

THESIS OF UNIVERSITY DISSERTATION (PH.D.)

**PRIMARY RAYNAUD'S SYNDROME:  
ROLE OF MICROCIRCULATORY FUNCTIONAL  
INVESTIGATION METHODS IN DISEASE DIAGNOSIS AND  
PROGNOSIS**

*Zoltan Csiki, M.D.*

DEBRECEN UNIVERSITY MEDICAL CENTER,  
3RD. DEPARTMENT OF MEDICINE  
DEPARTMENT OF CLINICAL IMMUNOLOGY  
*DEBRECEN, 2005*

Raynaud's phenomenon (RP) is an acrosyndrome of vascular origin presenting with paroxysmal vasomotor attacks of the extremities in which presence of an ischemic phase is compulsory. Under Raynaud's syndrome we understand paroxystic ischemic changes of the fingers caused by cold or emotions. The notion of Raynaud's phenomenon and the course of establishing the diagnosis is discussed in the literature. Because the lack of simple and everyday use objective tests the diagnosis is mainly based on anamnesis and clinical signs and symptoms. The patient must be sensible to cold and moisture. Cold, humidity and/or stress causes attacks characterised by: the skin of the fingers and/or toes and/or nose and/or ears and/or lips are blanching – ischemia, later on become cyanotic and finally become reddish – hyperemia. Hyperemia is a sufficient but not necessary component of the attacks. Some authors require the color changes to appear suddenly, with strict delimitation, since diffuse skin patchiness can occur in healthy as well.

The aim of my study is to determine the role of functional hand circulation methods in the diagnosis of patients presenting with Raynaud's phenomenon, disease course and design of efficient therapy.

I examined the separate and combined usefulness of three methods – capillaroscopy, laser doppler scanner, isotope hand perfusion scintigraphy – in my patients with Raynaud's syndrome. The number and composition of patient groups differed in the substudies.

## **THE AIMS OF THE STUDY BRIEFLY**

I. During isotopic measurement of hand microcirculation in primary and secondary and early and late Raynaud's I searched answers to the following questions:

a. Does the primary and secondary Raynaud's present any difference visually in the regional perfusion disturbance ?

b. With quantitative evaluation do the different Raynaud's groups differ between each other, does it present age related specificity or can we predict disease progression ?

II. Using the functional examination methods of the hand microcirculation (laser scanner doppler, radioisotopic method) do we observe any difference in the different phases of Raynaud's syndrome, in primary and secondary Raynaud's, in smoker and non-smoker patients. My aim was to determine the diagnostic value of the laser-scanner doppler method in the examination of microcirculation with comparison of the parameters of the known and used radioisotopic methods.

III. With study of the nailfold capillary patterns I tried to determine, whether the nutritional microcirculation network changes between early and late onset Raynaud's.

## **METHODS**

### *Special requirements of the examinations:*

The patients were examined after 30 minutes accommodation in room temperature ( $24,2\pm 0,3^{\circ}\text{C}$ ). Minimally four weeks before examination the patients were stopped from use of vasoactive treatments, beta-blocking drugs, Ca-channel antagonists, pentoxiphylline.

### **1. Capillary microscopy:**

To determine the morphology of nailfold capillaries we used capillaroscopy (Nikon fluorescent microscope, model 1990). The examination is not invasive, it gives an overview of the nailfold of the given finger. The course of the examination: the patients puts his finger on a special microscope table, we cover the nailbed with glycerine ointment and perform the examination using magnification of 40x-200x.

For the reason of statistical analysis both in early and late Raynaud's we used simplified morphological grouping. Based on capillary morphology we grouped our patients in 4 separate groups: 1. no capillary aberration; 2. avascular image; 3. giant capillaries; 4. scleroderma sign (avascularity+giant capillaries).

### **2. Isotopic hand perfusion scintigraphy using $^{99\text{m}}\text{Tc}$ DTPA:**

The examination does not require any preparation. The patient puts his hands with furled fingers on the surface of the collimator of the gamma-camera. We inject in bolus in a cubital vein 400 MBq  $^{99\text{m}}\text{Tc}$ -DTPA. The picture acquisition was performed with low energy, parallel borehole collimator equipped MB9200 type gamma-camera. Simultaneously with the injection we started a 60x1 second picture series and immediately after we recorded a 3 minute lasting static picture (steady state).

### **3. Laser scanner method**

#### *Course of the examination*

We collected 3 consecutive images from the palmar region of the non-dominant hand: 1. in resting situation; 2. after suprasystolic compression of the brachial artery in the so called „low blood” – „ischemic” state; 3. after release of the cuff in the „hyperaemic” state. The examinations were performed with Perimed Laser Doppler Imager (LDI).

### *Evaluation of the laser scanner examination*

On analogy to the isotopic examination we delimited two regions: the regions of the II.-V. fingers and the palmar region. Using the software of the instrument (Perisoft v. 2.1.) we measured in the two regions the lowest, the highest and the mean perfusion. The results were given in perfusion units (voltage). After this, taking as basal values the mean parameters of the steady state we measured the procentual change of the mean perfusion.

### **1. STUDY: Isotopic characteristics of hand microcirculation in primary and secondary and early and late Raynaud's syndrome**

In every of our examined patients we could observe the episodic, paroxysmal ischaemia of the fingers which classical occurs with three clinical phases. We did not include the patients with diabetes and/or hypertension as concomitant disease. Before examination the patients did not receive any vasoactive treatment. During processing we grouped our patients as primary and secondary Raynaud's according to clinical and laboratory criteria widely accepted in the literature. We studied the characteristics of the primary and secondary form based on the hand perfusion values of 84 patients.

The secondary form was observed most often linked to scleroderma, and in some more rare extent to systemic lupus, Sjögren syndrome, dermatomyositis.

We discuss the characteristics of the early and late form based on data of 127 patients (20 males, 107 females, mean age 40.3 years (14-63 years)). We considered late Raynaud's as disease occurring after the age of 40 according to the above mentioned criteria. In this study were included only patients in whom the following results were normal: cold agglutinins, antinuclear factor, paraprotein, cryoglobulines, Scl-70 antibody, Waaler-Rose.

The disease extent in the time of the study was mean 7.2 years (2-34 years). The first signs of the disease first appeared at the mean age of 33 years (4-62 years). In the case of 53 patients the disease onset was over 40 years (41%) and only in 2 patients (1.5%) over 60 years. In 7 patients (5.5%) the first symptoms presented under the age of 10.

### **EVALUATION:**

The evaluation of the hand perfusion scintigraphy was done with DIAG (digital data management programme for gamma camera) software. The evaluation of the results was performed partly visually and partly with quantitative method.

### *Visual evaluation:*

We examined the regional perfusion disturbance of the fingers which manifested in circumscribed decrease or lack of finger activity.

### *Quantitative evaluation:*

We determined the finger/palm ratio (FPR) based on the total scintillation on static images of the II-IV fingers and the palm region. Based on the fact, that according to clinical data during classical Raynaud's attack the thumb is very rarely affected and considering that the consideration of these data lowers the sensibility of the method we left out the thumb from the ROI (region of interest).

### *Statistical analysis*

We evaluated the frequency of regional perfusion disturbance in the primary and secondary group using chi square method. The differences between the left and right FPR-s were evaluated with paired Student's T-test, the differences between genders with 2 sampled t-probe and with d-probe the FPR values of the primary and secondary group after the F-probe performed to evaluate the variation of the groups. We searched correlation between age, patient's age at disease start, disease duration and FPR using variance analysis. We compared the FPR values of the early and late form using non-parametric Mann-Whitney probe.

## **RESULTS**

Visual evaluation: In the primary RS group from 33 patients in only 2 cases we found mild diminution of activity in the distal part of one-one finger. In the majority of patients from this group the finger activity was symmetrically low on both sides. In contrary, in the secondary form from 51 patients in 37 cases we observed smaller-greater regional perfusion disturbance which ranged from regional activity decline or lack of activity of one terminal phalanx to severe perfusion disturbance including more fingers or the palm.

The regional disturbance was significantly higher in the secondary RS group ( $p < 0.001$ ).

During Quantitative evaluation we correlated the FPR-s in the two groups:

- With paired t-test we determined that between the FPR values of the right and left hands there is no significant difference in neither groups ( $p > 0,05$ ). This is the reason why in the future all statistical probes refer to all the hands.

- The mean of the values of males and females did not differ in the primary or secondary groups ( $p>0,05$ ) that is why we use the values of both sexes together.
- In the primary RS group the mean FPR value measured on the left side was  $0,51\pm0,14$ , on the right side  $0,48\pm0,13$ , as in the secondary group on the left side  $0,53\pm0,17$ , on the right side  $0,56\pm0,24$ . When comparing the FPR values of the primary and secondary groups, we found that the FPR values of primary RS patients were significantly lower compared to the secondary group ( $p<0,05$ ).
- In the early nor in the late RS groups we did not find significant difference between the FPR values of the right and left hands ( $p>0,05$ ). Henceforth in data management we evaluated the data of both hands together.
- The FPR values obtained with Tc-99mDTPA hand perfusion scintigraphy showed difference between RP beginning before and after 40 years of age. The mean FPR value in early form was  $0,46\pm0,21$ , in late form  $0,56\pm0,14$ . The statistical analysis resulted in significantly lower FPR values in the early form compared to the late form ( $p<0.001$ ).
- We found significant correlation between patient age at the disease onset and FPR ( $p<0.001$ ).
- We did not find significant correlation between patient age at examination date and FPR and disease duration and FPR.

## **2. STUDY: Functional examinations of hand circulation in Raynaud's syndrome: comparison of laser scanner and radiosotope methods.**

### **PATIENTS**

We examined 58 patients with primary Raynaud's syndrome (6 males and 52 females). Mean age 40,1 (coefficient of variation 13,08), disease existence during examination was mean 6 years (2-15 years). The patients presented first time in hospital mean after 2 years of disease onset (0-12 years). From the patients 38 were smokers. In 23 cases the stress also could be found as precipitating factor, in the others (35 patients) only the cold could be found as provoking factor. The anamnesis of 42 patient was positive for headache. In the majority of patients (45 patients) only the fingers were affected, in 13 cases the toes were also involved. 53 patients presented typical triphasic attacks, in 5 cases only biphasic attacks were to be observed.

The mean age of the 16 non-smoker healthy control in the laser scanner study was 38.9 years (coefficient of variation 9.6).

#### *Statistical analysis:*

We compared the basic, post-ischaemia and reactive hyperaemia perfusion values of control and primary Raynaud's patients during laser examination with two tailed t-probe. We used the two tailed t-probe as well for the measurement of differences between finger FPR values and differences in laser values in smoking and non-smoker groups. Because the distribution differed from normal we used Mann-Whitney probe to compare the data of migraine and non-migraine subgroups. We characterised the relationship between FPR values and basal perfusion values measured with laser method using the Pearson correlation coefficient.

### **RESULTS**

- In primary Raynaud's patients compared to healthy controls we measured in basal conditions significantly lower perfusion values (PUmin, PUmax, PUmean) in the finger and palm regions as well.
- We did not find difference between the perfusion values of the fingers and palm of patients. After cuff compression, in „ischemic” phase this difference between patient and healthy group disappears: the perfusion values measured in the region of fingers and palm did not differ between the two groups. After decompression in the

„hyperaemic” phase in finger region of both groups we measured significantly higher perfusion values compared to baseline, difference could be found in PUmin, PUmax, PUmean as well.

- Although in healthy controls during hyperaemia phase we measured significantly higher perfusion values the magnitude of change referred to baseline did not differ compared to patients with primary Raynaud's.
- During visual analysis of hand perfusion scintigraphy we did not observe circumscribed diminution or elevation of activity in the region of fingers or palm. The finger-palm ratio (FPR) measured on both hands - left side 0.54 (coefficient of variation 0.17), right side 0.53 (coefficient of variation 0.14) – did not differ one from each other.
- The basal laser values of smoker vs. non-smoker primary RS patients did not differ (smoker PU mean:  $1,07 \pm 0,25$  vs. non-smoker PU mean:  $1,04 \pm 0,40$ ) but the amplitude of the hyperaemic response was significantly lower in smokers (smoker PU mean change: 0,36 vs. non-smoker PU mean change: 0,50), ( $p = 0,018$ ).
- The basic FPR values measured with hand perfusion scintigraphy were significantly lower in our smoking patients ( $FPR_{\text{smoker}}: 0,50 \pm 0,2$  vs.  $FPR_{\text{non-smoker}}: 0,72 \pm 0,12$ ) ( $p = 0,0011$ ).
- Comparing the hand perfusion values of headache and non-headache primary Raynaud's patients we did not find difference between the laser parameters (PUmin, PUmax, PUmean, PUchange) neither between radioisotopic FPR values ( $FPR_{\text{migraine}}: 0,52 \pm 0,15$  vs.  $FPR_{\text{non-migraine}}: 0,57 \pm 0,19$ ) ( $p > 0,05$ ).
- We found significant linear connection ( $p < 0,05$ ) between basal laser values PUmax and radioisotopic FPR values.

### **3. STUDY: Analysis of nailfold capillary morphology in primary Raynaud's syndrome and early and late Raynaud's phenomenon.**

*Comment: The patients of this study are the same as in Study 1. and 2.*

#### *Statistical analysis*

We examined the frequency of capillaroscopic changes in early and late Raynaud's phenomenon determining the confidence interval.

### **RESULTS**

- In the majority of our patients (84%) normal capillary morphology was observed with rare avascular regions. In some cases (9%) enlarged capillaries were observed and in only 2 cases (3%) bushy capillaries. We did not have patients with nailfold bleeding or extravasation on capillaroscopic image.
- We found normal capillary morphology in the majority of early (43%) and late (55%) onset Raynaud's phenomenon patients. Diffuse avascularity was observed more rarely: 24 % vs 21 % and giant capillaries: 18 % vs. 11%. In only some cases we found capillary pattern typical to scleroderma 16 % vs 13 % in early and late onset disease.
- The presence of distinct capillary pattern is not specific to the age specific subtypes of the disease (early vs. late onset form) ( $P>0,05$ ).

## DISCUSSION

The microcirculation of the skin is made from two distinct networks: one superficial – nutritive – and one deeper – mainly termoregulatory – system. Different methods were developed for the examination of these systems. The nutritive system of the skin can be examined with the help of capillary microscopy where the microscope shows in micrometer deep the end capillary network of the skin. The number of capillaries, their density and shape correlates with some diseases.

The laser doppler method examines mainly the termoregulatory capillary system of the skin in deep of approximative 1 micrometer. In 1993 the laser doppler method was further developed and the laser scanner method – laser imager was born. This method allows us to make a color coded map of the examined region using laser doppler without direct contact with the skin surface. Multiple articles described the clinical usefulness of the laser scanner method. The method was succesfully used for the examination of wound healing, diabetic neuropathy, determination of neovascularisation in skin cancer, vasoactive effects of acupuncture.

The use of radiopharmaceuticals allows us to visualise the microcirculation of the hand as a whole, including the superficial and deep palmar arches which establishes link between the system of the radial and ulnar arteries and the smaller feeding arteries originating from them. As a radiopharmaceutical we used dietilene-triamin-pentaacetate (DTPA) which is suitable also for isotopic circulatory examinations. At present we have at our disposition only few methods for everiday use in clinical practice which are suitable for quick and objective evaluation of of the global circulation of the hands. In our study we studied together the superficial and deeper microcirculatory system of the hand in patients with Raynaud's phenomenon.

Raynaud's phenomenon is a frequent acrosyndrome of vascular origin. According to a spanish study the mean prevalence of the disease is 3.7%, in females is higher 4.7%, in males 3.2%. The diagnosis of the disease is made based on the attack itself (paroxysmal discoloration of the fingers caused by cold exposition). In primary Raynaud's syndrome the disease is idiopathic occurs alone and no other disease can be observed in the background. In the case of secondary Raynaud's syndrome the circulatory disturbance of the fingers is associated with known systemic disease of origin.

Based on our actual knowledge it was not surprising that the anatomy of the superficial capillary bed was mainly normal. This justifies that the nutritive capillary system of the skin is conserved in primary Raynaud's syndrome. Indifferent of age and gender in healthy the capillaries of the acral region (including those of the nailfold) are uniformly represented. According to our present knowledge the age of the subject does not have significant effect on the capillary morphology. As single alteration we can observe in 25% of elderly the dilatation of the apical region of the capillaries. This later morphological characteristic does not have any effect to the microcirculation of the given region. In Raynaud's syndrome the morphological characteristics of the nailfold capillaries bear diagnostic value. In primary Raynaud's syndrome no or minor capillary changes can be observed. Secondary Raynaud's syndrome presents with disturbances in the shape and density of the nailfold capillaries (avascularity and/or giant capillaries). In our present study we found microscopical alterations in similar extent both in early and late onset Raynaud's syndrome. The capillary morphology seems to be independent of age in Raynaud's syndrome patients as we have previously seen in healthy subjects.

Our examinations done on more than 100 patients proved, that the DTPA can be used with success for characterisation of hand circulation. It gives essential visual information about the palm and finger microcirculation for the clinician. Frequently shows the exact place of lowered circulation regions, of macrovessel circulation disturbances and helps the introduction of aimed therapy.

Our examinations sustain the data from literature according to which the primary Raynaud's syndrome presents symmetrically affecting the fingers of both hands. In our study we nearly did not find any regional perfusion disturbance. In contrast to this in secondary form we observed a very diversified picture: from the slight symmetric perfusion disturbance of the fingers to severe regional circulatory insufficiency which could be manifested also in loss of circulation of a given finger. Despite the fact that we have measured significantly lower FPR values in the primary form the clinical signs were more severe in the secondary form. This can be explained possibly by the regional ischemia observed in the later group.

Despite the fact that we observed this phenomenon more frequently between females, we did not find significant differences between genders based on FPR values in both groups. The phenomenon affects mostly young females and the late onset form is to be observed more rarely. With the help of 127 patients we studied the characteristics of late onset (after the age of 40) Raynaud's phenomenon. We were interested if there were differences in the occurrence, diagnostics of this later form compared to the early form. According to our experience the

disease starting before the age of 40 is characterised with narrowed finger microcirculation as compared to the late onset form, indifferent of disease duration. This may be related to the differences in microvascular reactivity between the two age groups. This means that the hand microvasculature in the two groups reacts to different noxae or stimuli with different scale of spasm or dilatation.

Using hand perfusion scintigraphy we could observe significant correlation between patient age at disease onset and extent of hand microcirculation narrowing. But this was not demonstratable between disease existence and finger circulation. The result of our study shows, that despite the fact that the early onset of disease goes hand in hand with more severe symptoms we should not fear from disease progression with time. This supposition is more reasonable taking into consideration that the method used for characterisation of finger circulation is independent from patients age in this group of patients.

Because we did not have previous experience with the laser method, to prove the validity of our measurements we used healthy controls as well. In basal conditions the lower perfusion values of the fingers of primary Raynaud's syndrome patients was to be expected compared to healthy controls. It was interesting to observe that the superficial perfusion of patients palm was also lower than the controls despite the fact that generally the patients complain only to cold in their fingers. In contrast to the perfusion values obtained with laser doppler which did not show difference between finger and palm circulation, based on the FPR values the finger radioactivity acquisition was significantly lower than the palm acquisition. The rich blood content of the palmar tissues is preserved, so it is understandable that the patient feels cold only in his fingers despite the fact that the superficial thermoregulation of the whole hand is affected in the disease. The extent of postocclusive reactive hyperaemia did not differ between the non-smoker primary Raynaud's patients and healthy controls, this confirms the observations of Ringquist and colleagues according to whom the endothelium dependent vasodilatation of primary Raynaud's syndrome patients in room temperature did not differ from healthy controls. This means that the vasoreactivity of the skin capillaries is maintained but the response reaction runs its course with lower perfusion levels. If we compare our results with the known pathophysiological causes of Raynaud's phenomenon some interesting questions are to be posed. Between the pathogenetical theories main role is played by the 'local fault' theory of Thomas Lewis. The smooth muscle of the finger arteries overreacts to some external stimuli - often cold or emotional overload - and in this process the main role is played by the hyperreactivity of smooth muscle to normal sympathetic stimuli. With both measuring methods based on our measurements we could observe

difference in basal values of finger circulation. We expected difference in the range of „hyperreactivity” in patients suffering from headache and in patients without this complaint. Our measurements did not confirm this supposition. The pathomechanism of the symptom is much more complex. Lindblad and coworkers proved disturbances in the activity of alpha-1 receptors in Raynaud’s syndrome, the others assign importance to the imbalance of the production of vasoactive materials by the endothelial cells. According to Rustin and coworkers in the sera of Raynaud’s syndrome patients can be found factors which inhibit endothelial cells in prostacyclin production or excretion.

The harmful effect of smoking on circulation could be measured in this group as well. The lower FPR values measured by radioisotopic method in smokers prove the hypothesis that the low finger perfusion is even more lowered by smoking and this correlates with the results of Goodfield and coworkers according to whom the capillary flow of smokers is lower than of the non-smoking people. The decrease in amplitude of hyperaemic response in smokers measured by laser doppler shows the narrowing of vascular reserve as well. We think that is a relation between the amplitude of the postischemic hyperaemic response and the endothelial function but this needs further studies.

The treatment of Raynaud’s phenomenon is determined by its type and severity. In the same time the number of methods able to quantify disease severity and prognosis is low and their objectivity and accuracy is questionable. Numerous methods were used to objectivise the vasospasm, but their use and diagnostic value in RS is ambiguous: pletysmography, point laser doppler, radioactive isotopic clearance methods.

Based on our results we consider a reasonable suspicion that besides capillary morphology characterisation is of utmost importance the examination of the functional circulation of the RP patients which can be done using the isotopic or the laser scanner imaging method. With the use of isotopic hand perfusion method large vessel disease can be filtered out as well eg. carpal tunnel, TOS, small artery thrombosis. From practical point of view it looks useful to filter patients with very low FPR values (narrowed microcirculation) and to follow them up closely irrespective of their primary or secondary disease.

If with further study we could prove the relationship between the endothelial function and extent of the hyperaemic response this method can be used in clinical practice as a useful, cheap, noninvasive screening method.

## **Summary:**

Raynaud's phenomenon is a frequent disease in moderate climate population – as is Hungary. The disease even in its mild form is a debilitating one causing suffering to the patients from whom the majority are active breadwinners. This is the reason why it is of outmost importance the follow up of these patients, their expense efficient diagnosis and treatment planning to obtain an optimal treating period. With our work by the study of usefulness of two methods we opened new possibilities in the diagnosis of patients with cold hands. As until now the diagnosis was based on patient complaints, clinical picture, laboratory and statical morphological examinations based on our work, we consider that the diagnostic protocol should be extended with functional examination methods eg. isotopic circulatory examinations and laser doppler imaging. These methods not only help the diagnosis but give us possibility for the objective patient follow up and point to the coexistence of eventually associated diseases. The big dilemma of clinicians dealing with RS is the early recognition of signs pointing to secondary disease. To know the predictive value of the above mentioned methods for primary and secondary disease we should exactly know their specificities and limitations.

## **New results – Observations :**

1. The nutritive capillary system of the skin is conserved in primary Raynaud's syndrome.
2. We confirmed the results from literature stating that the age does not have significant influence on capillary morphology. The apical capillary dilatation – as a minor aberration – does not have any effect on microcirculation.
3. We determined that in secondary Raynaud's syndrome beneath symmetrical perfusion disturbances of the fingers severe regional flow deficiency may occur what could explain the more severe clinical symptomatology.
4. We showed, that the Raynaud's symptomatology beginning before the age of 40 presents with more severe microcirculatory disturbances which are independent of disease duration. We proved using hand perfusion scintigraphy that the age of the patient at disease start and the deterioration of hand microcirculation presents significant correlation. The microcirculatory disturbance does not progress with age. The basic perfusion values measured with laser scanning of the smoking and non-smoking patients did not differ, but the postocclusive-reactive hyperaemia was significantly more pronounced in smokers. The basic FPR values measured using hand perfusion scintigraphy were significantly lower in our smoker group.
5. Based on our results we consider a reasonable suspicion that besides capillary morphology characterisation is of utmost importance the examination of the functional circulation of the RP patients which can be done using the isotopic or the laser scanner imaging method. The advantage of the laser doppler method is its non-invasiveness, reproducibility, the availability of standardised measurement techniques and that besides patient follow up the method is also appropriate for the determination of the efficacy of different therapeutic methods.

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