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 (PWV_{CF}) and carotid–radial PWV (PWV_{CR}) were recorded with the Complior device. Aortic AI was derived from pressure wave analysis (SphygmocorR). PWV_{CF} and PWV_{CR} 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 PWV_{CF} and PWV_{CR} 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 PWV_{CF} and PWV_{CR} with age but a negative association with MAP (R^2=0.57 and 0.51, respectively, both P<0.001), whereas MAP and heart rate were independently associated with AI (R^2=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. Whether changes in arterial structure and function are involved is unknown. Structural and functional changes of the arteries are important features in 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 were calculated from measurements of pulse transit time and the distance between 2 recording sites (PWV=distance (m)/transit time (s)), according to the foot-to-foot method.16,20 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.2 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=√E/2Rh, where R is arterial radius.21

**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 sphygmomanometric 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,22 and from this average ascending aortic BP and AI were then derived as previously described.19,23 In our hands (D.L.), within-session coefficient of variation for derived AI measures using Sphygmocor is 6.8±7.3% (n=25) and is comparable to those of Wilkinson et al.23 and Savage et al.24

**Statistical Analysis**
Data are expressed as mean±SD. A 2-sided P<0.05 was considered significant.

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

**TABLE 1. Characteristics of Hemoglobin SS and Healthy Hemoglobin AA Participants**

<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>

Measurements
All measurements were performed in triplicate after 15 minutes of supine rest in a quiet room.

Peripheral Hemodynamics: Brachial BP and Heart Rate
Brachial systolic BP, diastolic BP, and heart rate (HR) were recorded at 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.

PWVs
PWV was determined by a validated20 noninvasive automated device (CompriO; Artech-Medical). Carotid–radial and carotid–femoral...
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$_{CR}$ and PWV$_{CF}$ 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$_{CR}$ and PWV$_{CF}$ increased with age, diastolic BP, and MAP, and with total cholesterol (all $P<0.05$) (Table 2). PWV$_{CF}$ and PWV$_{CR}$ were positively associated with hemoglobin level and negatively associated with hemoglobin SS status (all $P<0.05$). Neither PWV$_{CF}$, nor PWV$_{CR}$ 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$_{CF}$ and PWV$_{CR}$ 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 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$_{CF}$ and PWV$_{CR}$ 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$_{CF}$ with age but a negative association with MAP (model

### 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.
TABLE 5. Determinants of Aortic AI

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>SE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>-0.22</td>
<td>0.14</td>
<td>-1.81</td>
<td>0.08</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>0.34</td>
<td>0.15</td>
<td>2.24</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>0.55</td>
<td>0.12</td>
<td>4.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemoglobin SS (yes=1, no=0)</td>
<td>-0.06</td>
<td>3.77</td>
<td>-0.39</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Stepwise multiple regression analysis; n=40.
Model R²=0.58; F=11.17.
Model P<0.0001.
β indicates regression coefficient; AI, augmentation index.

$R^2=0.56$, $F=13.69$, $P<0.001$). Similarly, PWV$_{CR}$ was independently negatively associated with MAP and positively related to age ($R^2=0.51$, $F=10.63$, $P<0.001$). No effect of hemoglobin level on both PWV$_{CF}$ and PWV$_{CR}$ was seen in the multivariate analyses.

In the univariate analysis, AI was positively associated with MAP and negatively associated with HR (Figure), and increased with hemoglobin level ($r=0.29$, $P=0.046$).

In the stepwise multiple regression analysis performed taking into account MAP, hemoglobin level, and HR, only MAP and HR were independently associated with AI ($R^2=0.65$, $F=16.66$, $P<0.001$).

Discussion

The major findings of this study are that arterial stiffness as assessed by PWV and wave reflections determined by aortic AI are lower in SS patients as compared with AA subjects and that PWV is paradoxically negatively associated with MAP in SS patients.

We are not aware of another study exploring these hemodynamic variables in SS patients.

Arterial Stiffness and Cardiovascular Variables in Study Participants

The present study confirms previous observations of higher PWV with aging, higher BP, and total cholesterol in the entire study population. As previously reported, AI increased with aging, smaller height, higher total cholesterol, and decreased with faster HR.

Arterial Stiffness in SS Subjects

Increased PWV$_{CF}$ has been previously reported in normotensive blacks compared with whites. This was not the case for SS black patients in the present study. PWV$_{CF}$ and PWV$_{CR}$ 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 PWV) in patients with β-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 SS may have contributed to the improved arterial distensibility we observed. Moreover, as observed in studies in animals, 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. Furthermore, hemoglobin SS status is associated with impaired flow-mediated dilation, a marker of endothelial function. In addition, SS patients disclose a markedly a lower basal vascular resistance compared with AA and a blunted vasoconstriction in response to 100% oxygen. 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. 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.

AI depends on arterial stiffness, timing, and site of arterial wave reflections. 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, which again could be explained by increased basal NO bioavailability.

**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. 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. 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, vasoo-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.

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**References**


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