Twenty SS patients were closely matched for age, gender, height, and body mass index to 20 healthy AA subjects (Table 1). The sickle cell group consisted of ambulatory patients with clinical, electro-
PWV was determined by a validated noninvasive automated device (ComploR; Artech-Medical). Carotid–radial and carotid–femoral PWVs of pulse pressure. Diastolic BP, and MAP was estimated as diastolic BP plus one-third of heart rate (HR) were recorded at the brachial artery of the right arm using an automated sphygmomanometer (Omron HEM 705 CP-E). Pulse pressure was calculated as systolic BP minus diastolic BP, and MAP was estimated as diastolic BP plus one-third of pulse pressure.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SS (n=20)</th>
<th>AA (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>24±7</td>
<td>24±6</td>
<td>0.98</td>
</tr>
<tr>
<td>Gender, f/m</td>
<td>8/12</td>
<td>10/10</td>
<td>0.54</td>
</tr>
<tr>
<td>Body mass index, kg/m</td>
<td>21±2</td>
<td>21±3</td>
<td>0.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166±10</td>
<td>165±12</td>
<td>0.78</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>81±9</td>
<td>80±12</td>
<td>0.85</td>
</tr>
<tr>
<td>Brachial systolic blood pressure, mm Hg</td>
<td>113±12</td>
<td>117±13</td>
<td>0.35</td>
</tr>
<tr>
<td>Brachial diastolic blood pressure, mm Hg</td>
<td>65±8</td>
<td>75±8</td>
<td>0.0004</td>
</tr>
<tr>
<td>Brachial pulse pressure, mm Hg</td>
<td>48±7</td>
<td>42±9</td>
<td>0.02</td>
</tr>
<tr>
<td>Aortic systolic blood pressure, mm Hg</td>
<td>96±10</td>
<td>105±11</td>
<td>0.009</td>
</tr>
<tr>
<td>Aortic diastolic blood pressure, mm Hg</td>
<td>67±9</td>
<td>77±8</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>80±9</td>
<td>90±8</td>
<td>0.001</td>
</tr>
<tr>
<td>Augmentation index, %</td>
<td>2±14</td>
<td>11±8</td>
<td>0.02</td>
</tr>
<tr>
<td>Carotid–femoral pulse wave velocity, m/s</td>
<td>4.5±0.7</td>
<td>6.9±0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Carotid–radial pulse wave velocity, m/s</td>
<td>6.6±1.2</td>
<td>9.5±1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>8±1</td>
<td>14±2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>184±3</td>
<td>186±6</td>
<td>0.56</td>
</tr>
<tr>
<td>Fasting blood glucose, g/dL</td>
<td>0.91±0.08</td>
<td>0.90±0.12</td>
<td>0.7</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.53±0.04</td>
<td>0.39±0.07</td>
<td>0.47</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.72±0.08</td>
<td>0.68±0.06</td>
<td>0.48</td>
</tr>
</tbody>
</table>

There were no significant group differences in clinical and cardiovascular variables. The age of SS and AA participants did not differ significantly. SS and AA group differences in clinical and cardiovascular variables were compared using unpaired Student t test. Univariate analysis was used to examine associations between PWV, AI, and brachial BP, HR, height, body mass index, age, C-reactive protein, hemoglobin level, total cholesterol, and fasting blood glucose. Stepwise multiple regression analysis was performed to determine the distance between 2 recording sites (PWV=distance (m)/transit time (s)), according to the foot-to-foot method. In our hands (D.L.), intraobserver within-session coefficients of variation for aortic and brachial PWV with the ComplioR device are 3.8±1.3% and 2.6±1.6%, respectively (n=25). The reproducibility of our PWV determinations is comparable to those of Asmar et al. PWV is related to arterial distensibility (D) by the equation of Bramwell-Hill: PWV=1/(D×ρ), whereas ρ represents blood density, and to the Young modulus of the arterial wall (E) and wall thickness (h) by the Moens-Korteweg equation: PWV=V/Erh², where R is arterial radius.

Central Hemodynamics: Aortic BP and Aortic AI
Aortic BP and AI were obtained from noninvasive pulse wave analysis using applanation tonometry (Sphygmocor; Atcor Medical). A high-fidelity applanation tonometer (SPC-301; Millar Instruments) was used to obtain accurate recordings of the radial artery pressure waveforms, which were calibrated with sphygmonanometric systolic BP and diastolic BP measured at the brachial artery of the right arm. An average radial pressure waveform was generated from 20 sequential radial pressure waveforms. A corresponding average aortic pressure waveform was then automatically generated by a transfer function, and from this average ascending aortic BP and AI were then derived as previously described. The reproducibility of derived AI has been previously validated. In our hands (D.L.), within-session coefficient of variation for derived AI measurements using Sphygmocor is 6.8±7.3% (n=25) and is comparable to those of Wilkinson et al. and Savage et al.

**Statistical Analysis**
Data are expressed as mean±SD. A 2-sided P<0.05 was considered significant.
whether age, height, HR, MAP, hemoglobin SS status, hemoglobin level, and total cholesterol were independent confounders of PWV and AI. Because BP and HR are determinants of PWV and AI, respectively, we also corrected SS and AA differences in PWV for MAP and AI for HR by using analysis of covariance. All statistical analyses were performed with Statview 5 software (SAS Institute Inc).

**Results**

**Comparison of PWV, AI, and Other Hemodynamic Parameters Between SS and AA Participants**

Brachial systolic BP did not differ between SS patients and AA subjects (\(P=0.35\)) (Table 1). Both MAP and diastolic BP were lower in the SS patients than in the AA subjects (both \(P<0.01\)). Brachial pulse pressure was larger in SS than AA (\(P=0.02\)).

PWV<sub>CR</sub> and PWV<sub>CF</sub> were lower in SS than in AA subjects (both \(P<0.0001\)). Similarly, AI was lower in SS patients than in AA subjects (\(P=0.02\)). PWV adjusted for MAP and AI adjusted for HR remained lower in SS than in AA (both \(P<0.05\)).

**Relation Between PWV, AI, and Cardiovascular Variables in the Whole Study Population**

Both PWV<sub>CR</sub> and PWV<sub>CF</sub> increased with age, diastolic BP, and MAP, and with total cholesterol (all \(P<0.05\)) (Table 2). PWV<sub>CF</sub> and PWV<sub>CR</sub> were positively associated with hemoglobin level and negatively associated with hemoglobin SS status (all \(P<0.05\)). Neither PWV<sub>CF</sub>, nor PWV<sub>CR</sub> was related to HR. AI was positively associated with age, height, and total cholesterol, and inversely related to HR (all \(P<0.05\)). AI was also positively related to hemoglobin level and negatively associated with hemoglobin SS status (all \(P<0.05\)). To determine whether MAP and hemoglobin SS status were independent predictors of PWV and AI, multiple stepwise regression analysis was performed with adjustment for age, height, HR, hemoglobin level, and total cholesterol, and revealed that PWV<sub>CF</sub> and PWV<sub>CR</sub> were independently negatively associated with hemoglobin SS status and positively related to MAP (Table 3 and Table 4, respectively), whereas AI was independently positively associated with MAP and total cholesterol (Table 5). No effect of hemoglobin SS status level on both PWV and AI was seen.

**Arterial Stiffness and Hemodynamic in SS Patients**

In the univariate linear regression analysis restricted to SS patients, both PWV<sub>CF</sub> and PWV<sub>CR</sub> decreased with higher MAP and increased with age (Figure), and with a higher hemoglobin level (r=0.31 and +0.33, respectively, both \(P<0.05\)).

Stepwise multiple regression analysis restricted to SS and performed with adjustment for age, hemoglobin level, and MAP showed an independent positive association between PWV<sub>CF</sub> with age but a negative association with MAP.

### TABLE 3. Determinants of Aortic PWV

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\beta)</th>
<th>SE</th>
<th>(t)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>0.36</td>
<td>0.23</td>
<td>0.13</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemoglobin SS (yes=1, no=0)</td>
<td>-0.78</td>
<td>0.53</td>
<td>-5.69</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Stepwise multiple regression analysis; \(n=40\).
Model \(R^2=0.68\); \(F=18.809\).
Model \(P<0.0001\).
\(\beta\) indicates regression coefficient.

### TABLE 4. Determinants of Carotid–Radial PWV

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\beta)</th>
<th>SE</th>
<th>(t)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>0.43</td>
<td>0.16</td>
<td>0.39</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemoglobin SS (yes=1, no=0)</td>
<td>-0.81</td>
<td>0.32</td>
<td>-7.31</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Stepwise multiple regression analysis; \(n=40\).
Model \(R^2=0.71\); \(F=22.550\).
Model \(P<0.0001\).
\(\beta\) indicates regression coefficient.
Arterial Stiffness in SS Subjects

Increased PWVCf has been previously reported in normotensive blacks compared with whites. This was not the case for SS black patients in the present study. PWVCf and PWVCR were markedly decreased in SS patients as compared with AA subjects, suggesting less stiffness along the arterial tree in SCD population.

Both SS and AA groups were living in the same environment and were comparable with respect to age, gender, HR, body mass index, height, fasting blood glucose, and total cholesterol, factors that influence arterial stiffness. Therefore, observed differences cannot be attributed to those factors.

In this study, MAP and hemoglobin SS type emerge as independent determinants of the reduction in arterial stiffness in the whole population.

BP is a major determinant of arterial stiffness. As previously reported, we observed lower peripheral BP in SS patients. The lower BP can explain the reduced PWV in SS patients.

An unexpected finding in the present study is the inverse relationship between MAP and PWV in SS patients, especially in the lower mean BP range. The underlying mechanism is unknown. This observation suggests a possible vascular deleterious effect of chronic severe hypotension on arterial wall properties. However, whether this negative relationship between PWV and MAP is caused by genetic influence or acquired because of recurrent vaso-occlusive crises is not clear and needs to be investigated by further studies. An alternative explanation may be that low MAP represents a status of pronounced arteriolar and arterial dilatation. Whereas mild-to-moderate relaxation of vascular smooth muscle cells brings arterial strain on the elastic fibers and decreases arterial stiffness, more pronounced dilatation shifts the strain to the collagen fibers resulting in increased arterial stiffness.

A potential limitation to our observation is the confounding influence of anemia on PWV. However, there are several
reasons to believe that anemia cannot explain all our findings. First, anemia did not decrease arterial stiffness in both central elastic arteries (assessed by carotid artery stiffness index) and peripheral muscular arteries (assessed by brachio-radial peripheral wave velocity [PWV]) in patients with beta-thalassemia major. Second, according to the Bramwell-Hill equation, a lower blood density is expected to increase PWV. Last, multivariate analysis, after adjustment for several variables including hemoglobin level, revealed that SS status was independently and negatively associated with PWV, whereas hemoglobin level did not enter in the model (Tables 3 and 4).

It seems likely that NO-mediated vasodilatation induced by increased basal NO bioavailability in SS7,8,11,31 may have contributed to the improved arterial distensibility we observed. Moreover, as observed in studies in animals,11 increased basal cyclic guanylate monophosphate production in aortic rings could have also contributed to lower PWV in SS. However, the full integrity of endothelial NO production system in SCD remains controversial. Several studies support a disturbance in vascular function and stimulated NO bioactivity in SS.4–6,11,32–34 Furthermore, hemoglobin SS status is associated with impaired flow-mediated dilation.7,9,31 a marker of endothelial function. In addition, SS patients disclose a markedly lower basal vascular resistance compared with AA11 and a blunted vasoconstriction in response to 100% oxygen.9 Thus, whether changes in endothelial function related to SS status may explain the higher arterial distensibility we observed remains unclear.

**Pressure Wave Reflection in SCD**

AI is a marker of aortic wave reflections.19 In the present study, AI was lower in SS patients than in the healthy AA group. Furthermore, multivariate analysis revealed that AI increased with higher MAP, whereas it decreased with faster HR. Our observations are in keeping with previous studies, which observed strong inverse association between AI and HR.27,28

AI depends on arterial stiffness, timing, and site of arterial wave reflections.18,19 Thus, lower AI in SS patients can be related to lower PWV, and hence reduced arterial stiffness, but could also reflect changes in timing and site of the reflected wave. The latter mechanism could be the result of reduced peripheral resistance observed in SCD,3 which again could be explained by increased basal NO bioavailability.7–9

**Conclusion**

SCD is associated with both lower arterial stiffness and wave reflections. SCD patients show a paradoxical negative association between PWV and MAP, suggesting that low MAP does not protect them against arterial stiffness impairment.

**Perspectives**

Increased arterial stiffness and wave reflections are determinants of cardiovascular morbidity and mortality.15,16,19 This study provides the first evidence that those 2 cardiovascular risk predictors are markedly lower in SS patients despite increased cardiovascular disease prevalence in this population.1,12–14 Our findings are of public health relevance by ruling out the potential contribution of arterial wall structure and function alteration in the pathophysiology of cardiovascular disease in SCD population. Regarding these observations, and consistent with previous report,13 vaso-occlusion rather than arterial wall abnormalities seems to remain the principal mechanism explaining increased risk of cardiovascular events like stroke in SS and outlines the importance of aggressive management of acute events in SS and active prevention of red cell sickling risk factors in this high-risk population. However, because of the limited size of participants in the present study, our data need to be confirmed in a larger-scale study enrolling SCD patients and other patients with various type of chronic anemia, because their effects on vascular compliance have been less explored.

**Acknowledgments**

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**References**


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