Diastolic dysfunction in sickle cell

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In adults with sickle cell disease (SCD), echocardiographic evidence of diastolic dysfunction is an independent risk factor for death that is additive to pulmonary hypertension.1 In this issue of Blood, Johnson and colleagues describe echocardiography and polysomnography results from 44 children with SCD. Because their echocardiograms were ordered for clinical indications, potentially biasing toward more symptomatic patients, the reported prevalence of increased left ventricular mass should be interpreted with caution. Nevertheless, the results demonstrate left ventricular hypertrophy and diastolic dysfunction significantly correlating with low TcO2, both asleep and awake, and with systolic blood pressure.2 This confirms the association of left ventricular hypertrophy, diastolic dysfunction, and low waking TcO2 in 310 children with SCD reported by Dham et al.3

Low transcutaneous oxygen saturation (TcO2) in patients with sickle cell disease (SCD) has long been of concern to hematologists. Desaturations are explained by obstructive sleep apnea in only a minority of cases and have been associated with markers of activated endothelium, platelets and leukocytes, leukotriene B4, high von Willebrand factor, low hemoglobin, and high reticulocyte count.4,5 Johnson et al show in this issue that sleep and waking TcO2 are equally strong correlates of diastolic dysfunction in children with SCD, in agreement with their previous publication correlating awake and nocturnal TcO2.6 Although in their study of 44 patients, Johnson et al observe only a trend toward a link between low saturation and high tricuspid regurgitation velocity, an echocardiographic marker of pulmonary arterial pressure, this association has been confirmed more definitively in previous larger studies of 117 adults (P = .002) and 391 children (P = .003) with SCD.7,8 It is unclear whether low TcO2 is a cause or result of these cardiovascular changes.

In the general adult population, left ventricular hypertrophy and diastolic dysfunction have clearly been linked to systemic hypertension. The resting blood pressure range is lower among persons with SCD than in the general population, but Pegelow and others have documented in sickle cell patients that relative systemic hypertension that still falls within population norms predicts early mortality.9 Johnson et al’s study supports this concept with their multivariate analysis showing that systolic blood pressure percentiles are independent predictors of left ventricular mass index. The association of relative systolic hypertension and adverse clinical outcomes is a repetitive theme in SCD, meriting deeper investigation and treatment trials.

Finally, the current SCD paper links together the constellation of desaturation, hypertension, and diastolic dysfunction, although the causative sequence remains to be established. In adults without SCD, a similar syndrome that involves obstructive sleep apnea is a risk factor for cardiovascular disease.10 This syndrome is often linked to obesity, hypoxia, sympathetic activation, endothelial dysfunction, oxidative stress, and inflammation. The striking partial overlap between these 2 syndromes of intermittent/chronic hypoxia,
hypertension, and diastolic dysfunction invites additional comparisons and more detailed research.

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REFERENCES


Comment on Libourel et al, page 22

Arterial thrombosis complicates myeloma?

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Patients with MM have a high risk of VTE.1 The relationship between MM and ATE is less clear. In this issue of Blood, Libourel and colleagues report a high incidence of ATE in MM patients undergoing chemotherapy.2

Patients with hematologic malignancies are known to be at a higher risk for venous thromboembolism (VTE) than the general population.1 The pathophysiology of thrombosis in cancer is complex. Malignant cells interact with monocytes and macrophages and induce release of nosogenic cytokines that might induce endothelial damage (eg, tumor necrosis factor, interleukin-1, interleukin-6), and activation of platelets and coagulation factors including factors XII and X. Procoagulant molecules such as cysteine protease and tissue factor are highly expressed in cancer cells and can directly activate factors X and VII.4 Chemotherapy augments the risk of cancer-associated thrombosis by inducing vascular damage. As is the case with VTE, arterial thromboembolism (ATE) is increasingly being recognized as a complication of cancer (or its therapy), although the underlying mechanism is poorly understood. In one study, for example, the incidence of ATE among 66 106 hospitalized adult neutropenic patients with cancer was 1.5%.5

A recent report used population-based data from Sweden that included 18 627 patients with multiple myeloma (MM) and 5326 patients with monoclonal gammopathy of undetermined significance (MGUS), and found that their risk of both ATE and VTE was significantly higher than that of matched controls.4 Similarly, Libourel et al report a higher-than-expected ATE frequency in 195 newly diagnosed MM patients receiving 3 different chemotherapy regimens: thalidomide/adriamycin/dexamethasone (TAD), vincristine/adriamycin/dexamethasone (VAD), or bortezomib/adriamycin/dexamethasone (PAD), followed by high-dose therapy and stem cell transplantation.2 Of note, although oral immunomodulatory drugs (IMiDs) have been associated with VTE in patients with MM, ATE frequency was not significantly different among the 3 treatment arms. However, the results might have been confounded by the fact that TAD-treated patients were given low-molecular-weight heparin for VTE prophylaxis.

Not surprisingly, the risk of arterial thrombosis was strongly associated with smoking and hypertension but also with higher FVIII:C level, even after adjustment for age, tumor burden, and assigned treatment arm. Six of 11 events occurred during or shortly after induction chemotherapy, raising possible etiologic contribution from vascular injury, necrotic tumor cells, or superimposed infections. Similarly, 5 events occurred after stem cell transplantation, presumably during disease remission, suggesting that the observed ATE risk was related to established risk factors rather than myeloma. Regardless, the observations from the current study further support the potential value of prophylactic aspirin therapy to prevent both VTE and ATE during antymyeloma therapy, especially considering that 6 of the 11 events occurred despite systemic anticoagulant therapy with low-molecular-weight heparin or vitamin K antagonists. Whether or not the outcome would have been different had the patients received therapeutic rather than prophylactic drug doses is unknown. Studies in MM patients treated with thalidomide have demonstrated the risk of VTE is reduced by full-dose warfarin but not low–fixed-dose warfarin.1 On the other hand, a number of studies have confirmed that aspirin can reduce the risk of VTE with IMiDs.1 Further studies are warranted and the authors are correct in advocating that future trials should have arterial thrombosis as well as venous thrombosis as an end point.

Libourel et al make an important observation. They found an unusually high incidence of arterial thrombosis, a complication generally considered rare in MM patients. They leave us with questions regarding the mechanism and prevention of ATE, no doubt prompting a closer look at all these questions in the future.

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