Enhanced Cholinergic Cutaneous Vasodilation in Raynaud's Phenomenon

Faisel Khan, PhD; Jay D. Coffman, MD

Background Vasodilator function was determined in patients with Raynaud's phenomenon during intra-arterial infusions of the endothelium-dependent and -independent vasodilators, methacholine and sodium nitroprusside, respectively. Reactive hyperemia, induced by 5 minutes of arterial occlusion with exercise, was also measured.

Methods and Results Total blood flow was measured in the fingertip and forearm by venous occlusion plethysmography, and blood flow in the forearm skin was determined with laser Doppler flowmetry. Basal fingertip blood flow was not significantly different between control subjects and patients with Raynaud's phenomenon. Infusions of methacholine had no significant effect on fingertip blood flow in control subjects, whereas patients with Raynaud's phenomenon showed a significant increase in fingertip blood flow. Basal total forearm blood flow was significantly lower in patients with Raynaud's phenomenon than in control subjects. Infusions of methacholine and sodium nitroprusside produced dose-related increases in total forearm blood flow that were of similar magnitudes in the two groups, as were the reactive hyperemic responses. Laser Doppler measurements of forearm skin blood flow, however, showed a significantly greater vasodilator response to methacholine in patients with Raynaud's phenomenon than in control subjects. Infusions of sodium nitroprusside produced a relatively small vasodilator response in the skin of the forearm that was smaller than that to methacholine and not significantly different between the two groups.

Conclusions In Raynaud's phenomenon, a greater vasodilator response to infusions of methacholine in the fingertip, where changes in blood flow mainly reflect those of skin, and in the skin of the forearm may reflect increased responsiveness of cutaneous blood vessels to stimulation of the endothelium. The mechanism involved is unclear but may result from a general abnormality of blood vessels in the skin, which is related to the pathophysiology of cutaneous vasospasm.

Key Words • Raynaud's phenomenon • vasodilation • endothelium • flow

Raynaud's phenomenon is manifested classically by pallor of the digits, reflecting arterial vasospasm followed by cyanosis and rubor. The two major theories to explain the vasospasm seen in patients with primary Raynaud's disease are an increased sympathetic nervous activity and a local abnormality in the digital blood vessels. Possible factors contributing to the local abnormality are increased sensitivity of \( \alpha_1 \)-adrenoceptors and serotonin receptors on the finger blood vessels. In addition, lower digital pressures may play a role in promoting vasospasm of the digits because of a decrease in the transmural arterial distending pressure. In secondary Raynaud's phenomenon, the pathophysiology could be related to an underlying condition and may involve digital artery occlusions, a low digital artery pressure, a thickened vessel wall, or an increase in blood viscosity. The precise pathophysiology of Raynaud's phenomenon, however, remains unclear. Consequently, current therapy for Raynaud's phenomenon does not provide complete relief of symptoms; therefore, further elucidation of the mechanisms producing vasospasm of the digits is required. The role of platelet vasoactive factors, \( \beta \)-adrenoceptors, neuropeptides, and the endothelium in Raynaud's phenomenon may provide useful insight into the disease.

The role of the endothelium in Raynaud's phenomenon may be of particular importance because the endothelium plays an important role in the regulation of vascular tone by producing various factors such as endothelium-derived relaxing factor, endothelium-derived hyperpolarizing factor, prostanoids, and endothelin. Abnormalities of endothelial function might be responsible for the impaired vascular function seen in various diseases such as hypercholesterolemia, hypertension, and diabetes mellitus. Vasospasm of the coronary artery may be due to a defect in endothelial vasodilator function, which is of considerable interest because it has been proposed that variant angina, migraine, and Raynaud's phenomenon may be related and caused by a generalized underlying defect. The purpose of the present study, therefore, was to assess the functional integrity of the vascular endothelium in patients with Raynaud's phenomenon. To determine if there was a generalized abnormality of the vascular endothelium, blood flow responses in the fingertip and forearm were measured during brachial artery infusions of the endothelium-dependent vasodilator methacholine.

Methods

Patients and Subjects

A total of 12 women with Raynaud's phenomenon (age range, 24 to 66 years; mean±SEM age, 42.5±4 years) and 14 normal subjects (8 women and 6 men) (age range, 21 to 57 years; mean±SEM age, 31.4±3 years) participated in the study, which was approved by the institutional review board for human studies. All participants gave informed consent. Baseline clinical characteristics of the participants are given in Table 1. Not all normal subjects or patients had both forearm and fingertip blood flow (FABF and FTBF, respectively) studies performed. No participant had evidence of atheroscler-

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From the Peripheral Vascular Section, Evans Memorial Department of Clinical Research, Boston University Medical Center, Boston, Mass.

Correspondence to Jay D. Coffman, MD, Peripheral Vascular Section, Evans 411, The University Hospital, 88 East Newton St, Boston, MA 02118.
rosis, hypertension, or hypercholesterolemia. Patients with Raynaud’s phenomenon, gave a clear history of episodic attacks of well-demarcated color changes of the digits in response to cold. Five patients had elevated antinuclear antibodies (2 with 1:320, 2 with 1:640, and 1 with 1:1280), and 3 had mildly elevated levels of 1:80. Nailfold capillaries were normal in all patients, and there were no systemic symptoms except for 2 patients who had heartburn. Four patients were taking vasoactive agents (3 receiving nifedipine and 1 receiving an angiotensin-converting enzyme inhibitor), which were stopped 1 week before the day of study. No participant had taken nonsteroidal anti-inflammatory medication for at least 4 days before the study, and cigarette smoking was stopped on the night before the study.

**Experimental Protocol**

Studies were performed in a temperature-controlled laboratory set at 21°C to 22°C, with participants relaxed in the supine position and dressed in only a hospital gown. After 20 minutes equilibration, a 20-gauge catheter was placed into the brachial artery just above the level of the elbow under sterile conditions after local anesthesia with 2% lidocaine. The catheter was connected to a three-stopcock bank for infusion of drugs and measurement of arterial blood pressure and was maintained with 0.9% saline. If the drugs were used, they were dissolved just before infusion and administered with constant-infusion pumps (Harvard Apparatus, South Natick, Mass). Vasoconstrictor responses were measured in the fingertip and the forearm in separate experiments.

**Measurement of FTBF**

Total FTBF was measured by air-displacement venous occlusion plethysmography with the hand positioned slightly above heart level. The plethysmograph consisted of a finger cuff attached to the fingertip beyond the interphalangeal joint and made airtight with caulking compound. Venous occlusion was produced with a 2.5-cm pneumatic cuff placed proximally to the finger cuff. At the start of each experiment, the lowest venous occlusion pressure required to produce the maximum rate of increase in the volume of fingertip was determined and ranged from 60 to 70 mm Hg. Changes in fingertip volume were measured with a Varidyne low-pressure transducer (MP 45-14; Varidyne, Northbridge, Calif) connected to the outlet of the finger cuff with stiff plastic tubing and recorded with a Hewlett-Packard 8805B preamplifier and recorder. To calibrate the recording system, a known quantity of air was introduced into the system. The volume of the fingertip used was determined by water displacement. Finger blood inflow angles were measured manually using at least three pulse beats; cuff artifacts were excluded.

After an additional 20 minutes equilibration, baseline measurements of FTBF were made every 15 seconds during infusion of 0.9% saline and averaged over 10 minutes. Vasoconstrictor responses were then measured during increasing doses (10, 20, and 40 µg/min) of intra-arterial infusions of methacholine chloride (Sigma Chemical Co, St Louis, Mo) dissolved in 0.9% saline. Each dose was infused for 4 minutes, and FTBF was measured every 15 seconds. If FTBF increased, then measurements for that dose were averaged once a stable level was achieved. If no increase occurred, then all measurements after 90 seconds were averaged. All subjects and patients received all three doses; the dose was not increased if very large increases in FTBF occurred in the patients. Therefore, 1, 4, and 5 patients received 10, 20, and 40 µg/min, respectively. In the normal subjects, the dose was not increased if systemic mean blood pressure decreased by 5 mm Hg or more or capillary blood flow increased. Therefore, 2 and 8 normal subjects received 20 and 40 µg/min, respectively.

**Measurement of FABF**

These experiments were performed on occasions separate from those for measurement of FTBF. FABF was measured by venous occlusion plethysmography using a precalibrated mercury-in-Silastic strain gauge positioned 4 cm below the elbow joint. Venous occlusion was produced using a pneumatic cuff placed around the upper arm. Hand circulation was excluded during measurements of FABF by placing a cuff around the wrist and inflating it to 200 mm Hg. Venous occlusion pressure was determined in the same way as for measurements of FTBF and was 35 to 45 mm Hg.

Blood flow in the forearm skin was also measured continuously using a laser Doppler flowmeter (PF3; Perimed, Sweden) placed midway on the dorsal aspect of the forearm. The flowmeter settings were 4-KHz bandwidth and 0.2-second time constant. The output signal was measured in units of voltage and recorded on a pen recorder.

Baseline measurements of FABF by venous occlusion plethysmography were made every 30 seconds during infusion of 0.9% saline and averaged over 10 minutes. Methacholine then was infused in increasing doses (0.03, 0.3, 3, and 10 µg/min) for 4 minutes each. Measurements of FABF were made every 30 seconds, and the last 2 minutes of measurements were used for subsequent analyses. At the end of infusion of methacholine, saline was infused until FABF returned to baseline.

To determine the endothelium-independent vasodilator response, sodium nitroprusside (SNP; Abbott Laboratories) dissolved in 5% dextrose in water was infused in increasing doses (0.03, 0.3, 3, and 10 µg/min) for 4 minutes each. Syringes containing SNP were protected from exposure to light. At the end of this infusion period, baseline FABF was reestablished.

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**TABLE 1. Clinical Characteristics of Control Subjects and Patients With Raynaud’s Phenomenon**

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=14)</th>
<th>Patients With Raynaud’s Phenomenon (n=12)</th>
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</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>6/8</td>
<td>0/12</td>
</tr>
<tr>
<td>Age, y</td>
<td>31.9±2.9</td>
<td>42.5±4.0*</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>100±2.5</td>
<td>112±6.1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>60.2±2.0</td>
<td>63.1±3.2</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>194.6±11.5 (n=10)</td>
<td>203.0±10.4 (n=10)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>54.1±3.6 (n=10)</td>
<td>51.3±4.4 (n=10)</td>
</tr>
<tr>
<td>Smokers</td>
<td>3/14</td>
<td>2/12</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein.

All values are mean±SEM.

*P<.05.
before the upper arm cuff was inflated to 200 mm Hg for 5 minutes to produce an ischemic stimulus. During the last 2 minutes of ischemia, the forearm was exercised by repetitive hand squeezing of a gauze roll. On release of the cuff, subsequent reactive hyperemia was measured over 2 minutes to determine the ischemic response of the forearm. At the end of each study, a sample of blood was withdrawn from the brachial artery for measurement of plasma cholesterol levels.

Intra-arterial blood pressure was measured continuously via the nearest stopcock to the brachial artery catheter using a Hewlett-Packard pressure transducer (model 1280C). Mean blood pressure was calculated electronically. Vascular conductance was estimated by dividing average blood flow by mean arterial blood pressure and was expressed in units of milliliters per minute per 100 mL of tissue per millimeter of mercury.

Statistical Analysis

Data are expressed as mean±SEM. Vasodilator responses to methacholine in the fingertip of patients with Raynaud’s phenomenon in the present study were compared with responses from control subjects determined in a previous study. Because dose-response curves could not be obtained for FTBF measurements during infusions of methacholine, the average FTBF for the highest dose given was used for statistical comparisons using the t test for unpaired data. Differences in FABF and vascular conductance dose-response curves were determined by ANOVA of independent groups for repeated measures followed by Scheffé post-hoc testing. Comparisons of nonserial measurements between groups were determined by the t test for unpaired data. The null hypothesis was rejected at P<0.05.

Results

Baseline characteristics of control subjects and patients with Raynaud’s phenomenon are given in Table 1. Control subjects were significantly younger than patients with Raynaud’s phenomenon (P<0.05).

Measurement of FTBF

In control subjects, basal FTBF was 5.8±1.7 mL/min per 100 mL tissue in men compared with 9.7±4.8 mL/min per 100 mL tissue in women (P<0.5). Basal vascular conductance in men was 0.07±0.02 U versus 0.13±0.06 U in women (P<0.4). Basal FTBF and vascular conductance were not significantly different between control subjects (n=10, 6 men and 4 women) and patients with Raynaud’s phenomenon (n=10, 10 women) (Table 2). At the highest dose given, methacholine caused no significant changes in total FTBF and vascular conductance in control subjects, whereas patients with Raynaud’s phenomenon showed a relatively large increase in these parameters, which were significantly greater than the corresponding values for control subjects (P<0.02 for FTBF and vascular conductance). The largest FTBF obtained was 50 mL/min per 100 mL tissue. There was a fall in mean systemic blood pressure at the highest dose of methacholine in control subjects (83±2 to 78±2 mm Hg, P<0.01) and in patients with Raynaud’s phenomenon (89±2 to 80±2 mm Hg, P<0.01). There were no significant changes in mean blood pressure with the other doses of methacholine.

Measurement of FABF

Table 3 shows that basal FABF and vascular conductance before infusions of methacholine and SNP were lower in patients with Raynaud’s phenomenon (n=9, 9 women) than in control subjects (n=14, 6 men and 8 women). Intra-arterial infusions of methacholine produced dose-dependent increases in FABF and vascular conductance that were not significantly different between control subjects and patients with Raynaud’s phenomenon (Fig 1). After the final infusion of methacholine, FABF and vascular conductance returned to basal levels within 25 minutes.

FABF and vascular conductance responses to infusions of SNP are shown in Fig 2. There were no significant differences in the dose-dependent increases in FABF and vascular conductance between the two groups. At the highest dose of SNP (10 μg/min), FABF and vascular conductance were of magnitudes similar to those achieved at the highest dose of methacholine in both control subjects and patients with Raynaud’s phenomenon (Table 3). Similar responses were found for the two groups when comparing FABF and vascular conductance responses to methacholine and SNP for control subjects consisting only of women (n=8) and patients with Raynaud’s phenomenon (n=9, 9 women). There were no significant differences in systemic blood pressure between patients with Raynaud’s phenomenon and normal subjects with methacholine or SNP by ANOVA; however, there were decreases in blood pressure with the 10-μg/min doses of both agents in both groups.

In contrast to measurements of blood flow in the entire forearm, basal values of blood flow in forearm skin as measured by laser Doppler flowmetry showed no significant differences between control subjects and patients with Raynaud’s phenomenon (Fig 3). In addition, the blood flow response to intra-arterial infusions

<table>
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<tr>
<th>Table 2. Basal Fingertip Blood Flow and Vascular Conductance in Response to the Highest Dose of Methacholine Used in Control Subjects and Patients With Raynaud’s Phenomenon</th>
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<tr>
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<td><strong>Control Subjects</strong> (n=10)</td>
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<td><strong>Patients With Raynaud’s Phenomenon</strong> (n=10)</td>
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<tr>
<td></td>
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<tr>
<td><strong>Before methacholine</strong></td>
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<tr>
<td>Fingertip blood flow, mL/min per 100 mL tissue</td>
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<td></td>
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<tr>
<td>Vascular conductance, U</td>
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<tr>
<td><strong>During methacholine</strong></td>
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<tr>
<td>Fingertip blood flow, mL/min per 100 mL tissue</td>
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<td></td>
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<td>Vascular conductance, U</td>
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<td>All values are mean±SEM.</td>
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<td>*P&lt;0.02 comparing control subjects with patients.</td>
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<th>Control Subjects (n=14)</th>
<th>Patients With Raynaud’s Phenomenon (n=9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow, mL/min per 100 mL tissue</td>
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<td></td>
<td></td>
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<tr>
<td>Before methacholine</td>
<td>3.1±0.4</td>
<td>2.0±0.2</td>
<td>.058</td>
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<tr>
<td>Before sodium nitroprusside</td>
<td>3.8±0.5</td>
<td>1.9±0.2</td>
<td>&lt;.005</td>
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<td>During methacholine (10 µg/min)</td>
<td>25.3±3.3</td>
<td>25.2±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>During sodium nitroprusside (10 µg/min)</td>
<td>21.7±3.4</td>
<td>16.1±2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular conductance, U</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before methacholine</td>
<td>0.04±0.01</td>
<td>0.02±0.003</td>
<td>&lt;.05</td>
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<tr>
<td>Before sodium nitroprusside</td>
<td>0.05±0.01</td>
<td>0.02±0.002</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>During methacholine (10 µg/min)</td>
<td>0.34±0.04</td>
<td>0.30±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>During sodium nitroprusside (10 µg/min)</td>
<td>0.30±0.05</td>
<td>0.20±0.04</td>
<td>NS</td>
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</tbody>
</table>

All values are mean±SEM.

*P refers to comparison between control subjects and patients.

of methacholine was significantly greater in patients with Raynaud’s phenomenon than in control subjects (P<.01 by ANOVA, Fig 3). There was, however, no significant difference between the two groups in the blood flow response to intra-arterial infusions of SNP. Fig 3 also shows that the maximal response to the highest dose of methacholine was significantly greater than the maximal response to the highest dose of SNP in both control subjects (P<.02) and patients with Raynaud’s phenomenon (P<.005). Comparison of the dose-dependent increase in blood flow in forearm skin in response to infusions of methacholine in only female control subjects (n=6) with that in patients with Raynaud’s phenomenon did not quite reach statistical significance.

Fig 1. Plots of changes in (A) total forearm blood flow and (B) vascular conductance during intra-arterial infusions of methacholine in control subjects (n=14) and patients with Raynaud’s phenomenon (n=9).

Fig 2. Plots of forearm (A) blood flow response and (B) vascular conductance to intra-arterial infusions of sodium nitroprusside in control subjects (n=14) and patients with Raynaud’s phenomenon (n=9).
Coffman and Cohen\textsuperscript{11} showed that a muscarinic cholinergic vasodilator mechanism is present in the fingertip of normal subjects that mediates an increase in blood flow through the capillaries. In confirmation that infusions of methacholine increase blood flow through the capillaries, a relatively large blood flow was observed in the skin of the forearm where shunts are absent. Although we did not measure the partition of blood flow through arteriovenous shunts and capillaries in the fingertips of our patients, the relatively large increase in blood flow in response to infusions of methacholine (average flow of 20.9 with flows as large as 50 mL/min per 100 mL tissue) must have included flow through arteriovenous shunts because mean capillary blood flow averages only about 10 mL/min per 100 mL of tissue in a warm environment.\textsuperscript{13} In histoch-emic studies of skin in the digits of humans, acetylcholine-esterase has been localized in the arteriovenous shunts.\textsuperscript{14} The reason for the greater cutaneous vasodilator response to infusions of methacholine in patients with Raynaud’s phenomenon is unclear. Stimulation of muscarinic receptors by acetylcholine results in the production of endothelium-derived relaxing factor,\textsuperscript{10} which is thought to be nitric oxide (NO) or a related nitroso compound. Vasodilation in response to methacholine may also be due in part to an NO-independent mechanism. Vallance et al\textsuperscript{15} reported that brachial artery infusions of N\textsuperscript{G}-monomethyl-L-arginine, a specific inhibitor of the synthesis of endothelium-derived NO, did not block completely the vasodilator response to infusions of acetylcholine. The NO-independent mechanism may be due to the production of endothelium-dependent hyperpolarizing factor, as seen in isolated blood vessels in animals.\textsuperscript{16,17} It is therefore possible that an increase in the NO-independent mechanism accounts for the greater cutaneous vasodilator response to methacholine in patients with Raynaud’s phenomenon. NO appears to play only a relatively minor role in the cutaneous vasodilator response to methacholine because SNP, which liberates NO to vascular smooth muscle,\textsuperscript{18} had a small effect on blood flow in the skin of the forearm. Consistent with this finding is the lack of effect of SNP in the fingertips.\textsuperscript{19} Alternatively, infusions of methacholine may result in the production of prostacyclin, although inhibition of the cyclooxygenase pathway by aspirin has no significant effect on the vasodilator response in the forearm of normal subjects.\textsuperscript{14}

It is noteworthy that in the present study, a considerable vasodilator response to methacholine in patients was observed in the fingertips, where vasospasm is most often experienced, but also in the skin of the forearm, where symptoms of Raynaud’s phenomenon are not seen. This finding indicates that in Raynaud’s phenomenon, there may be a generalized abnormality in the blood vessels of skin that is related to the pathophysiology of vasospasm. It has been postulated that vasospasm may be widespread, as demonstrated by the correlation of Raynaud’s phenomenon, migraine headaches, and variant angina in patients.\textsuperscript{8,20} Miller and coworkers\textsuperscript{8} found that 7 of their patients and none of the control subjects had all three entities. Raynaud’s phenomenon results from a spasm of digital arteries; a decrease in cerebral regional blood flow, evidently due to vasoconstriction, preceded migraine headaches; and coronary artery vasospasm has been shown by angiography to occur in patients with variant angina. In scleroderma, a disease commonly manifesting Raynaud’s phenomenon, a generalized vascular abnormality presis-
posing to vasospasm may occur in the renal and pulmonary vasculature.\textsuperscript{21,22} It is known that patients with migraine headaches and primary Raynaud's disease have abnormal peripheral vascular reactions to physiological stimuli.\textsuperscript{23,24} It is difficult to fit the finding of enhanced cholinergic cutaneous vasodilation into a theory of generalized vasospasm, but patients with Raynaud's phenomenon often have excess vasodilation responses after their vasospastic attacks, and vasodilation is thought to occur during migraine headaches. Anticholinergic agents, however, have not been reported to be of benefit in either condition.

A limitation of this study is that controls and patients were not matched for age and sex. It is doubtful that the greater average age of our patients with Raynaud's phenomenon than of the control group could have been responsible for the enhanced cutaneous vasodilator response to methacholine. In vivo and in vitro studies of human blood vessels have shown endothelium-dependent vasodilation not to be altered by age.\textsuperscript{25-29} and, in some animal studies, to be diminished.\textsuperscript{27} One study reported a larger mean finger blood flow in young men and older women than in younger women at a room temperature of 24°C.\textsuperscript{29} However, another group found comparable finger blood flows in men and women at a warm temperature,\textsuperscript{28} which agrees with findings in the present study. Length of acclimation to a neutral or warm environment most likely determines whether young women will have FTBF comparable to that of young men. There is evidence that women have an increased vasoconstrictor response of their digital blood vessels to a cold stimulus,\textsuperscript{28,29} but gender had no effect on the release of endothelium-derived relaxing factor by bradykinin.\textsuperscript{25}

In summary, intra-arterial infusions of methacholine produced endothelium-dependent vasodilator responses that were enhanced in the fingertip and skin of the forearm but not in forearm skeletal muscle in patients with Raynaud's phenomenon compared with responses in control subjects. The reason for an enhanced vasodilator response in patients with Raynaud's phenomenon is unclear but may reflect an underlying fundamental abnormality of blood vessels in the skin related to the pathophysiology of vasospasm. Finally, the enhanced vasodilator response to muscarinic receptor stimulation may provide a beneficial form of therapy to patients with Raynaud's phenomenon. The development of oral cholinergic drugs with specificity for cutaneous muscarinic receptors or the iontophoresis of cholinergic agents on the fingers should be considered.

Acknowledgments

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References


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