Mini Review

Interventional Cardiology

# Blood pressure dynamics in sickle cell vaso-occlusive crisis: A mini-review

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## Abstract

Systemic hypertension during a sickle cell vaso-occlusive crisis is an important determinant of outcome of a vaso-occlusive episode in children with sickle cell disease. Previous studies related to blood pressure dynamics in sickle cell crisis lack scientific rigor and have not documented patterns of swings in blood pressure during crises. A significant proportion of patients develop transient but significant systemic hypertension, particularly those with severe vaso-occlusive crisis and pain scores of at least 8 in a 10-point scale. The hypertensive episodes usually respond to pain control with adequate doses of analgesics. However, those with blood pressures recorded in excess of stage 2 hypertension thresholds may require short-term non-pharmacological and pharmacological interventions to prevent escalation to hypertensive emergency.

**Keywords:** Blood pressure • Sickle cell crisis • Cerebrovascular events • $_{L}$-Arginine

## Introduction

A normal Blood Pressure (BP) is an important determinant of good cardiovascular health. A low or high blood pressure may have significant adverse effects on the heart, kidneys and the brain. If untreated significant blood pressure variability may impact on patient outcomes. In many pediatric clinics, blood pressure measurements are not routine as in the adults, thus creating a setting for inadvertent omission of hypertensive patients. This is particularly so in the busy emergency pediatric units in resource-constrained settings where facilities for patients' monitor are limited. The dramatic nature of presentation of children with sickle cell vaso-occlusive crisis may draw attention to the pain at the expense of other silent ongoing pathologies such as blood pressure elevations. This mini-review seeks to highlight the necessity for blood pressure monitoring and the potential for analgesics and non-pharmacological intervention in ameliorating abnormal blood pressure dynamics in children with sickle cell vaso-occlusive crisis.

## Literature Review

### *Blood pressure in non-crisis steady state sickle cell patients*

Sickle Cell Disease (SCD) is a genetic hematological condition characterized by substitution of thymine for adenine in the sixth codon of the β-globin chain gene with consequent replacement of hydrophilic glutamic acid by hydrophobic valine in the sixth position (β6Glu→Val) [1] resulting in chronic anaemia. During the non-crisis steady state, patients with sickle cell disease often have blood pressure readings that are usually lower than values obtained in non-sickle cell normal individuals [2-5]. The mechanism of the lower blood pressure measurements is attributable to progressive renal tubular defects caused by medullary and papillary ischemia from repeated vaso-occlusion in the vasa recta [2,3,6]. Loss of medullary tubules results in hyposthenuria

and natriuria and therefore a lower BP [7]. Furthermore, Pigelow, et al. [5] speculated that there may be preferential survival of those with lower blood pressure, because of the increased mortality noted in those patients with hypertension. Other mechanisms for the lower blood pressure in SCD such as altered vascular reactivity to angiotensin II, impaired response to major endothelial vasodilators such as nitric oxide, and decreased peripheral vascular resistance have been considered [3,8-10] and since none of these hypothesis have undergone thorough scientific scrutiny, they merit further investigation.

### *Blood pressure pattern in sickle cell vaso-occlusive crisis*

Sickle cell crisis is a term used to describe acute exacerbation in the manifestation of sickle cell disease such as vaso-occlusive bone pain crisis, aplastic crisis, acute chest syndrome, acute cerebral syndrome and sequestration crisis. The crisis state is a state of physical, emotional and oxidative stress to the patient. A transient increase in BP levels and/or increased BP variability is therefore not uncommon. Publications on blood pressure dynamics during sickle cell crisis show varying results and are mostly anecdotal [11,12]. Hemodynamic responses during sickle cell vaso-occlusive crisis including widened pulse pressure and an increase in heart rate and cardiac output may result in a transient rise in BP. These haemodynamic changes such as an increase in cardiac output were reported by Singer, et al. [11] in 8 adults with sickle cell crisis, while Onalo, et al. [4] reported a mean increase in heart rate of 12 beats per minute in 84 children with sickle cell vaso-occlusive crisis. Since blood pressure is a product of cardiac output and systemic vascular resistance, an increase in cardiac output is expected to increase the blood pressure. However, the Systemic Vascular Resistance (SVR) has been shown to dip by 27% during sickle cell crisis [11], which ameliorates the effect of high cardiac output on blood pressure levels. Contrary evidence to a drop in SVR may be concluded from a study by Lamarre, et al. [13] who documented an inverse correlation between nitric oxide levels and systemic vascular resistance. Nitric oxide is excessively consumed during a severe sickle cell crisis which may be associated with an increase in systemic vascular resistance, which, with the associated increase in cardiac output, may favour an elevation in blood pressure.

Evidence shows that the mean blood pressure [11] during a crisis approximates that of normal controls but, is about 5 mmHg above the steady state baseline (p=0.018) in a cohort of 8 adults with sickle cell crisis, 8 adults with non-crisis SCD and 36 non-sickle cell normal individuals. It can be concluded that patients in crisis have a higher blood pressure than those in a steady state, but may be normotensive if BP values are compared to normal values for patients who do not have SCD. Consequently some authors have erroneously concluded that sickle cell crises patients are normotensive.

Although Singer, et al. [11] and Ernst, et al. [12] did not conclude on the presence of hypertension during sickle cell crisis in their cohort of adult patients, Onalo, et al. [4] reported stage 1 hypertension in 40.2% of children hospitalized for vaso-occlusive episodes. The differences in the observations may be due to the age disparities of the cohorts studied. Baroreceptor responses to the haemodynamic effects of sickle cell crises such as stretch and distension on the vascular wall progressively decreases with age which may partly explain the dissimilarities [14-16]. Other explanations include variations in sample size. For example the Singer, et al. [11] study had a cohort of 8 adults, while the Onalo, et al. [4] study had a cohort of 84 children. The Ernst study [12] which had the largest sample size (106 adults with 459 vaso-occlusive episodes) did not distinguish between patients with normal BP (using definition adopted for non-crisis sickle cell disease patients) from those with relative hypertension and those with overt hypertension. Furthermore, the mean pain scores varied between the studies. In the Singer, et al. [11] series the pain score was 5 ± 2, suggesting mild to moderate pain which may provoke a milder sympathetic response that may not be enough to raise the BP, while in the Onalo, et al. [17] study, 30.3% of the patients had a pain score of 10 and 42.4% had pain scores of 8 and 9. The authors from the latter report demonstrated a 14 mmHg increase in systolic BP among children admitted with severe vaso-occlusive bone pain crisis. Only 5.6% of the patients had stage 2 hypertension at a pain score of 7, whereas 30% of patients with pain score of 10 had stage 2 hypertension. This correlation suggests a relationship between severity of pain and blood pressure elevation.

Acute pain generates an increase in sympathetic nerve activity [18], which may cascade into an increase in the BP. Various animals and human models [18-20] have demonstrated a correlation between painful stimulus and increase in BP. Forearm ischemia produced by transient blockade to blood flow by an inflated blood pressure cuff results in pain and the degree of pain correlates with the level of increase in BP and vascular resistance [19].

In addition, tissue ischemia results in infarction and tissue damage which causes the release of inflammatory cytokines and nuclear factor-KB that interacts with neuroendocrine pathway and increases sympathetic activity and vasoconstriction mediated through the postjunctional α1 and α2 adrenoceptors and cause an increase in the peripheral vascular resistance and therefore the blood pressure [21].

### *Clinical relevance of transient hypertension in sickle cell crisis*

Acute elevations in BP in response to stressors are often mild to moderate and have little clinical relevance. However, in a small proportion of patients, the BP elevation may be severe. Acute

severe hypertension (defined as acute elevation of BP from baseline with potential for life threatening end-organ damage) has been recorded in children with other severe sudden illnesses such as acute gastroenteritis who had no prior history of hypertension and whose clinical and biochemical parameters showed normal renal function [22]. BP values that fall under the definition of acute severe hypertension are usually in excess of stage 1 hypertension values and some authors [23] have shown that end organ effects of hypertension can seen in patients with BP values ≥ 95$^{th}$ percentile+30 mmHg. Other studies [24-26] undertaken in paediatric emergency departments have documented hypertensive emergency in 16%-54% patients, but only 0.4% had hypertensive crisis with end organ damage [27-29].

Although the clinical relevance of transiently elevated blood pressure is disputable, some authors [23] have initiated antihypertensive drugs in some patients with acute gastroenteritis who had transient hypertension with a mean systolic and diastolic BP of 150 ± 14 mmHg and 105 ± 11 mmHg, respectively with rapid resolution. There are arguments for and against treatment of transient elevations of stage 2 hypertension related to clinical stressors. There is a school of thought that acute blood pressure elevation beyond the level for stage 2 hypertension is not innocuous due to potential for end organ damage [22].

Literature abounds linking acute elevations in BP to various neurological problems such as poor sleep quality [30,31], strokes, a higher prevalence of silent cerebral infarcts and memory loss [32]. In the cooperative study of sickle cell disease [33] that involved 3,647 patients followed for an average of 5.2 ± 2.0 years, the relative risk of cerebrovascular accident was 1.31 per 10 mmHg increase in systolic blood pressure, p=0.033. However, it is not certain if the elevations in BP preceded the development of stroke or that the stroke was due to vascular occlusive disease [34].

Elevations in BP in stroke patients have also been documented and are required to maintain cerebral perfusion and keep the ischemic tissue viable. It may however aggravate cerebral oedema and can induce haemorrhagic transformation of an ischemia stroke in some patients. Therefore, the nature of BP fluctuations in SCD patients with acute cerebral syndrome should be acknowledged as this may be an important prognostic factor in the management of such patients.

Other documented complications of acute BP elevations can cause blindness, chest pain, personality changes, poor mental concentration ability, aortic dissection, pulmonary oedema and acute kidney injury [26-32].

### *Level of intervention required for transient hypertension in sickle cell crisis*

The transient nature of BP elevations during sickle cell crises which is mostly related to level of pain demands mainly pain control. High grade costly analgesia involving the use of opioid derived medications has excellent result. However, there has been a resurgence of the use of oral $_{L}$-Arginine and conventional analgesics with rapid resolution of pain associated with normalization of elevated BP in children with sickle cell vaso-occlusive crisis. A recent study by Onalo, et al. [17] confirmed this link and showed that non-drug interventions such as oral Arginine may have an equivalent BP lowering effect to analgesic agents.

Antihypertensive therapy may be indicated in a small number of patients with hypertensive emergencies in some cases of transient BP elevations such as was documented in children with acute gastroenteritis [22]. The pattern of BP elevation documented in the latter cohort [22] is similar to BP elevations seen in patients with sickle cell vaso-occlusive crises.

## Conclusion

Increased blood pressure variability with transient hypertension is not uncommon in children with sickle cell crises. Stage 2 hypertension may be documented in a small proportion of patients with Sickle Cell crises pain control and management of other associated stressors can lower blood pressure levels significantly within a few days. The need for antihypertensive should be individualized, particularly in those with symptomatic severe hypertension (blood pressures>95$^{th}$ +30 mmHg).

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