Cryodynamic Hand Angiography in the Diagnosis and Management of Raynaud’s Syndrome

JOSEF RÖSCH, M.D., JOHN M. PORTER, M.D., AND BERNARD J. GRALINO, M.D.

SUMMARY Cryodynamic hand angiography (CHA) with angiograms done before, just after, and during rewarming following hand immersion in ice water was performed in 39 patients with Raynaud’s syndrome and eight volunteers without it. The normal response to cold stimulus was angiographically evident as mild, transient digital arterial constriction. Most of the patients with Raynaud’s syndrome, in addition to organic obstructive disease, exhibited basal vasoconstriction and exaggerated persistent cryogenic vasospasm of the hand arteries. Similar angiographic studies done in 32 cases two days after the selective intra-arterial administration of reserpine revealed no differences in normal subjects but substantially decreased vasospasm in patients with Raynaud’s syndrome. CHA with postreserpine studies was found to be diagnostically useful in Raynaud’s syndrome, revealing the degree of organic arterial disease and functional vasospasm. In addition, correlation of postreserpine studies with observed clinical responses to long-term vasodilator drug therapy indicated that CHA has a good chance to predict the probable outcome of such therapy in Raynaud’s syndrome.

THE COLD EXPOSURE TEST, a determination of digital temperature fall, and, in particular, its recovery time to normal following cold exposure, has been a useful technique in the diagnosis of Raynaud’s syndrome. Normally, the temperature of a finger or hand immersed in ice water falls abruptly to 10 to 20°C with rewarming in 5 to 10 minutes. In patients with Raynaud’s syndrome, similar temperature decreases occur, but recovery time is prolonged several-fold. Angiography of the hand has also been used in the diagnosis of Raynaud’s syndrome, in particular for evaluation of anatomic vascular changes and documentation of the results of various forms of therapy. We have combined both methods into a third, cryodynamic hand angiography (CHA), which we performed 88 times in 47 subjects; 39 with Raynaud’s syndrome and eight volunteers without it. Study objectives were: (1) to study by arteriography the reaction of hand arteries to cold exposure in normal subjects and patients with Raynaud’s syndrome; (2) to assess the diagnostic value of this new method, and (3) to assess the effects of intra-arterially administered reserpine in Raynaud’s syndrome.

Case Materials

Of 47 subjects, 29 were female and 18 male, ranging in age from 22 to 74 years (mean 44 years). In 34 patients, Raynaud’s syndrome was related to systemic diseases with immunological alterations such as scleroderma (18 patients), lupus erythematosus (7 patients), polymyositis (1 patient), polyarthritis (1 patient), mixed connective tissue disorders (3 patients), and collagen vascular disorders (4 patients). Five patients with Raynaud’s syndrome had no detectable autoimmune disease. Diagnoses were established by detailed clinical and laboratory evaluation, including a standardized cold exposure digital temperature test, multiple immunologic studies and skin biopsy. In fifteen of the 39 affected patients, Raynaud’s symptoms were classified as mild (occasional attacks of digital vasospasm not exceeding two to three attacks per week in cool weather, non-progressive, with minimal functional impairment); in 12 as moderate (daily attacks in cool weather with some progression and moderate functional impairment), and in 12 as severe (frequent attacks with significant progression and evidence of previous or current ulcerations). Of the eight volunteers without Raynaud’s symptoms who were studied in order to establish the normal angiographic response to cold exposure, five (mean age 31 years and range 24 to 35 years) had no atherosclerosis, while three (mean age 65 years and range 58 to 74 years) did.

Method

The study was done in a warm room (20 to 22°C) with the subject well covered; the examined hand was kept in direct contact with the subject’s body until the injection, to avoid hypothermia. First a baseline (resting) angiogram was done at the subject’s usual skin temperature at the fingertips, as determined prior to the procedure by a thermistor probe. About 10 minutes later, after reviewing films from the first study, the subject’s hand and distal forearm were immersed for 20 seconds in a plastic bag filled with an ice-water mixture. During the immersion, the subject moved his fingers. Immediately afterwards, the hand was blotted dry and a cold exposure (ice) angiogram was performed. Nineteen subjects also had a rewarm angiogram, which was done 5 minutes (nine subjects) or 10 minutes (ten subjects) after the cold exposure angiogram. Between these angiograms, the hand rested on a pad at room temperature. In 36 subjects, one hand (in Raynaud’s syndrome the more symptomatic one) was examined. Nine subjects had studies of both hands. Following the study, in all patients with Raynaud’s syndrome and in two of the volunteers without it, reserpine (0.5 mg) was selectively injected into the brachial artery prior to removal of the catheter. Forty-eight hours later, follow-up (postreserpine) studies were done on 32 subjects, 30 with...
Raynaud's syndrome and two without it (table 1). All repeat studies included baseline and cold exposure angiograms; in 14 subjects, they also included a rewarm angiogram.

All angiograms were performed under local anesthesia after premedication with meperidine (50 to 100 mg), except for one volunteer who was examined under general anesthesia. The percutaneous transfemoral approach was used for catheter introduction and subjects were given 40 units of heparin per kg of body weight. A 100 to 120 cm long, straight-tipped catheter was used (polyethylene, thin-wall 5Fr in younger and slim patients, Torcon 6Fr in older and obese patients). For introduction of a straight-tipped catheter in the latter patients, particularly in the examination of the right hand, a preshaped catheter was first manipulated into the axillary artery. With the help of a 240 cm long guidewire, this was then exchanged for the final catheter, which was positioned halfway down the brachial artery. Meglumine iothalamate (Conray 60) was used as contrast agent in doses of 15 to 24 ml delivered in 4 to 6 seconds. Injection rates varied from 3 to 6 ml per second, depending on the size of the brachial artery and flow velocity as assessed by a small test injection of contrast agent. Serial magnification films of the hand were exposed one per second for 12 seconds following a delay period based upon the fluoroscopically observed time required for the test injection to reach the wrist. In baseline, cold exposure and rewarm angiograms, the same doses of contrast medium and filming sequences were used.

Angiograms were evaluated and graded separately for the presence of organic obstructive disease and functional vasospasm. Obstructive disease in digital and palmar arteries was graded as follows: grade 0: no areas of stenoses or occlusion; grade 1: areas of stenoses and/or a single total occlusion; grade 2: two or three occlusions; grade 3: four or more occlusions. In radial and ulnar arteries, findings were classified as grade 0: normal; grade 1: moderate stenosis (es); grade 2: severe stenosis(es); grade 3: occlusion. Vasospasm was graded as follows: grade 0: no vasospasm; grade 1: diffuse concentric narrowing of proper digital arteries; grade 2: no filling of proper digital arteries plus attenuation of common digital arteries; grade 3: no filling of common digital arteries plus attenuation of palmar arches; grade 4: no filling distal to the radial and ulnar arteries. Half grades were used to quantitate intermediate degrees of vasospasm. Data were statistically analyzed using the Wilcoxon rank-sum test.18

Results

No complications occurred. Patients frequently complained about discomfort or pain during hand immersion in ice water and after injection of contrast agent. Selective intra-arterial reserpine administration produced no immediate subjective or objective changes, but 4 to 6 hours later most patients with Raynaud's syndrome indicated their fingers started to feel warmer. No response to reserpine was reported by the two volunteers who received it.

Volunteers without Raynaud's Symptoms

In the five volunteers who had neither Raynaud's syndrome nor atherosclerosis, CHA revealed similar findings. Baseline angiograms showed excellent filling of hand arteries from palmar arches, common and proper digital arteries to arcuate branches and vascular loops in fingertips. No basal vasospasm was seen, and similarly, no organic disease was present except in one subject who used vibrating tools and had grade 1 organic disease in his third to fifth common digital arteries (fig. 1A). Cold exposure angiograms showed vasoconstriction ranging from grade 1 to 2 with relatively lesser involvement of the thumb arteries (fig. 1B, table 2). Rewarm angiograms done in three patients showed a return to normal. In the subject with grade 1 organic disease, a minimal attenuation persisted in the involved common digital arteries (fig. 1C). In two patients who received selective reserpine after the initial study, follow-up angiograms 48 hours later showed no change.

In three elderly patients with general atherosclerosis and no Raynaud's symptoms, the baseline angiograms showed multifocal obstructive disease (table 2). While the arteries in general were somewhat more tortuous and slightly narrowed, no basal vasospasm was present. Cold exposure angiograms in two patients showed cold-elicited vasoconstriction (mean grade 1.5), while in the third there were no changes from the baseline angiogram.

In this group, the digital temperature recovery time following cold exposure was normal (< 10 minutes). The digital temperature decrease in the patient who showed no spasm on the cold exposure angiogram was only of minor degree (3° C).

Raynaud's Syndrome

Baseline angiograms in most of the 39 patients with Raynaud's syndrome revealed a combination of basal vasospasm and organic obstructive disease (table 2, figs. 2A, 4A, 5A). Basal vasospasm present in 35 patients ranged from grade 0.5 to 2.5, and often impaired the quantitative evaluation of organic disease in digital arteries. This could better be assessed on postreserpine studies which showed substantial decrease of vasospasm. The degree of basal spasm did not correlate with the severity of clinical symptoms.

| Table 1. Distribution of Patients and Their Cryodynamic Angiographic Studies |
|----------------------------------|-----------------|-----------------|-----------------|
| Diagnosis                        | No. of patients | Baseline & cold exposure angiograms | Baseline & cold exposure angiograms |
| Raynaud's syndrome               | 39              | 48*                          | 16              |
| Volunteers without               | 8               | 8                            | 3               |
| Raynaud's symptoms               |                 |                               |                 |

*Nine patients had studies of both hands.
Organic obstructive arterial changes were present in 34 of the 39 patients with Raynaud's syndrome and involved the radial and ulnar, but mostly the digital arteries (table 2). The extent of obstructive disease corresponded to the clinical severity of Raynaud's symptoms and the difference between average disease grades of all arteries in patients with mild symptoms (mean 1.0, range 0 to 1.7) and those with severe symptoms (mean 2.0, range 1–2.7) were statistically significant (P < 0.05). Patients with moderate symptoms (mean 1.1; range 0.3–2.7) showed no significant difference from either of the other two groups.

Cold exposure angiograms revealed increased vasospasm in all patients (mean 2.6; range 2–4) (table 2, figs. 2B, 3, 4B, 5B). The increase in grade of cold exposure vasospasm over baseline vasospasm varied in range (mean 1.5; range 0.5–3). Statistically, a significant difference was found between the degree of total vasospasm on cold exposure angiograms of patients with Raynaud's syndrome and that of volunteers (P < 0.05); however, their increase of vasospasm over baseline vasospasm was not significantly different from the cryogenic vasoconstriction of volunteers (fig. 3).

Rewarm angiograms done in 16 patients of this group showed persistence or minimal decrease of the cryogenic vasospasm (mean 2.5; range 2–3.5) (table 2, figs. 2C, 3). No differences in the degree of vasospasm decrease were found in patients who had rewarm angiograms 5 minutes (8 patients) or 10 minutes (8 patients) after the ice study.

Postreserpine study done 48 hours after the initial examination in 30 patients of this group showed no basal vasospasm on the baseline angiograms in eight patients, including four who had not had vasospasm on the pre-reserpine studies and four others whose original basal vasospasm had a mean grade of 1.5. Basal vasospasm also substantially decreased in the majority of the other 22 patients (table 2, fig. 2D). The average postreserpine basal vasospasm grade of 0.5 reflected a mean decrease of 0.7 in comparison with preresorpine studies (fig. 6). On the cold exposure angiograms after reserpine, the cryogenic vasospasm

| Table 2. Summarized Findings of Cryodynamic Hand Angiograms in the 47 Examined Patients |

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Mean grade and range ( ) of obstructive disease</th>
<th>Mean grade and range ( ) of vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radial artery</td>
<td>Ulnar artery</td>
<td>Digital arteries</td>
</tr>
<tr>
<td>Young volunteers without Raynaud's symptoms</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic volunteers without Raynaud's symptoms</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raynaud's syndrome</td>
<td>39</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0-3)</td>
<td>(0-3)</td>
</tr>
</tbody>
</table>
FIGURE 2. Cryodynamic hand angiography before (A,B,C) and two days after (D,E,F) selective intra-arterial reserpin administration in a 35-year-old man with Raynaud's syndrome. A) Preresserpine baseline angiogram demonstrates advanced vasospasm of digital arteries and palmar arches and slight spasm of forearm arteries. B) Preresserpine cold exposure angiogram shows further increase of vasospasm. C) Preresserpine rewarm angiogram done 10 minutes after cold exposure angiogram shows only minimal decrease of the cryogenic vasospasm. D) Postreserpine baseline angiogram demonstrates minimal degree of basal vasospasm in some of the proper digital arteries and minor organic disease. E) Postreserpine cold exposure angiogram shows minor cryogenic vasospasm in digital arteries. F) Postreserpine rewarm angiogram done 10 minutes after the cold exposure study reveals almost complete relief of the cryogenic vasospasm.

was elicited by cold exposure but it was in general milder in degree than on the initial examination (mean 1.2; range 0.5–2) which represents a mean decrease grade of 1.4 from the preresserpine studies (figs. 2E, 6). In 12 patients in whom the postreserpine study also included a rewarm angiogram, a fast return almost to a pre-cold exposure vascular appear-
The differences in degree of vasospasm on prereserpine and postreserpine studies were found to be statistically significant ($P < 0.05$).

In correlating CHA findings with results of long-term therapy with oral guanethidine and phenoxybenzamine, no relation was found between its outcome and degree of organic arterial disease and degree of basal or cryogenic vasospasm on the initial prereserpine study (table 3). The postreserpine study, and in particular the decrease in degree of both the basal and cryogenic vasospasm, however, showed to be a good indicator of the therapeutic outcome (table 3, fig. 7). At a one year mean follow-up period, 11 patients who judged their therapeutic results as excellent, with complete subsidence of Raynaud's symptoms, had a mean decrease of basal vasospasm of 1.1 (range 0.5–2.5), cryogenic vasospasm of 1.9 (range 1–2.5) and a fast return to baseline angiographic appearance (fig. 2F). Fourteen patients who considered their therapeutic response good, with significant reduction of frequency and severity of attacks, had a mean decrease of basal vasospasm of 0.9 (range 0–2), cryogenic vasospasm of 1.2 (range 0–2), and substantial, fast relief of the latter (fig. 4). Five patients who judged therapeutic results as poor, with little improvement of Raynaud's symptoms, had decrease of baseline vasospasm of 0.1 (range 0–0.5) and of cryogenic vasospasm of 0.5 (range 0–1.5) (fig. 5). Difference in spasm decrease between the groups of patients with excellent and poor results were statistically significant ($P < 0.05$). Patients with good therapeutic outcome showed no significant difference from either of the other two groups.
Digital temperature recovery times were abnormal in 38 of the 39 patients with Raynaud's syndrome, averaging 33 and ranging from 20 to 45 minutes. The other patient had an initial temperature recovery time of 10 minutes. The temperature recovery time was determined during treatment in 32 patients; in 27 it returned to normal, while in the other five it decreased substantially.

**Discussion**

No effort was made to differentiate between Raynaud's disease, phenomenon, and/or syndrome, categorizations which have caused confusion. Immunologic evaluation suggests that in most patients, Raynaud's symptoms are secondary to autoimmune or other immunological aberrations and therefore should be classified as Raynaud's syndrome.  

In the past, hand angiography has been mostly done by puncture of the brachial artery, a technique which often causes spasm in patients with Raynaud's syndrome. General anesthesia, stellate block, preinjected vasodilators, hand warming and oral alcohol have been used to minimize vasospasm and thereby demonstrate detailed organic changes in the peripheral arteries. Spasm of hand arteries is, of course, an important condition underlying Raynaud's syndrome, and properly the objective of study. We have used the transfemoral approach to minimize artificial spasm due to brachial trauma; for the same reason, we have avoided adjunctive efforts to eliminate the disease-connected vasoconstriction. The 20 second ice water immersion period for CHA was chosen as a tolerable maximum for the usual patient with Raynaud's syndrome. Whether rewarming delays were for 5 or 10 minutes appeared to make no significant difference. A 10 minute delay, however, is probably better since it encompasses normal rewarming limits.  

CHA of our patients with Raynaud's syndrome revealed various combinations of organic obstructive disease, basal

**Table 3. Correlation of Findings of Cryodynamic Hand Angiograms with Results of Long-term Spasmolytic Therapy of 30 Patients**

<table>
<thead>
<tr>
<th>Results of therapy</th>
<th>No. of patients</th>
<th>Mean grade of obstructive disease</th>
<th>Initial study mean grade of vasospasm</th>
<th>Postreserpine study mean grade of vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean grade of obstructive disease</td>
<td>Baseline angiogram</td>
<td>Cold exposure angiogram</td>
</tr>
<tr>
<td>Excellent</td>
<td>11</td>
<td>1.0</td>
<td>1.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Good</td>
<td>14</td>
<td>1.4</td>
<td>1.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Poor</td>
<td>5</td>
<td>1.0</td>
<td>1.2</td>
<td>2.4</td>
</tr>
</tbody>
</table>
vasospasm, abnormally high and persistent vasospastic response to cold with a substantial decrease in functional changes 48 hours after intra-arterial reserpine administration. Organic obstructive disease was present in 87% of our patients involving mainly digital arteries, and particularly the proper digital arteries which often showed multiple occlusions. Major vessels were also involved, with the ulnar artery showing more advanced changes than the radial artery.

Basal vasospasm evident on baseline angiograms of 90% of our patients with Raynaud's syndrome ranged from diffuse narrowing of proper digital arteries to severe constriction of common digital arteries with attenuation of palmar arches and apparent absence of distal flow. This wide range of spastic changes, the lack of their correlation with clinical symptoms, as well as the presence of advanced spasm with no distal visualization, even in patients with almost normal resting digital skin temperatures, suggest that the severity of angiographically visualized basal vasospasm is an inconsistent reflexion of the response of hyperactive hand arteries to angiographic procedural stress, a response which differs widely in individual patients. The improvement in vasospasm which we observed following selective intra-arterial reserpine, as well as the reportedly lower incidence of spasm on angiograms done under general anesthesia,6-8 supports this hypothesis.

Vasoconstriction associated with cold exposure is a functional, physiological response, and in our experience appeared despite general anesthesia or selective reserpine administration. Normally, the response is of short duration and disappears in 5 to 10 minutes. It was present in all but one of our subjects, including volunteers. Nevertheless, the severity and particularly the persistence of cold-elicited vasospasm can be pathologic and, as such, are characteristic features of Raynaud's syndrome. Normally, cold exposure vasoconstriction ranges from diffuse attenuation of the proper digital arteries to their complete constriction with narrowing of common digital arteries. In patients with Raynaud's syndrome, the cryogenic response superimposed on basal vasospasm results in more advanced spasm and sometimes completely constricts even palmar arches. The cryogenic vasospasm persists for a long period and in our series we saw no or little change in its degree on angiograms done 5 to 10 minutes after cold exposure.

The intra-arterial administration of reserpine does not influence the appearance or degree of normal cold-elicited vasoconstriction; however, it reduces the severity and duration of the pathologic vasospasm seen at rest and after cold exposure in patients with Raynaud's syndrome. Intra-arterial reserpine, acting as a neuronal norepinephrine depleter, causes a regional sympathetic blockade, alleviates vasoconstrictor activity and increases nutritive blood flow. Its action is prolonged, and animal studies have shown that a single intra-arterial injection depletes norepinephrine for about 14 days.6-8

CHA, particularly the information gained from the rewarming angiograms, was accurate in the diagnosis of Raynaud's syndrome. It was clearly positive in all of our patients with Raynaud's syndrome, even one whose cold exposure digital temperature test was borderline normal. The diagnosis of Raynaud's syndrome, however, is usually easily made clinically and with the use of noninvasive methods. The major contribution of CHA relates to quantitating the disease and, in our belief, to predicting the therapeutic results. Baseline prereserpine angiograms show the degree of basal vasospasm and occasionally the extent of organic involvement of the hand arteries; cold exposure angiograms reveal the character of vasospastic response. Postreserpine studies provide detailed information about obstructive arterial disease and appear to afford means for predicting the results of

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**FIGURE 6.** Correlation of mean grades of vasospasm on prereserpine and postreserpine cryodynamic hand angiograms in patients with Raynaud's syndrome.

**FIGURE 7.** Correlation of mean grades of vasospasm on the pre-reserpine studies (A) and postreserpine studies (B) with results of long-term vasodilator drug therapy.
therapy decreasing sympathetic activity. According to our experience, when such studies show a substantial decrease of basal and cryogenic vasospasm, good results can be expected. With diminishing relief of vasospasm after reserpine, the therapeutic expectation seems to be proportionally less favorable. Even when our results showed statistical significance, further studies on more patients with longer follow-up periods will be necessary to provide the final answer about the prognostic value of CHA in the management of Raynaud's syndrome.

Acknowledgment

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