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Evaluation of Finger Blood Flow with Tc-99m MDP (methylene diphosphonate)

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Background: *A variety of methods were used to establish objective diagnostic criteria of Raynaud's phenomenon. We intended to introduce another method, using radionuclide (Tc-99m methylene diphosphonate) scintigraphy, which is more objective, simple and economical than the past methods.*

Methods: *The finger blood flow with radionuclide scintigraphy was evaluated in 10 patients of Raynaud's syndrome, 12 patients of connective disease without Raynaud's symptoms, and 20 normal persons. After immersing one hand in ice water (4°C) for 30 seconds, the hand was exposed to 22°C room air for 15 minutes, and then the patients received the intravenous (IV) bolus of 20 μCi of Tc-99m methylene diphosphonate (MDP). At the same time, scintigraphic image of both hands started with the region of interest, including the second, third, fourth and fifth fingers distal to the metacarpophalangeal (MCP) joints. Computer recording of the counts in the region of interest every 2 seconds for 310 seconds was started on IV bolus injection.*

Results: *The 310 seconds cumulative digital blood flow ratio of cold exposed hand to room air exposed hand was significantly lower in Raynaud's group ($p<0.001$), and the ratio of initial slope of activity curve was also lower in the Raynaud's group ($p<0.001$). Of the 8 patients showing Raynaud's syndrome, 4 patients of scleroderma and 1 patient of multiple myeloma showed no improvement of finger blood flow in the cold exposed hand after 2 weeks of pharmacological therapy, but 1 patient of mixed connective tissue disease, 1 patient of Behcet's syndrome and 1 patient of SLE showed much improved finger blood flow after combined administration of vasodilator, calcium channel blockers and anti-platelet drugs.*

Conclusions: *The evaluation of finger blood flow with ^{99m}Tc-MDP could be considered to be one of the simple, economical and new methods that can be used in the follow-up, objective assessment of therapeutic effect, and giving an aid in the study of the pathophysiology of the Raynaud's phenomenon.*

Key Words: *Raynaud's phenomenon, ^{99m}Tc-MDP scintigraphy*

The first description of a group of patients with finger ischemia presumably caused by digital artery vasospasm was published by Raynaud[1] in 1862. In 1932, Allen and Brown[2] emphasized the wide spectrum of the disorders and attempted to distinguish the Raynaud's phenomenon from the Raynaud's disease. They defined Raynaud's disease as a vasospastic episode precipitated by cold or emotions, usually being bilateral, associated with little or no gangrene, and having no underlying medical disease for more than 2 years. Raynaud's phenomenon, on the other hand, was a

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marker for a variety of underlying medical conditions, frequently asymmetric, involving fewer digits, and having an increased risk of developing gangrene.

A wide variety of medical conditions have been associated with Raynaud's phenomenon. The general categories include connective tissue disease, hematologic abnormalities, arterial diseases, neurologic disorders, occupational causes, drugs and toxins. Among them, the connective tissue diseases are most frequently linked with Raynaud's phenomenon.

Raynaud's phenomenon is frequently the first symptom of several connective tissue diseases. Seventy to 80 percent of sclerodema patients present with Raynaud's phenomenon[3]. Several factors controlling the finger blood flow include intrinsic vascular tone[4], adrenergic activity[5,6], blood viscosity[7~10] and body fluid components etc[11,12].

A variety of methods to establish objective diagnostic criteria include immunological tests, nerve conduction studies, thermocouple (Porter et al)[13], thermography (Chucker et al)[14], calorimetry (Mendlowitz et al)[15], plethysmography (Sumner and Strandness et al)[16], ultrasound, laser doppler flowmetry (Wigley et al)[17], magnification and cryodynamic hand arteriography (Porter & Rosch et al)[18], and measuring blood viscosity (Pirofsky et al)[7].

Coffman and Cohen used regional isotope clearance to measure capillary flow by monitoring the disappearance rate of $Na^{131}I$ in saline which was injected into the pad of a finger tip[19]. Lim and his colleagues reported the radionuclide angiographic method using technetium 99m-red blood cell in 1987[20].

We measured cumulative radioactivity which was the integrated radioactivity of each hand for 310 seconds after intravenous bolus injection of ^{99m}Tc-MDP. Cumulative blood flow ratio of the cold exposed hand to room air exposed hand, measured by Tc-99m MDP, was considered as an efficient, economical and new method to evaluate the finger blood flow.

METHODS AND MATERIALS

Forty two patients from the the hospitalized population at the National Medical Center in Seoul were included in the study. At the time of entry into the study, all patients were classified into 3 groups. 10 patients who were dignosed to have associated connective tissue diseases were classified as having Raynaud's phenomenon (group 1). They had Raynaud's history and symptoms, and showed typical color change in our cold water challenge. 12 patients had connective diseases without Raynaud's phenomenon (group 2) according to the criteria of Allen and Brown[2]. Normal control group consisted of 20 persons who had no evidence of Raynaud's phenomenon or connective tissue disease (group 3) by history or serologic study.

On the day of the radionuclide imaging, all patients rested in sitting position for 20 minutes in a room whose temperature was maintained at 22° C. After that, they immersed one of their hands into the ice water (4°C) to the wrist for 30 seconds, and sat in that room for another 15 minutes with their hands at the heart level. The patients were instructed not to wipe or shake off the water from their hands. Then, they all received 20 μCi of Tc-99m MDP by IV bolus at the ante-cubital fossa. We got scintigraphic image of both hands with the region of interest (ROI), including the second, third, fourth and fifth fingers distal to MCP joint in each hand (Fig. 1). Computer recording of activity at each ROI every 2 seconds for 310 seconds were started just after IV bolus injection. We also observed if the

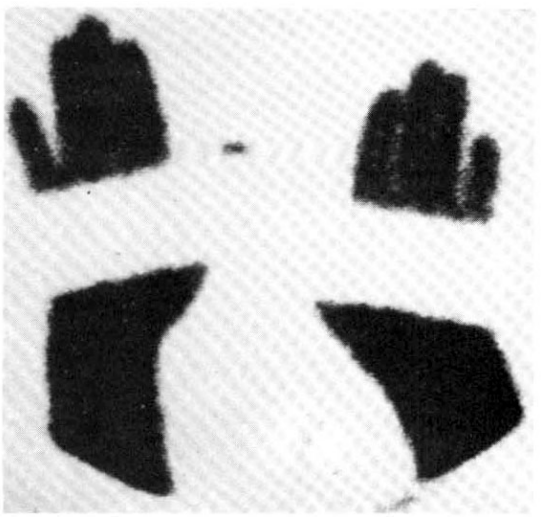

Fig. 1. Dorsal view of static blood pool image of both hands of a normal subject with the region of interest including the second, third, fourth, fifth fingers distal to MCP joint which was marked by lead plate.

patients showed typical skin color change of hands and symptoms (Fig. 2). Repeated imaging was done in 10 patients with Raynaud's phenomenon after the administration of calcium antagonist (nifedipine 30-60 mg/day), vasodilator (captopril 50 mg or doxazosin 1-6 mg/day), and antiplatelet druge (aspirin 300 mg/day) for about 2 weeks.

Several parameters were used in this study. The first was the ratio of activity in cold exposed hand to room air exposed hand, 15 minutes and 20 minutes after cold provocation. The second was uptake increase in the same hand, room air or cold water exposed hands, respectively, from the time

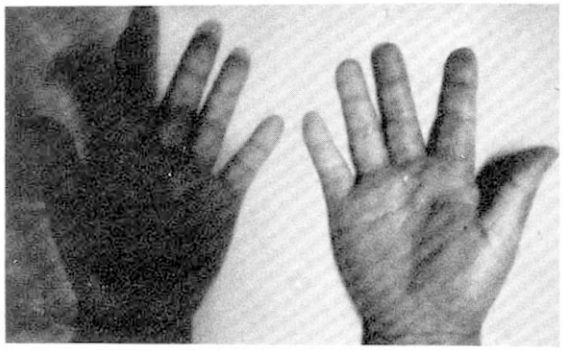

Fig. 2. Typical skin color change (Raynaud's phenomenon) after cold water exposure.

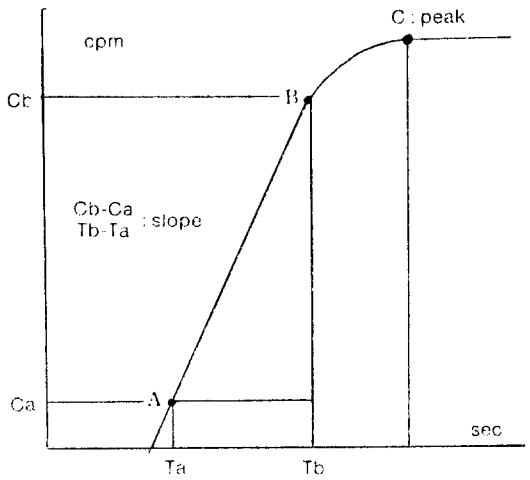

Fig. 3. Initial slope ratio which was the ratio of initial slope of cold exposed hand to that of room air exposed hand.

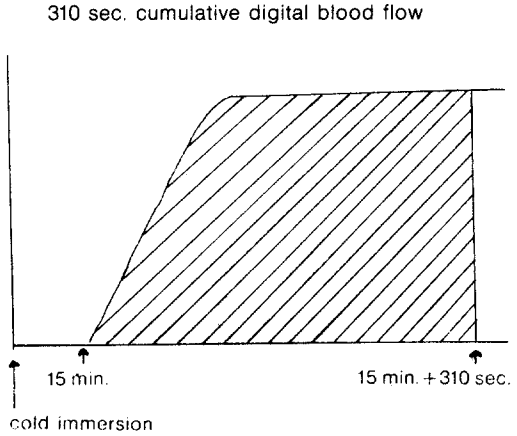

Fig. 4. 310 second cumulative digital bood flow. The hatched area below the time activity curve for 310 seconds was considered as cumulative blood flow.

of 50 counts per minute (CPM) in cold exposed hand to 310 seconds. The third was initial slope ratio which is the ratio of initial slope of cold exposed hand to room air exposed hand. The slope of activity curve from the beginning of uptake to the initial peak was compared between the two hands (Fig. 3). The fourth was 310 second cumulative digital blood flow ratio of cold water exposed hand to room air exposed hand. The areas below the time activity curve of the region of interest of each hands for 310 seconds from IV bolus injection of ^{99m}Tc-MDP was considered as cumulative blood flow (Fig. 4). One way ANOVA test was used for statistical evaluation purposes. Results were given as mean±SD.

RESULTS

The study population's clinical and laboratory findings are given in Table 1. The comparison of several parameters of both hands was done (Table 2). The ratio of activity in cold exposed hand to room air exposed hand were 0.329±0.315 (mean±SD) in group 1, 0.534±0.242 in group 2, 0.549±0.053 in group 3, 15 minutes after their cold exposure, respectively. There was no statistical significance among groups. As in the initial slope ratio, the ratio of activity of patients with Raynaud's pheomenon (0.427±0.156) (group 1) was lower than that of normal control group (0.739±0.185). The differences were $p<0.001$. Otherwise, the

Table 1. Study Population's Clinical and Laboratory Findings

	Raynaud (+)	Raynaud (−)	
		A.C. (+)	A.C. (+)
Number (Female/Male)	7/3	7/5	6/16
Age (year: F/M)	46/57	37/40	52/42
WBC (/mm³)	6366±1301	8427±3714	7587±2524
Hb (g/dl).	10.7±1.64*	12.8±2.00	13.7±2.37
Plt (/mm³).	316500	399630	367000
ESR (mm/hr)	59.0±42.0	57.9±37.6	27.6±20.5
aPTT (sec.)	32.8±7.33	33.3±3.84	31.1±5.28
Globulin (g/dl)	3.65±0.71	3.76±0.74	3.22±0.58
Chole./TG (mg/dl)	250±116.7/274±195.1	193±35.9/118±44.2	180±55.6/117±41.9
Ca/P (mg/dl)	9.2±1.19/3.5±0.81	9.5±0.54/4.40±2.39	9.7±07/4.1±1.95
C3/C4	68.6±39.8/33.7±16.0	102.3±25.97/38.6±27.8	-
FANA (+): RF (+): VDRL (+)	50: 66: 16 (%)	42.9: 33: 10 (%)	-

*: $p<0.05$

Table 2. Comparison of Several Parameters of Both Hands

	Raynaud (+)	Raynaud (−)	
	(group 1)	A.C. (+) (group 2)	A.C. (−) (group 3)
cold exposed/room air hand ratio			
15 min. after exposure	0.329±0.135	0.534±0.242	0.549±0.503
20 min. after exposure	0.749±0.445	0.922±0.190	0.848±0.154
initial slope ratio	0.429±0.156*	0.829±0.161	0.739±0.185
310 sec. cumulative digital blood flow ratio	0.456±0.104*	0.852±0.156	0.817±0.106

*: $p<0.001$ versus group 2 & 3.
A.C.: associated conditions

Table 3. Comparison of Uptake Increase in the Same Hand from the Time of 50 CPM to 310 Seconds

	Raynaud (+)	Raynaud (−)	
		A.C. (+)	A.C. (−)
cold exposed hand	16.093±8.977	27.114±19.409	29.850±21.393
room air hand	6.750±2.773	14.877±11.168	11.578± 3.431

Not significant

initial slope of group 2 was 0.829±0.161. No significant difference was noted between group 2 and 3. In 310 second cumulative digital blood flow ratio, the ratio of Raynaud's was 0.456±0.104. The ratio of normal control group was 0.817±0.106. There was a high significance ($p<0.001$). 310 cumulative digital blood flow was an integrated value of count graph for 310 seconds.

Table 3 showed comparison of uptake increase in the same hand from the time of 50 CPM to 310 seconds. The uptake increase in cold exposed hand of Raynaud's group was 16.093 compared with 29.850 of normal control group. The increase in room air exposed hand of Raynaud's group was 6.750 and that of normal control was 11.587. There was no significant, statistical difference between both groups in cold exposed and room air hand, respectively.

Table 4 presented the data in 10 patients of Raynaud's before and after 2 weeks of medical therapy. In 4 patients of scleroderma, initial slope ratio before treatment was 0.428±0.104 (mean±

Table 4. Post-treatment Follow-up in Secondary Raynaud's Phenomenon

	Before Tx		After Tx	
	cold/room ratio 20 min.	310 sec. cumul. digit. bl. folw	cold/room ratio 20 min.	310 sec. cumul. digit. bl. flow
Scleroderma (n=4)	0.545 ±0.128	0.440 ±0.073	0.487 ±0.195	0.615 ±0.082
Polymyositis (n=4)	0.560	0.373	0.461	0.653
MCTD (n=4)	0.668	0.398	1.000	0.744
Behcet's synd. (n=4)	0.640	0.468	0.692	0.812
SLE (n=4)	0.503	0.411	0.572	0.809

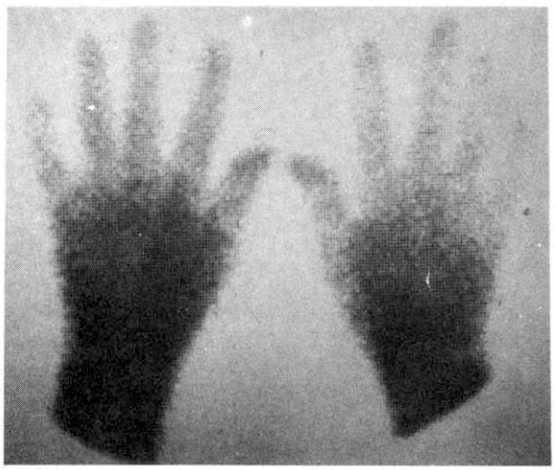

Fig. 5. A static image of scleroderma patient before treatment. There was decreased blood flow of right third, fourth, fifth fingers.

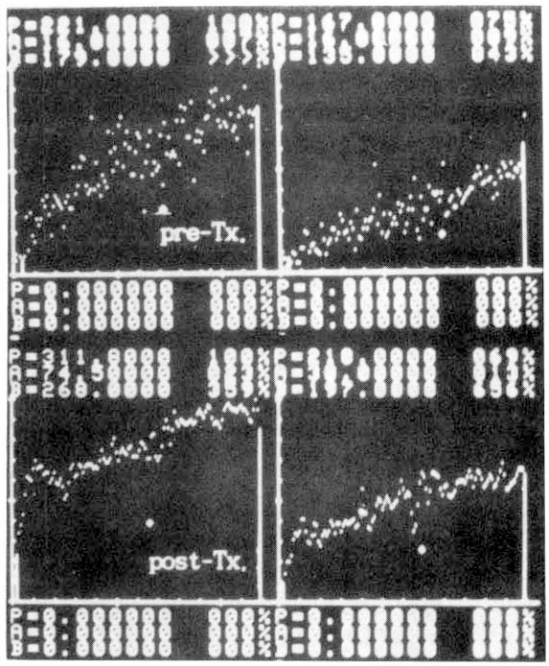

Fig. 6. Time activity curve in the same scleroderma patient in Fig. 5. The top panel was a time activity curve of pre-treatment and the low panel was a curve of post-treatment.

SD) and after treatment was 0.630±0.168. The change of initial slope ratio between before and after treatment indicated improved blood flow rate in cold hands after 2 week therapy. When compared with 310 sec. cumulative digital blood flow, we found that there was somewhat improvement in digital blood flow. The 310 cumulative digital blood flow ratio was 0.440±0.073 before treatment and 0.651±0.082 after treatment.

In 4 patients of scleroderma, the ratio of activity in the cold exposed hand to room air exposed hand, 20 minutes after cold exposure changed from 0.545±0.128 (mean±SD) before treatment to 0.487±0.195 after treatment, which indicated no significant statistical difference. When comparing with 310 sec. cumulative digital blood flow ratio, we found that there was minimal change in digital blood flow.

When comparing with 310 sec. cumulative digital blood flow ratio, we found that there was minimal change in digital blood flow. The 310 sec. digital blood flow ratio was 0.440±0.073 before treatment and 0.651±0.082 after treatment. The similar result was noted in the patient of polymyositis. But in one case of MCTD, there was considerable improvement in digital blood flow after 2 weeks therapy as the value of 0.668 chan-

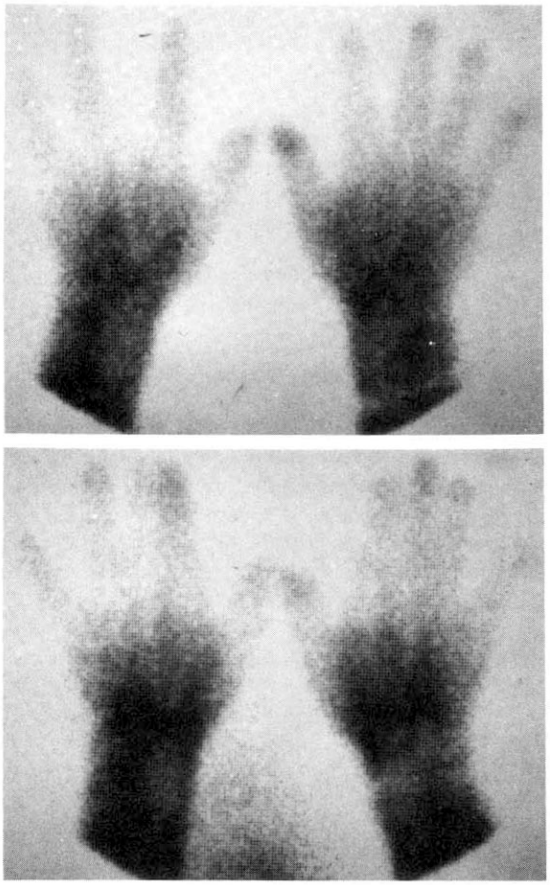

Fig. 7. The upper panel showed markedly decreased radionuclide uptake in left middle finger of MCTD patient. Shown in the low panel, uptake in left middle finger in the same patient increased to some extent after 2 weeks of therapy.

ged into 1.000 in the ratio of activity in cold exposed hand to room air expsed hand, 20 min. after cold exposure and 0.398 into 0.744 in 310 sec. cumulative digited blood flow ratio. We observed a similar degree of digital blood flow improvement in 1 patient of Behcet's syndrome and 1 patient of SLE.

Fig. 5 showed a static image of scleroderma patient before treatment and decreased blood flow of right third, fourth and fifth fingers below the metacarpal area. Fig. 6 showed time activity curves before and after treatment in the same scleroderma patient in Fig. 5. The top panel was a time

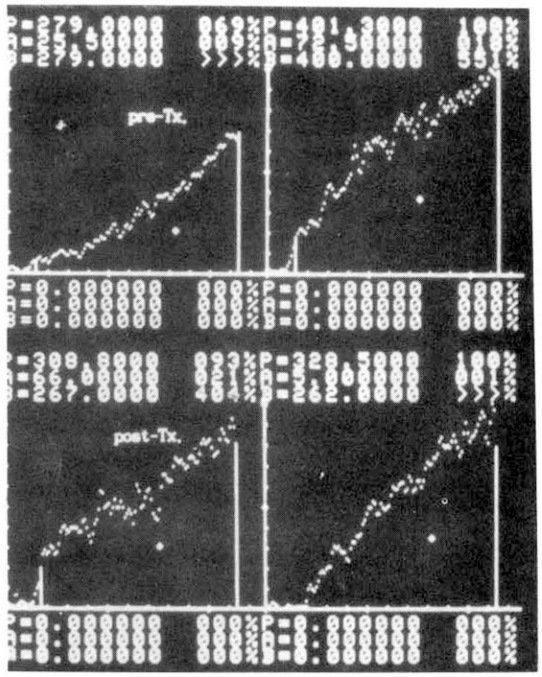

Fig. 8. Same MCTD patient's time acitivity curve in which the digital blood flow was much better after treatment.

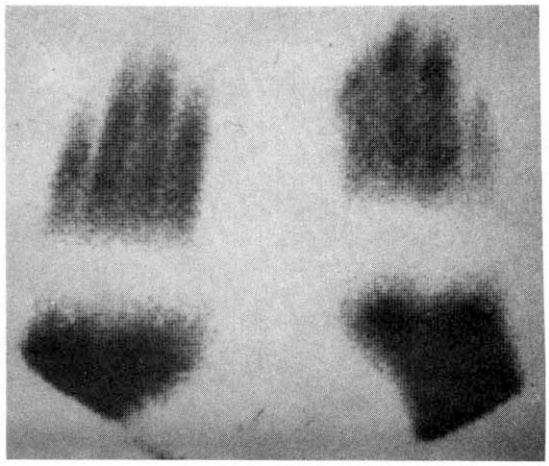

Fig. 9. Reduced blood flow of right little finger in a localized scleroderma patient.

activity curve of pre-treatment and the low panel was a curve of post-treatment. We could know minimal improvement in blood flow even after the treatment. The static image of MCTD patient was in Fig. 7. The upper panel showed markedly decreased radionuclide uptake in left middle finger. Shown in the lower panel, the uptake in left middle finger in the same patient increased to some extent after 2 weeks of therapy. Fig. 8 demonstrated the same MCTD patient's time activity curve in which the digital blood flow was much better after treatment. We could see reduced blood flow of right little finger in a localized scleroderma patient (Fig. 9).

DISCUSSION

Our knowledge of the pathophysiology, diagnosis and the treatment of Raynaud's phenomenon has increased markeldy since the original description of the entity by Maurice Raynaud in 1862. However, Raynaud's phenomenon remains a riddle despite over 125 years of research. In 1923, Sir Thomas Lewis[21] first showed that the digital vessels in patients with Raynaud's attacks are abnormally responsive to cold even in the absence of sympathetic innnervation. Lots of tests to evaluated the finger blood flow has been done until now. But patient history is still though to be the most reliable method of diagnosis. Several labortory tests, including immunologic tests and radiograph, should be included. Nerve conduction studies are also needed to exclude entrapment syndrome.

There were additional laboratory techniques for diagnostic accuracy. Porter et al[22] used a thermocouple to measure the changes in skin temperature of the fifth finger after ice water immersion for 20 seconds. In the 30 controls, recovery averaged 10 minutes, wheras in 23 patients with Raynaud's phenomenon the average was 30 minutes. Thermography, which measures thermal gradients along fingers, utilized a similar technique. The method of our radionuclide scitigraphy referred to the study of the thermocouple by Porter et al.

Plethysmography counted the increased volume of the digits because of the influx of blood. Sumner and Strandness[16] found that 78 percent of 105 people with cold sensitivity produced a "peaked" and "peaked and obstructed" wave form. A similar form was seen in only 4 percent of control group. Plethysmography has been found to be a useful tool to follow the course of the treatment. Coffman and Cohen[19] reported measurements of total digital flow plethysmographically and of capillary flow by radioisotope disappearance rate in Raynaud's phenomenon.

Ultrasound can also be used to evaluate blood flow. Both ultrasound and plethysmography may be helpful in providing the location and degree of blockage in the vessels.

Using cryodynamic hand arteriogram, Rosch et al[18] reported that 35 of 39 patients had basal digital vasospasm, whereas 34 of the same 39 patients also had organic obstruction involving primarily digital arteries. Porter et al[23] reported that arteriogram seldom needed to establish the dignosis of the Raynaud's. These authors utilized arteriography to evaluate a suspected surgically correctable proximal arterial lesions.

Laboratory testing for Raynaud's phenomenon is only partially successful and may not be entirely producible, even after rigid standardization. Raynaud's phenomenon continues to be a diagnosis based on a carefully taken history.

A wide variety of therapeutic management of Raynaud's ayndrome are available but there are no definite and easy parameters to predict the outcome of therapeutic effect. There were no data to support that early dignosis and treatment of Raynaud's influences outcome when associated with connetive disease.

We investigated digital finger blood flow with radionuclide scitigraphy after ice water exposure. MDP was used in this study by reason that the uptake of Tc-99m MDP is proportional to the amount of blood flow and most of Tc-99m MDP is circulated in blood during 5 minutes after intravenous administration[24].

In comparison with 3 groups, we concluded that in 10 patients of Raynaud's, 310 seconds cumulative digital blood flow ratio was significantly low and the initial slope ratio of cold exposed hand to room air exposed hand which was also low was the important parameter. There was no significance in the parameters such as the ratio of activity in cold exposed hand to room air exposed hand, and uptake increase in the same hand.

Of 8 patients with Raynaud's phenomenon, 4 scleroderma and 1 multiple myeloma patients had minimal change in digital finger blood flow of cold exposed hands even after 2 weeks of therapy with vasodilators, calcium channel blockers or antiplatelet drugs. 1 MCTD, 1 Bechect's syndrome, and

1 SLE patient had improved finger blood flow after therapy.

Here, the benefits of our simple clinical test to allow both an objective diagnosis and objective assessment of therapeutic response were apparent.

In summary, the method to evaluate finger blood flow with a radionuclide is a simple, ecomomical and objective assessment of the follow-up and therapeutic effects and gives an aid in the study of the pathophysiology of the Raynaud's phenomenon.

REFERENCES

1. Raynaud M: *On local asphyxia and symmetrical gangrene of the extremities. In Selected monographs. London: New Sydenham Society, 1888, 1862*
2. Allen BR: *Griseofulvin in Raynaud's phenomenon: Lancet 2:840-841, 1971*
3. Kleinsmith D: *Raynaud's syndrome: An overview. Sermin Derm 4:104-113, 1985*
4. Lewis T: *Experiments relating to the peripheral mechanism involved in spasmotic arrest of the circulation on the finger: A variety of Raynaud's disease. Heart 157:101, 1029*
5. Peacock JH: *Peripheral venous blood concentration of epinephrine and norepinephrine in primary Raynaud's disease. Circ. Res 7:821-827, 1959*
6. Jamieson GG, Ludbrook J, Wilson A: *Cold hypersensitivity in Raynaud's phenomenon. Circulation 44:254-264, 1971*
7. Pringle R, Walder DN, Weaver JPA: *Blood viscosity and Raynaud's disease. Lancet 1:1086, 1965*
8. Caputi CA, De Carolis G: *Peripheral vascular disease: Flow studies and clinical results after isoolemic hemodilution-case reports. Angiology 124-127, 1986*
9. Govle KB, dormandy JA: *Abnormal blood viscosity in Raynaud's phenomenon. Lancet 1:1317 -1318, 1976*
10. Jansen T, Nieison SL, Skovberg F: *Blood viscosity and local response to cold in primary Raynaud's phenomenon. Lancet 2:1001-1002, 1977*
11. Halpern A, Kuhn PH, Shaftel HE, et al: *Raynaud's disease, Raynaud's phenomenon and serotonin. Angiology 11:151-167, 1960*
12. Marshall RT, Shepherd JT, Thompson ID: *Vascular responses in patients with high serum titers of cold agglutinin. Clin Sci 12:255-263, 1953*
13. Francis G, Hagan AD: *Nitrolgycerine ointment: A review. Angiology 28:873, 1977*
14. Chucker R, Fowler RC, Motomiya Y, Singh B, Hurley W: *Induced temperature transients in Raynaud's disease measured by thermography. Angiology 22:580, 1971*
15. Mendlowitz M, Naftchi N: *The digital circulation in Raynaud's disease. Am J Cardiol 4:580, 1959*
16. Sumner DS, Strandness DE: *An abnormal finger pulse associated with cold sensitivity. Ann Surg 175:294-298, 1972*
17. Kvernebo K, Slangsvold CE, Stranden E: *Laser Doppler Flowmetry in evaluation of skin postischemic reactive hyperemia. J Cardiovasc Surg (Torino) 30:70-75, 1989*
18. Rosch J, Porter JM, Gralino BJ: *Cryodynamic blood angiography in the diagnosis and management of Raynaud's syndrome. Radiology 55: 807-814, 1977*
19. Coffman JD, Cohen AS: *Total and capillary fingertip blood flow in Raynaud's phenomenon. N Engl J Med 285:259, 1971*
20. Lim SM, Chung JK, Lee MC, Kim SJ, Choi SJ, Koh CS: *Measurement of finger blood flow in Raynaud's phenomenon by Radionuclide Angiography. Korean Nuclear Journal 21:183-190, 1987*
21. Lewis T: *Experiments relating to the peripheral mechanism involved in spasmodic arrest of the circulation in the fingers. A variety of Raynaud's disease, Heart 15:7, 1929*
22. Porter JM, SniderRL, Bardona EJ: *The dignosis and treatment of Raynaud's phenomemom. Surgery 77:11-23, 1975*
23. Porter JM, Rivers SP, Anderson CJ, et al: *Evaluation and management of patients with Raynaud' s syndrome. AM J Surg 142:183-189, 1981*
24. Subramanian G, McAfee JG, Blair RJ, et al: *Technetium-99m methylene diphosphonate-A superior agent for skeletal imaging. comparison with other technetium complexes. J Nucl Med 16: 744, 1975*