

Intracardiac or intrapulmonary shunts were present in at least 35% of adults with homozygous sickle cell disease followed in an outpatient clinic

Sickle cell disease (SCD) is an inherited anemia in which the beta chain of adult hemoglobin (Hb) is mutated ('sickle', HbS). Deoxygenated HbS (deoxyHbS) polymerizes within red blood cells (RBCs), resulting in membrane damage and hemolysis, which is toxic to the vascular endothelium. SCD is characterized by lifelong anemia, vasculopathy, organ damage, recurrent and chronic pain, and significant cumulative morbidity and mortality.

Most patients with homozygous HbSS experience cardiopulmonary complications during their lifetimes,¹ including restrictive cardiomyopathy,² recurrent acute chest syndrome, chronic thromboembolic disease, and pulmonary hypertension.³⁻⁵ A less well-described cardiopulmonary complication of SCD, and one that plausibly increases systemic exposure to deoxyHbS-containing RBCs, is right-to-left shunting (RLS). RLS may be detected by agitated saline-contrasted echocardiography,⁶ and may be due to a bypass in or near the heart (intracardiac) or *via* arteriovenous malformations (AVMs) in the lungs (intrapulmonary). Intrapulmonary AVMs may be visualized by iodinated-contrast chest computed tomogram (CT) scan.⁷ A recent prospective study reported a high prevalence of RLS (predominantly intrapulmonary) in children with HbSS and stroke⁸ compared to children without either diagnosis, and we had earlier reported similar, but preliminary, findings in adults with HbSS.⁹ However, the overall prevalence of intracardiac and intrapulmonary RLS in adults with HbSS is unknown, as saline-contrasted echocardiography is not routinely performed.

Here, we wanted to estimate the prevalence of RLS, and its clinical and laboratory associations, in adults with HbSS, using data derived from routine clinical care.

A cross-sectional retrospective study was undertaken in all adults with HbSS who were followed at University Hospitals-Cleveland Medical Center (UHCCMC) at Case Western Reserve University (CWRU) between 2012 and 2017 (n=190, 106 females and 84 males). Clinical and laboratory data were gathered at clinical baseline as part of routine clinical care. This analysis was approved by the Institutional Review Board of UHCCMC.

Forty-eight percent of all study cases (91 of 190) under-

went contrast echocardiography in order to evaluate hemoglobin desaturation and/or subjectively defined 'excessive' reticulocytosis. Contrast echocardiography is a technique whereby the presence and location of RLS is determined based on whether and when bubbles move from the right heart to the left heart relative to administration of agitated saline in a vein. Immediate appearance (within 3 beats) signifies an intracardiac shunt, while delayed appearance (after 4 or more beats) suggests an intrapulmonary shunt.

Forty-five percent (86 of 190) of all adults with HbSS followed in our clinic were on hydroxyurea and 10% (19 of 190) were receiving chronic exchange transfusions. Twenty-five percent (48 of 190) of all subjects with HbSS had a history of cerebrovascular disease (stroke, transient ischemic attacks, or abnormalities on magnetic resonance imaging).

Contrast-enhanced chest CT scans, performed for clinical care during this interval, were available for review on 32 subjects who were found to have RLS on contrast echocardiography. A thoracic radiologist, blinded to clinical context (RG), reviewed each scan. Baseline pulse oximetry, performed in the pulmonary function lab, was available for 52 subjects, 42 of whom had RLS and 10 of whom did not.

Continuous variables were described using mean and standard deviation (SD), and nominal variables were described as N (%). Continuous variables were compared using Wilcoxon rank sum tests, and nominal variables were compared using Fisher exact test. $P=0.05$ was considered significant. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Ninety-one of 190 (48%) adults with HbSS at our center underwent contrast echocardiography while at clinical baseline. Subjects who underwent contrast echocardiography, compared with those who did not, had more active disease, and were more likely to have been treated with hydroxyurea (55% vs. 36%; $P=0.013$), had a higher mean tricuspid regurgitation velocity (TRV, 2.6 ± 0.6 vs. 2.2 ± 1.0 meters/second (m/s); $P=0.016$), and higher mean lactate dehydrogenase (LDH) level (509 ± 246 vs. 396 ± 183 U/L; $P<0.001$).

Seventy-four percent of people who underwent contrast echocardiography had RLS (67 of 91) (Table 1). These subjects also had higher LDH levels (550 ± 260 vs. 398 ± 159 U/L; $P=0.005$), higher total bilirubin (3.3 ± 2.1 vs. 2.3 ± 1.8 mg/dL; $P=0.006$), and a higher absolute reticulo-

Table 1. Clinical characteristics of patients with or without a right-to-left shunt on bubble echocardiography.

| | RLS n=67 | no RLS n=24 | P |
|---|----------------|----------------|-------|
| Age (years) | 31.1 (9.4) | 37.4 (13.9) | 0.077 |
| Hb (g/dL) | 8.6 (1.5) | 8.7 (1.8) | 0.710 |
| Hb F (%) (n=66, 24) | 6.3 (5.5) | 8.9 (7.6) | 0.211 |
| ARC ($\times 10^9/L$) | 354 (171) | 274 (125) | 0.043 |
| LDH (U/L) (n=66, 24) | 550 (260) | 398 (159) | 0.005 |
| Total bilirubin (mg/dL) | 3.3 (2.1) | 2.3 (1.8) | 0.006 |
| TRV (m/s) (n=61, 19) | 2.5 (0.7) | 2.6 (0.5) | 0.577 |
| 6-MWD (m) (n=43, 10) | 448 (86) | 468 (105) | 0.659 |
| History of acute chest syndrome | 33/67 (49.25%) | 11/24 (45.83%) | 0.816 |
| History of stroke | 8/67 (11.94%) | 5/24 (20.83%) | 0.316 |
| Baseline Hb desaturation (n=52 evaluated) | 16/42 (38.10%) | 1/10 (10.00%) | 0.138 |

cyte count (ARC) (354 ± 171 vs. $74 \pm 125 \times 10^9/L$; $P=0.043$), but no difference in total hemoglobin (Hb) (8.6 ± 1.5 vs. 8.7 ± 1.8 g/dL; $P=0.70$), when compared with screened subjects without an RLS (24 of 91).

Among people with identified RLS, 43% had an intracardiac shunt and 57% an intrapulmonary shunt ($n=29$ and 38, respectively). Intracardiac shunting was associated with a statistically significantly higher TRV (2.8 ± 0.7 vs. 2.4 ± 0.6 , respectively; $P=0.018$) when compared with intrapulmonary shunting, but could not otherwise be distinguished by baseline medical history or clinical laboratory values.

Of 67 patients with RLS, 32 had contrasted chest CT scans available for review. Vascular abnormalities seen in 15 subjects with intrapulmonary shunts included a dilated central 'classical' pAVM ($n=1$), pulmonary telangiectasias ($n=2$), prominent peripheral pulmonary vessels ($n=5$), both telangiectasias and prominent peripheral pulmonary vasculature ($n=3$), and none ($n=4$). Only one of these anomalies was felt to be accessible to interventional radiology for treatment. Seven of 17 individuals with intracardiac shunts had prominent peripheral pulmonary vasculature seen on chest CT, none of which were large enough for intervention.

Baseline pulse oximetry in 52 patients who had contrast echocardiography was obtained as part of pulmonary function testing. Ninety-four percent of subjects with Hb desaturation at rest ($SpO_2 \leq 95\%$ or on oxygen supplementation) had RLS on echo (16 of 17); however, 74% of subjects without Hb desaturation at rest also had RLS (26 of 35; $P=0.18$).

In our study, right-to-left shunting was diagnosed in 35% of an adult population with HbSS (67 of 190) when evaluated at clinical baseline by contrast echocardiography. This may have been an underestimate, since only 91 of 190 clinic subjects were screened. In addition to selection bias, this study was limited by its retrospective nature and by incomplete data, such as a limited number of subjects with baseline pulse oximetry. The relatively long time over which these data were accrued, without repeat studies, prevented us from understanding how RLS changed in individuals over time. Nonetheless, our data suggest that there are physiological consequences to RLS in patients with SCD, which warrant prospective evaluation.

Here, RLS was associated with an elevated ARC, LDH, and total bilirubin. Adult subjects with HbSS and RLS had a higher ARC despite a comparable total Hb. Although the association between Hb desaturation and RLS was not statistically significant in the population overall, functional shunting from RLS and resultant Hb desaturation, rather than anemia, may have driven reticulocytosis in some patients, contributing to overall disease burden. Dowling *et al.* evaluated a subset of children with HbSS and a history of stroke, and compared them with control children with neither diagnosis, and found RLS in 45.6% of children with HbSS and stroke compared with 23.6% in control children. However, the striking difference was not in intracardiac shunts, which were present in 21.8% and 18.7% of affected and non-affected children, respectively, but rather in intrapulmonary shunts, in 23.8% of affected children versus 5.7% of control children.⁸ We did not see any evidence for more cerebrovascular disease in our affected adult population, but this may be due to poor sensitivity for this complication and selection bias. In addition, subjects with both an intracardiac and an intrapulmonary shunt could not be identified in this study, but the findings of pulmonary vascular changes on CT scans of subjects

with intracardiac shunts suggested that these conditions may co-exist, and that the predicted number of intrapulmonary shunts may be under-estimated.

The etiology of intrapulmonary RLS is unknown. Peripheral arterio-venous shunts have been described in SCD.¹⁰ The association of systemic and localized hypoxia with angiogenesis in other disease processes is well established.¹¹ We postulate that deoxy-HbS-containing RBCs obstruct the pulmonary vasculature, leading to local hypoxemia, shunting, and eventual defective neo-vascular formation. Comparisons between intracardiac and intrapulmonary RLS, in our small study, showed a statistically significant lower TRV in patients with intrapulmonary shunts. This may be explained by lower overall pulmonary vascular resistance in patients with pAVMs,⁷ since dilated peripheral vessels and telangiectasias may represent a physiological 'pop-off' for increased pulmonary vascular pressure.

We speculate that there is a subset of pediatric and adult patients with RLS for whom shunting and, possibly, Hb saturation worsens at night, with exertion, or during clinical exacerbations. One could imagine significant sequelae if RLS exacerbated when fat emboli were being released into the venous circulation during crisis, allowing these toxic emboli direct access to the systemic circulation, potentially resulting in paradoxical emboli, the clinical observation of an altered mental status, and/or multi-organ failure. We are currently investigating the causes of reticulocytosis in patients with RLS (particularly if they are prone to night-time or exertional Hb desaturation) and the impact that these intrapulmonary shunts may have during clinical exacerbation.

Right-to-left shunting is common in adults with HbSS, showing provocative associations with high LDH, total bilirubin, and reticulocytosis, and could plausibly exacerbate morbidity if associated with excessive hemoglobin desaturation *in vivo*. This important clinical phenotype warrants a larger prospective study in order to fully characterize its origins and consequences.

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