Breathing Patterns During Vaso-occlusive Crisis of Sickle Cell Disease*

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**Study objectives:** To determine the effect of sickle cell pain and its treatment on patients’ breathing patterns, and to compare the effect of thoracic cage pain to pain at other sites.

**Design:** Prospective, observational study.

**Setting:** Sickle Cell Center Day Hospital.

**Patients:** Twenty-five patients with sickle cell disease admitted to the Sickle Cell Center Day Hospital for treatment of vaso-occlusive crisis (VOC) [10 patients with chest (thoracic cage) pain].

**Interventions:** Breathing patterns were measured by respiratory inductive plethysmography. Tidal breathing data, including respiratory rate, tidal volume (VT), minute ventilation, and the rib cage contribution to VT, were collected at baseline and then following treatment with opioid analgesia.

**Measurements and results:** The patients with chest pain had smaller VTs at baseline than those with pain at other sites (355 ± 37 mL vs 508 ± 141 mL, p = 0.003), and higher respiratory rates (23.2 ± 8.2 breaths/min vs 17.6 breaths/min, p = 0.03). These differences became insignificant following opioid treatment. Six patients had respiratory alternans (four patients in the chest pain group, and two patients with pain at other sites). All cases of respiratory alternans resolved following opioid administration.

**Conclusions:** Patients with VOC and chest pain have more shallow, rapid breathing than patients with pain elsewhere. Analgesia reduces these differences. As pain-associated shallow breathing and maldistribution of ventilation may contribute to the pathogenesis of acute chest syndrome, these results support the need for adequate pain relief and monitoring of ventilatory patterns during the treatment of VOC.

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**Key words:** acute chest syndrome; respiratory alternans; respiratory inductive plethysmography; sickle cell disease

**Abbreviations:** ACS = acute chest syndrome; %R/C/V = contribution of rib cage motion to tidal volume; RIP = respiratory inductive plethysmography; SCD = sickle cell disease; VOC = vaso-occlusive crisis; VT = tidal volume

Sickle cell disease (SCD) is characterized by recurrent episodes of debilitating pain thought to be caused by microvascular occlusion by sickled RBCs, leading to areas of ischemia and bony infarction.1 These painful episodes, referred to as vaso-occlusive crises (VOCs), are the major cause of morbidity for the majority of patients with SCD, and the frequency of these episodes correlates inversely with survival in patients ≥ 20 years old.2,3 Acute painful crises can also co-occur with acute chest syndrome (ACS), a life-threatening condition characterized by a widened alveolar-arterial gradient and evolving pulmonary infiltrates.4–7

Patients with thoracic cage (chest and back) pain have been documented to have at increased risk of pulmonary complications, including ACS during treatment of VOC.8 One possible explanation is that thoracic cage pain could cause splinting of the chest wall with decreased tidal volumes (VTs), leading to areas of atelectasis and regional alveolar hypoxia, which could precipitate vasoconstriction of the pulmonary vasculature, sickling of RBCs, and further

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vascular occlusion. The use of incentive spirometry during VOC has been demonstrated to decrease the development of ACS, presumably by preventing atelectasis. Opioid analgesia continues to be a mainstay of treatment for VOC. It has also been suggested that opioid analgesia administered for pain control could cause depression of the respiratory drive leading to hypoventilation, which could cause global hypoxemia and precipitate ACS. Conversely, adequate control of thoracic cage pain might help prevent acute chest syndrome by reducing splinting, allowing larger V Ts, and avoiding regional hypoventilation and alveolar hypoxia.

The purpose of this study was to determine by objective measures the effect of sickle cell pain and its treatment on patients’ breathing patterns. We analyzed breathing patterns in patients with acute sickle cell pain before and after treatment, and compared the patients with chest pain to those with pain at other sites.

**Materials and Methods**

The Institutional Review Board of Montefiore Medical Center approved the study design. Written informed consent was obtained from all subjects prior to enrollment.

Patients with SCD were eligible for inclusion when they presented to the Sickle Cell Center Day Hospital for treatment of acute painful episodes if they had not received parenteral opioid therapy the day of hospital admission. Patients who were known to be pregnant, had chest wall anomalies, or diagnoses other than VOC were excluded. As standard procedure in the Sickle Cell Center Day Hospital, all patients were assessed initially and monitored continuously with ECG monitoring and pulse oximetry.

All patients completed a standardized pain assessment on admission to the hospital and at 30-min intervals after treatment was initiated. The assessment consisted of shading diagrams of human figures to indicate where the pain was located and numerical scores. The patient graded their overall pain on a scale of 0 to 3 and pain at nine sites on the same scale. The score for each site was summed for a total that ranged from a possible 0 (no pain at all) to 27 (maximal pain at all sites).

Breathing patterns were measured by respiratory inductive plethysmography (RIP) [Respirtrac 204; Non-Invasive Medical Systems; Miami Beach, FL]. After initial calibration using the qualitative diagnostic calibration method, volumetric calibration was then performed by having the patient breathe 10 breaths from a 700-mL bag. After collecting baseline data for a minimum period of 5 min, parenteral opioid analgesia was administered according to the Sickle Cell Center Day Hospital protocol as previously described. Ten minutes after administration of the opioid, incentive spirometry was performed for 10 maximal efforts, as part of the standard treatment in the Sickle Cell Center Day Hospital. Twenty minutes after administration of the opioid, data collection was terminated.

The RIP data were analyzed using the software (RespiEvents, Version 5.2c; Non-Invasive Medical Systems). Values for VT, minute ventilation, and contribution of rib cage motion to VT (%RC/VT) were computed breath by breath for 2-min intervals before treatment and at the end of the protocol. The breaths immediately before and after the incentive spirometry were analyzed to evaluate possible effects of the maneuver on respiratory patterns. The data were exported to statistics software (CSS Statistica, release 4.2; StatSoft; Tulsa OK), and means and SDs were calculated.

Statistical analysis was performed using CSS Statistica. Differences between groups were assessed using the t test for independent samples. Differences within groups before and after treatment were assessed using the t test for dependent samples. Correlations were analyzed using the Pearson product-moment correlation coefficient.

**Results**

Twenty-five patients completed the protocol (10 patients with chest pain). The mean age for patients in the chest pain group was 31 years (range, 22 to 45 years), and mean age was 33 years (range, 24 to 47 years) for the group with pain at other sites. No patient in either group had a diagnosis of ACS, and no patient had significant oxyhemoglobin desaturation develop (defined as a saturation measured by pulse oximetry of <92%). The mean ± SD pain sum score in the chest pain group was 13.0 ± 5.7 before treatment and 12.9 ± 6.7 following the opioid administration (differences not significant). The mean pain sum score in the group with pain at other sites was 9.2 ± 3.5 before treatment and 8.5 ± 3.9 afterwards (differences not significant). Eight patients had reductions in their total pain scores following the initial opioid administration (four patients in the chest pain group). None of the patients in the chest pain group had improvement in the scores for their chest sites, even if their overall pain scores decreased.

Tidal breathing parameters at baseline are summarized in Table 1. The patients with chest pain had smaller VTs at baseline and higher respiratory rates than the patients with pain elsewhere. There were no differences in minute ventilation, the %RC/VT, or the SD of %RC/VT over 2 min (a measure of variability in respiratory pattern) between groups before treatment. There was no correlation between VT and the %RC/VT (r = −0.07).

Following opioid treatment, the differences in VT,

| Table 1—Breathing Patterns at Baseline* |
|-------------------------------|-----------------|-----------------|-----------------|
| **Variables** | **Chest Pain** | **Other Pain** | **p Value** |
| Respiratory rate, breaths/min | 23 ± 8.3 | 17.7 ± 3.4 | 0.04 |
| VT, mL | 363 ± 54 | 501 ± 144 | 0.009 |
| RC/VT, % | 41 ± 13.6 | 40 ± 8.7 | NS |
| SD of RC/VT, % | 10.9 ± 4.3 | 15.7 ± 9.8 | NS |
| Minute ventilation, mL/min | 8.275 ± 2.988 | 9.269 ± 3.956 | NS |

*Data are presented as mean ± SD. NS = not significant.
respiratory rate, and the other tidal breathing parameters became insignificant (Table 2). There was no significant difference in VT or respiratory rate before and after treatment in either group. There was no oxyhemoglobin desaturation in either group before or after administration of analgesia. No patient demonstrated any change in respiratory pattern, respiratory rate, or VT immediately following incentive spirometry.

Respiratory alternans, a pattern of respiration characterized by alternating chest and abdominal predominance, was evaluated by plotting \%RC/VT on a breath-by-breath basis. Six patients had respiratory alternans (four patients in the chest pain group, and two patients with pain at other sites). All cases of respiratory alternans resolved following opioid treatment.

**Discussion**

We have shown that patients with VOC and chest pain have more shallow, rapid breathing than patients with pain elsewhere. The patients with chest pain compensate for their smaller VTs with a higher respiratory rate and therefore have no significant difference in minute ventilation. However, their rapid, shallow breathing pattern may mean that they had smaller levels of alveolar ventilation than did those without chest pain.

The response to opioid administration of individual patients was variable. Although analgesia administration appeared to reduce the differences in VT and respiratory rate between the chest pain and non-chest pain groups, the changes within each group were not significant. This is possibly due to the incomplete response to analgesia as reported in the pain scores. No patients reported complete relief from pain during the study period; some chest pain patients reported partial relief of pain in areas outside their thoracic cage. This variable response to the treatment limits our ability to completely evaluate the impact of analgesia on breathing patterns in the time course of our study, but chest pain does appear to alter respiratory patterns. Alternatively, our failure to detect significant change in breathing patterns following opioid administration may be due to the inability of our small sample size to detect a small effect.

The patients with chest pain did not have a reduced rib cage contribution to their VT despite their rapid, shallow breathing pattern. The \%RC/VT parameter measures rib cage contribution as a percentage of VT, so patients with lower VTs have less absolute chest wall movement even if their \%RC/VT is unchanged. The lack of correlation between \%RC/VT and VT is consistent with chest pain causing more shallow breathing through splinting, rather than merely altering the relationship between the rib cage and abdomen.

The presence of respiratory alternans may represent a response to unrelieved pain and an attempt to find a breathing strategy more comfortable for the patient. As such, it is perhaps comparable to the respiratory alternans seen in diaphragmatic fatigue, which also probably results from discomfort and an attempt to find a more comfortable breathing strategy. However, the respiratory alternans we observed is unlikely to be due to fatigue, because our patients did not have the respiratory overload condition (due either to excessive load or impaired strength) that produces fatigue. The disappearance of respiratory alternans with analgesia suggests that its resolution is either a response to the partial pain relief of the treatment or the sedation and central nervous effects of the opioid.

The increased risk of ACS that has been demonstrated in patients with chest pain and VOC is thought to indicate that chest pain is a marker for early ACS. An alternative explanation is that pain-associated shallow breathing may lead to maldistribution of ventilation and regional alveolar hypoxia, which, in an animal model, has been shown to cause local sickling and entrapment of RBCs in the pulmonary circulation. Thus, chest pain and the consequent splinting could contribute to the pathogenesis of ACS.

As pain causes shallow breathing with irregular patterns, such as respiratory alternans, our results suggest that effective pain management could be important in preventing pulmonary complications of SCD. It is encouraging that while the subjects’ minute ventilation tended to decrease following treatment, the decrease was small, nonsignificant, and may well have been only because dead space ventilation was less. It is also important to note that no patients had oxyhemoglobin desaturation develop. This was following one dose of opioid, how-

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**Table 2—Breathing Patterns Following Treatment**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Chest Pain</th>
<th>Other Pain</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>20.6 ± 7.4</td>
<td>16.8 ± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>VT, mL</td>
<td>376 ± 107</td>
<td>440 ± 107</td>
<td>NS</td>
</tr>
<tr>
<td>RC/VT, %</td>
<td>39 ± 10</td>
<td>43 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>SD of RC/VT, %</td>
<td>9.3 ± 7.7</td>
<td>17.3 ± 13.3</td>
<td>NS</td>
</tr>
<tr>
<td>Minute ventilation, mL/min</td>
<td>7,560 ± 3,066</td>
<td>7,973 ± 3,956</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD. See Table 1 for expansion of abbreviation.*

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ever, and does not rule out a deleterious effect of multiple doses over a prolonged treatment period.

Our results support the need for adequate pain relief with appropriate monitoring during the treatment of VOC. Analgesia must be adequate to allow patients to breathe comfortably and prevent the possible development of atelectasis and/or regional alveolar hypoxia. RIP may prove to be a useful adjunct to bedside monitoring for brief periods. The relationship between VTs, distribution of ventilation, and the development of ACS is speculative at this time, but warrants further investigation.

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