Reduction of Pulmonary Capillary Blood Volume following Cold Exposure in Patients with Raynaud's Phenomenon

Walter G. Barr, M.D.; and Patrick J. Fahey, M.D., F.C.C.P.

In a previous study we induced digital vasospasm with cold pressor stimulus, and an acute decrease in the lung diffusing capacity for carbon monoxide (Dsb) resulted. We hypothesized its cause to be spasm occurring simultaneously in the pulmonary vasculature and the digital arteries. We measured in this study the Dsb, the diffusing capacity of the pulmonary membrane (Dm), and the volume of blood in the pulmonary capillaries (Vc) after cold-induced digital vasospasm in patients with Raynaud's phenomenon. Control subjects showed no significant decrease in Dsb, Dm, or Vc after cold exposure. Eight of 12 subjects with Raynaud's phenomenon had a significant decrease in Dsb 60 min after testing (25.3 ± 6.6 vs. 19.8 ± 6.1 ml/min/mm Hg, p < 0.01). The acute decrease in Dsb was due to a significant decrease in Vc (54 ± 20 vs. 39 ± 10 ml, p < 0.05), while Dm was unchanged (52 ± 17 vs. 51 ± 20 ml/min). Four subjects who had a decrease in Dsb after cold challenge had repeated studies later after pretreatment with sublingual nifedipine. The magnitude of change in Dsb was similar to that observed in the untreated state (23.6 ± 10.6 vs. 20.9 ± 9.6 ml/min/mm Hg). We conclude that digital vasospasm is accompanied by an acute reduction in Vc in both primary and secondary Raynaud's phenomenon and indicates concurrent vasoconstriction within the pulmonary vasculature. (Chest 1988; 94:1195-99)

\[
\begin{align*}
Dsb &= \text{diffusing capacity of CO, single-breath method;} \\
Dm &= \text{diffusing capacity of alveolar capillary membrane;} \\
Vc &= \text{capillary blood volume; SLE = systemic lupus erythematosus}
\end{align*}
\]

Raynaud's phenomenon is recognized clinically by characteristic color changes in the fingers that occur after paroxysmal vasospasm of the digital arteries. Similar findings are less commonly observed in the toes, ears, and nose. Clinical observations now suggest that cold-induced vascular spasm is not limited to these acral regions. Raynaud's phenomenon has been associated with cerebral artery spasm and migraine headache as well as with coronary artery spasm. In patients with Raynaud's phenomenon and scleroderma, vasospasm in the circulation of the kidneys, heart, and lungs has been reported after cold challenge. For some patients with Raynaud's phenomenon the diagnostic changes in skin color seem to reflect a more generalized vasospastic disorder.

In a previous study we demonstrated an acute reduction in the lung diffusing capacity for carbon monoxide by single-breath method (Dsb) following the induction of digital vasospasm with cold pressor stimulus. We hypothesized that this was due to spasm occurring simultaneously in the pulmonary vasculature.

The current study was undertaken in a different laboratory with a different group of patients than our first study, but in addition to measuring Dsb in this study, we calculated the determinants of Dsb including the diffusing capacity of the pulmonary membrane (Dm) and the volume of blood in the pulmonary capillaries (Vc) before and following the induction of Raynaud's phenomenon. We reasoned that a decrease in Dsb accompanied by a decrease in Vc and no change in Dm would support our hypothesis that pulmonary vasospasm accompanies digital vasospasm. Finally, we wished to evaluate what effect pretreatment with nifedipine, a calcium channel-blocking agent known to reverse pulmonary vasospasm, would have on the change in Dsb.

**Material and Methods**

Five healthy (three female), nonsmoking laboratory personnel served as control subjects. They had no history of vascular disorders or Raynaud's phenomenon. The study group consisted of 12 nonsmoking subjects, all of whom regularly developed bilateral digital color changes typical of Raynaud's phenomenon following exposure to cold. Ten of the 12 patients studied were classified as primary or idiopathic Raynaud's phenomenon by the clinical criteria of Allen and Brown. Observations of skin capillaries were performed by in vivo widefield capillaroscopic technique on all patients as described by Maricq et al. The nailfolds of at least six fingers were examined by the senior author (W.G.B.). No patient had scleroderma-type capillary abnormalities. Patients were screened for the presence of anticentromere antibody, and all were negative. Two patients met American Rheumatism Association criteria for systemic lupus erythematosus (SLE). None of the patients or control subjects was taking vasoactive medication at the time studied. Two patients were taking nifedipine before the study and discontinued taking the drug 48 h prior to testing. Two patients were taking 10 mg/day of prednisone or less, and one patient was taking naproxen on the study day.

**Pulmonary Function Tests**

Expired lung volumes and flow rates were determined using a
dry rolling seal spirometer (P.K. Morgan, Inc.) Thoracic gas volume at functional residual capacity was measured by a variable pressure, constant-volume body plethysmograph (Cardiopulmonary Instruments). The Dsb was measured using the methods of Ogilvie et al.\(^8\) The mean value of three tests was determined at baseline and repeated 60 minutes after cold pressor testing. Sixty minutes was chosen, because our previous studies indicated that this period was associated with the largest decline in Dsb.\(^4\) Subjects inhaled five vital capacity breaths of 1.0 FlO\(_2\) immediately before measurement of Dsb with the 0.90 O\(_2\) concentration. This was done to wash out N\(_2\) and ensure an alveolar O\(_2\) of near 0.90. Determination of Vc and Dm was performed using the equation of Roughton and Forster:\(^11\)

\[
\frac{1}{D_1} = \frac{1}{D_{D}_{S}} + \frac{1}{D_{V}}
\]

where \(\Omega\) equals the reaction rate of carbon monoxide with Hb at standard conditions. By measuring Dsb at two different inspired O\(_2\) concentrations (0.21 and 0.90), paired values for Dsb and 0 are determined. This permits calculation of the value for Vc and Dm using the method of Cotes.\(^13\)

Predicted values for expired lung volumes, including vital capacity and forced expiratory volume in one second (FEV\(_1\)), were those of Morris et al;\(^13\) for lung volumes, of Ogilvie et al;\(^8\) and for Dsb, of Miller et al.\(^14\) Measurements were made in triplicate and the mean value determined.

**Cold Challenge Test**

Patients and control subjects were exposed to a standard cold water immersion test in which both hands were submerged in 15°C water for periods of 2 to 10 min as tolerated. Immersion periods of longer than 2 min were usually accomplished in additive 2-min increments with brief 1- to 2-minute intervals when patients were evaluated for the development of blanching or cyanosis. If test subjects did not develop digital blanching or cyanosis along with erythema following 10 minutes of ice water immersion, cold pressor testing was terminated. Two patients with primary Raynaud's phenomenon were exceptions. In one case exposure to a walk-in freezer (\(-20^\circ\)C) for 2 min produced Raynaud's phenomenon, while in the other case a 3-min walk outside on a winter afternoon (\(-3^\circ\)C) resulted in digital blanching.

**Nifedipine Testing**

Four patients with Raynaud's phenomenon who demonstrated an acute reduction of Dsb following cold pressor testing were tested on a separate day following administration of 10 mg of nifedipine sublingually 30 minutes before cold challenge.

**Statistical Analysis**

Mean values and standard deviation were calculated by standard equations.\(^15\) Student's \(t\) test was used to compare mean results; paired data were used when indicated.

**RESULTS**

Control subjects developed erythema of the digits following cold stimulus but no blanching or cyanosis. Of 12 patients with a history of Raynaud's phenomenon, eight developed finger blanching or cyanosis along with reactive erythema following cold challenge. Four patients who were classified as having primary Raynaud's phenomenon demonstrated only erythema after cold exposure. These patients did not have a fall in Dsb following cold challenge.

Baseline pulmonary function test results were within normal limits in all patients and control subjects (Table 1). Lung volumes and expiratory flow rates did not change significantly in either group following cold challenge. Control subjects did not show a significant change in Dsb (24.7±4.3 vs 23.5±4.0 ml/min/mm Hg, \(p>0.05\)), Vc (63±17 vs 57±20 ml, \(p>0.05\)), or Dm (51±15 vs 57±24 ml/min/mm Hg, \(p>0.05\)) after cold pressor testing.

Eight patients with Raynaud's phenomenon including six cases of primary disease and two patients with SLE demonstrated a significant decrease in Dsb measured 60 min after cold stimulus (Fig 1). In this group of responders the mean Dsb±SD was 25.3±6.5 ml/min/mm Hg before cold challenge vs 19.8±6.1 ml/min/mm Hg after (\(p<0.01\)). The acute decrease in Dsb was due to a significant decrease in Vc (54±20 ml before vs 39±10 ml after, \(p<0.05\)) (Fig 2). No

| Table 1—Clinical Characteristics of Subjects with Raynaud's Phenomenon* |
|-----------------------------|-----------------|-----------------|-----------------|
| Patient No. | Sex | Age, yr | Diagnosis | VC, L | TLC, L | Dsb, ml/min/mm Hg |
| Responder 1 | M  | 56  | Primary    | 4.7 (128) | 4.0 (87) | 19.6 (71) |
| 2 | F  | 66  | SLE         | 2.3 (80)  | 3.8 (80) | 15.6 (75) |
| 3 | F  | 35  | SLE         | 4.1 (97)  | 4.9 (77) | 20.8 (77) |
| 4 | M  | 24  | Primary     | 6.0 (120) | 7.2 (109) | 31.2 (87) |
| 5 | F  | 20  | Primary     | 5.0 (115) | 6.6 (106) | 28.1 (101) |
| 6 | M  | 24  | Primary     | 6.3 (106) | 7.4 (83)  | 35.2 (92) |
| 7 | F  | 25  | Primary     | 3.7 (91)  | 5.3 (90)  | 24.1 (90) |
| 8 | M  | 65  | Primary     | 4.3 (103) | 7.2 (107) | 27.8 (101) |
| Mean ± SD  | 40±20 | 4.6 (103) | 5.9 (94) | 25.3 (87) |

| Nonresponder 9 | F  | 37  | Primary    | 4.4 (108) | 6.8 (113) | 22.9 (88) |
| 10 | F  | 31  | Primary    | 4.4 (103) | 5.4 (86)  | 22.4 (83) |
| 11 | F  | 32  | Primary    | 3.6 (90)  | 4.9 (84)  | 22.4 (85) |
| 12 | F  | 58  | Primary    | 4.6 (99)  | 4.6 (99)  | 14.8 (70) |
| Mean ± SD  | 40±13 | 4.3±0.4 (100) | 5.4±1.0 (96) | 20.6±3.9 (82) |

*Values are mean ± SD. Definitions and abbreviations: Responder refers to the development of digital color changes of Raynaud's phenomenon following cold pressor testing. VC = vital capacity; TLC = total lung capacity; Dsb = lung diffusing capacity for carbon monoxide; SLE = systemic lupus erythematosus. ( ) indicates percent predicted value.

Reduction of Pulmonary Capillary Blood Volume (Bar. Fahey)
significant change in $D_m$ ($52 \pm 17$ vs $51 \pm 21$ ml/min/mm Hg, $p>0.05$) was observed in these seven patients after cold challenge.

The four patients who were treated with 10 mg sublingual nifedipine 30 min before cold pressor testing had a fall in $D_{sb}$ similar in magnitude to that seen in the untreated state (Table 2).

### Table 2—Effect of Nifedipine Prior to Cold Pressor Test ($N=4$)*

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{sb}$, ml/min/mm Hg</td>
<td>$23.6 \pm 10.6$</td>
<td>$20.9 \pm 9.6$</td>
</tr>
<tr>
<td>$Q_c$, ml</td>
<td>$62 \pm 27$</td>
<td>$43 \pm 12$</td>
</tr>
<tr>
<td>$D_m$, ml/min/mm Hg</td>
<td>$39 \pm 19$</td>
<td>$52 \pm 34$</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. Abbreviations: $D_{sb}$ = diffusing capacity of lung for carbon monoxide; $Q_c$ = volume of blood in pulmonary capillaries; $D_m$ = diffusing capacity of alveolar-capillary membrane.

**Discussion**

For nearly a half century there has been interest in the changes in pulmonary function that occur in patients with Raynaud's phenomenon following exposure to cold. In 1941 Altschule and co-workers measured lung volumes before and after cold exposure in three patients with Raynaud's phenomenon. Total lung capacity, vital capacity, functional residual capacity, residual volume, and tidal volume did not change. They concluded that "the blood vessels of the lungs do not react in a manner similar to the hands and feet."

The ability to easily and reproducibly measure diffusing capacity provides a tool with the capability of measuring the changes in pulmonary vascular blood volume that would be expected to accompany spasm in the pulmonary vascular bed. Emmanuel and co-workers measured $D_{sb}$ in patients with scleroderma during winter and summer months. They found lower values for $D_{sb}$ during the winter and speculated that cold-induced vasospasm of the pulmonary vessels might be responsible. This observation in part stimulated our previously reported study in which $D_{sb}$ was measured in patients with Raynaud's phenomenon, 15, 45, and 120 min after cold pressor testing. As in the study by Altschule et al, there was no change in lung volumes following cold exposure. However, we did observe an acute and significant reduction in the $D_{sb}$, but only in patients with normal baseline pulmonary function test results. Since other causes of acute reduction in $D_{sb}$ including anemia, peripheral pooling of blood, performance of Valsalva's maneuver, and development of airway obstruction were ruled out, we attributed the change to an acute reduction in the size or number of functioning pulmonary capillaries. We reasoned that the change occurred because of cold-induced spasm of the pulmonary circulation.

The current study was performed using a different group of patients in a new laboratory and corroborates our previous findings. Eight of 12 patients with Raynaud's phenomenon showed an acute reduction in the $D_{sb}$ following cold pressor testing. This group of eight patients included six with primary Raynaud's phenomenon and two patients with SLE who had normal pulmonary function tests. Further, we showed that the
fall in Dsb is secondary to a reduction in the pulmonary capillary blood volume, which would be anticipated in the setting of spasm within the pulmonary circulation. This finding is in keeping with other more invasive, direct evidence of cold-induced vascular spasm in the lung. Naslund and co-workers reported an acute increase in the pulmonary artery pressure following injection of chilled saline solution into the pulmonary artery of a patient with scleroderma. Furst et al demonstrated a decrease in pulmonary perfusion by lung scan in five of nine patients with scleroderma after immersion of the hands in ice water. Since the structure of the digital arteries is not unique, it might be surprising if Raynaud's phenomenon were limited to the acral areas. The pulmonary vasculature, which in the past had been viewed largely as a passive bystander controlled by changes in the systemic circulation, is now known to have intrinsic regulatory capabilities. The pulmonary arteries respond to a wide variety of physiologic and pharmacologic stimuli. They constrict vigorously in response to hypoxemia and acidemia, and in laboratory investigations to sympathetic stimulation, as well as parenterally administered catecholamines. Clearly, blood vessels in the lung and the extremities share some currently recognized stimuli to vasoconstriction.

The pathophysiology of Raynaud's phenomenon is not well understood. Theories include an overstimulation of the sympathetic nervous system, local vascular abnormalities, serum vasoconstrictor substances, and abnormalities of blood viscosity. It is likely that multiple factors are responsible and that they vary from patient to patient depending on the underlying disease. Until the pathogenesis of Raynaud's phenomenon is better understood, one can only speculate as to the reason pulmonary vessels might constrict when digital vasospasm is experienced.

Our data differ from those of Wise et al and Miller. Wise et al observed that patients with Raynaud's phenomenon in the absence of scleroderma experienced an increase in Dsb after sitting between two hypothermia blankets for 15 to 30 min. Immediately after the onset of Raynaud's phenomenon, while the patients were still seated on the hypothermia blanket, the Dsb was measured in triplicate at 5-min intervals. The group of patients with scleroderma showed no change in Dsb. Miller used immersion of the right hand in water at 15°C for 2 min as a cold pressor test and measured the Dsb during the second minute of hand immersion. He noted a significant increase in Dsb in the patients with isolated Raynaud's phenomenon and no change in normal control subjects or in patients with systemic sclerosis.

Only one of our control subjects and none of the patients experienced a significant increase in Dsb after cold challenge. These apparently conflicting results may be explained by differences in the nature of the cold stimulus or the time when the Dsb was measured. In our previous study we reported a reduction in Dsb at 15, 45, and 120 min after cold pressor testing. Values taken at 120 min were lower than those at 15 min. Studies measuring Dsb during or immediately following cold challenge may miss the decline in Dsb that we observed.

Patient selection may also play a role. A wide variability exists in the responsiveness of the pulmonary circulation among individuals. Within our group of patients, we found four with primary Raynaud's phenomenon who did not experience a reduction in Dsb following cold pressor testing. It seems unlikely that patient selection completely explains the differing results, since the findings in this study were similar to those in our previous study in spite of a different study population.

Shuck et al studied nine patients with scleroderma and directly measured pulmonary artery pressure and pulmonary vascular resistance following immersion of the patient's hand in cold water at 10 to 15°C. During Raynaud's phenomenon there was no significant rise in mean pulmonary artery pressure or pulmonary vascular resistance. They concluded that pulmonary vasospasm does not occur in patients with scleroderma during episodes of Raynaud's phenomenon. These results do not conflict with the data from our previous study, as well as those of Wise et al and Miller, which showed no change in the Dsb following cold pressor testing in patients with scleroderma. The lack of responsiveness in the pulmonary vasculature of these patients with scleroderma may be due to a fixed pulmonary vascular volume. Shuck et al did not report pulmonary function data on their patients. We have not observed a reduction in Dsb following a cold pressor test in any patient with lung volumes or Dsb below 65 percent of predicted. None of the patients in our current study had systemic sclerosis or evidence by capillary microscopy or serology to suggest a prescleroderma state.

Fisher and co-workers studied 27 patients with pulmonary hypertension treated with 20 mg of sublingual nifedipine. The six patients who experienced the greatest reduction in pulmonary arterial pressure were those with Raynaud's phenomenon. The authors concluded that Raynaud's phenomenon may be an indicator of those patients with an active pulmonary vasospastic process. Four of our patients were pretreated with 10 mg of nifedipine given sublingually 30 min before cold challenge. In spite of treatment, all patients experienced a fall in Dsb that was comparable to the reduction in the untreated state. These patients also developed Raynaud's phenomenon after nifedipine. It is possible that the dose of nifedipine we chose was too low or the stimulus too great to demonstrate...
any measurable improvement.

The clinical significance of pulmonary vasospasm in patients with Raynaud's phenomenon is not known. In patients who ultimately develop scleroderma it may be one of several factors contributing to the vasculopathy characteristic of that disease. In patients with idiopathic Raynaud's phenomenon it may have the same benign implications for the lungs that digital vasospasm has for the fingers. Only additional studies can clarify the true significance of these observations.

REFERENCES