

LASER-DOPPLER MEASUREMENT OF DIGITAL BLOOD FLOW REGULATION IN NORMALS AND IN PATIENTS WITH RAYNAUD'S PHENOMENON

Johannes K. Kristensen, Merete Engelhart and Torben Nielsen

Department of Dermatology, Rigshospital, Copenhagen, Denmark

Abstract. Finger blood flow was measured continuously by a laser-Doppler flowmeter in normal subjects and in patients suffering from primary or secondary Raynaud's phenomenon. In normals, skin areas with and without arteriovenous anastomoses could be differentiated. Blood flow in areas with shunt vessels decreased after a deep breath but not during venous stasis or the Valsalva manoeuvre, while in other skin areas a decrease in blood flow was observed after all three manoeuvres, suggesting a dual innervation of nutritional and shunt vessels. In patients with Raynaud's phenomenon (scleroderma) fingertip blood flow reacted in the same way as normal skin without shunt vessels. During direct and indirect cooling, finger blood flow in patients with secondary Raynaud's phenomenon reacted with the same *relative* reduction as normals but resting blood flow in the patients was significantly decreased and the rewarming period was greatly prolonged. In patients with primary Raynaud's phenomenon an even more prolonged decrease in blood flow was observed after direct or indirect cooling. Defective function of arteriovenous anastomoses is proposed as an explanation of the deviations from normal. A pathophysiological classification of Raynaud's phenomenon may be possible on the basis of the function tests described.

Key words: Raynaud's phenomenon; Cutaneous blood flow; Laser-Doppler flowmeter; Sympathetic nervous system

Finger blood flow in generalized scleroderma has been investigated mainly by isotope washout methods (3, 13) and venous occlusion plethysmography (2). As the tightness of the skin in scleroderma might interfere with the plethysmographic recording and as ¹³³Xenon clearance probably measures only capillary flow, while flow in arteriovenous anastomoses influences clearance to only a small degree (6), it might be an advantage to apply the laser-Doppler flowmeter to investigate digital blood flow regulation in scleroderma. This instrument has been described previously and it seems justified to conclude that a registration of total cutaneous blood flow can be achieved and expressed in relative terms (6, 10, 18). In generalized scleroderma, recent

morphologic investigations have shown involution of arteriovenous anastomoses in fingertips together with severe alterations of capillaries and arterioles by narrowing or complete obstruction (2). The morphologic changes might result in a decreased blood flow, impeding both the nutritional and the non-nutritional blood flow.

An explanation of Raynaud's phenomenon in scleroderma could be based on evidence of an abnormal regulation of digital blood flow in response to various kinds of sympathetic stimulation. Exposure to cold elicits cutaneous vasoconstriction which is most pronounced in the hands and feet (7, 8), a response which is chiefly mediated by the sympathetic nervous system. The skin vessels of a cooled hand also show a direct response to cold. Moderate cooling or exposure for brief periods to severe cold results in constriction of the resistance as well as capacitance vessels, a reaction of both local and reflex origin (7).

Straining against a closed glottis (termed the Valsalva manoeuvre) has been shown to increase activity in muscle sympathetic nerves via baroreceptor stimulation, but appeared to be without *consistent* effect in skin sympathetic nerves (1, 4, 5). Vasoconstriction seems to occur in muscle as well as in certain skin areas in response to these manoeuvres (19, 20).

Vasoconstriction is readily elicited in hand vessels after a gasp (20). There is no definite evidence of the location of the receptors responsible for this reaction mediated by sympathetic nerves but it has been shown that activity is increased in skin sympathetic nerves (but not in muscle nerves) (20).

In the fingertips, arteriovenous anastomoses and arterioles are regulated by the sympathetic nervous system (7, 19). During warm conditions as much as 80 per cent of blood flow in fingers may pass through arteriovenous anastomoses.

The present investigations were conducted in an

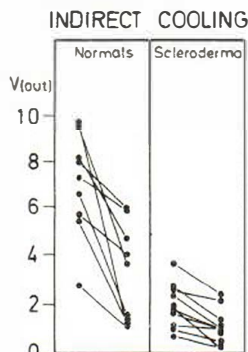


Fig. 1. Finger blood flow (expressed in units of volts) before and after immersion of the contralateral hand in ice-water. Mean fingertip "blood flow" is lower in the patients both before and after the stimulus, but the relative reduction is equal.

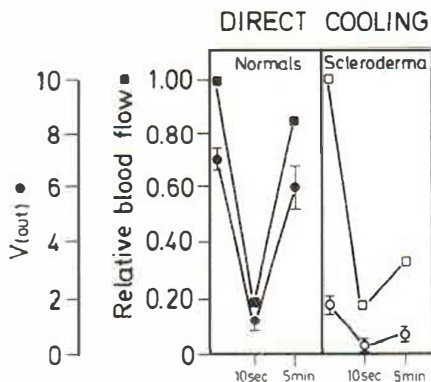


Fig. 2. Blood flow expressed in units of volts as well as in relative terms after a direct cooling stimulus. In the patients, blood flow is reduced to very low levels, and the rewarming period is prolonged.

effort to elucidate the function of the sympathetic nervous system and digital blood flow in generalized scleroderma.

MATERIALS AND METHODS

Experimental conditions

Healthy subjects ranging in age from 32 to 60 were studied, none of whom was taking any medication. Acroscleroderma patients aged 26 to 70 years, all suffering from Raynaud's phenomenon, were studied. The subjects were investigated sitting in a comfortable position. A single investigation lasted 30 minutes or less. Flow measurements were performed on the pulp of the second or third left finger unless stated otherwise in the following description. Room temperature was kept constant at 24°C. Skin temperature was measured regularly and was with few exceptions lower in the patients.

Flow measurement system

Skin blood flow was measured using the laser-Doppler flowmeter previously described (6, 10, 18). The signal is displayed in units of volts and is proportional to flow velocity. Root mean square voltage output was displayed continuously on a panel meter and on a pen recorder. Calibration was performed by placing the laser probe against a white reflecting surface and adjusting the pen recorder to zero. Reproducibility of the zero endpoint was frequently checked by performing vascular occlusion of the arm (6). The laser headpiece was fastened to the skin with double-sided adhesive tape, a set-up which permitted immersion in water if so desired.

Experimental protocol

1. *Direct and indirect cooling.* In 10 patients and 9 normal subjects the contralateral hand was immersed in ice-water for 10 seconds, the response was recorded, whereafter the

ipsilateral hand was immersed for 10 seconds and the response was again recorded.

2a. In 5 normals and 5 patients, blood flow reactions to a deep inspiration and the Valsalva manoeuvre were investigated and in normals results from fingertips were compared with the reactions to similar manoeuvres when the dorsal site of the finger and the distal part of the arm was investigated. The reactions were also investigated in a cooled finger (immersed in water at 20°C).

2b. One person with slight primary Raynaud's phenomenon was investigated as in 2a.

2c. *Control experiments.* In one normal person local anesthesia was induced at the base of the finger and reactions to a deep inspiration, the Valsalva manoeuvre and to venous stasis of 40 mmHg was investigated on the pulp and on the dorsum of the finger.

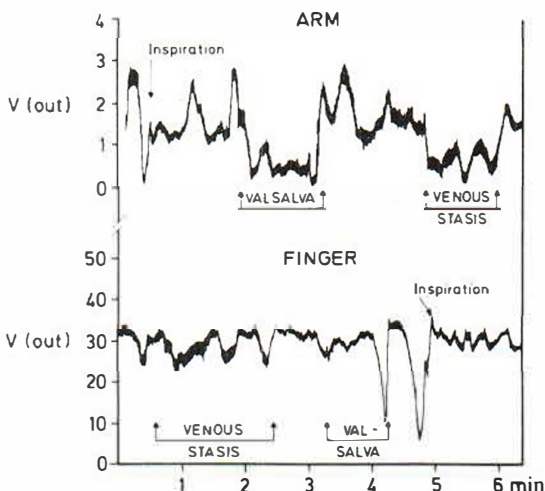


Fig. 3. Registration of blood flow curves from arm and fingertip. Note the difference in units of volts.

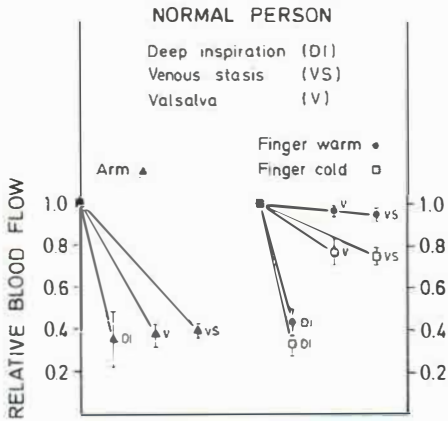


Fig. 4. Relative blood flow during various maneuvers in one normal person.

RESULTS

Arbitrary blood flow values in fingertips in generalized scleroderma were low as compared with that in normals (Fig. 1). Mean value in normals were $3.5 (V) \pm 0.4 \text{ SEM}$ ($N=9$) and in the patients of $0.97 (V) \pm 0.1 \text{ SEM}$ ($N=10$), a difference which was highly significant ($p < 0.001$). The reaction to indirect cooling had to be expressed in relative terms. No difference could be demonstrated, although the reduction in the patients was much smaller than in normals.

Direct cooling of the hand and fingers provided the same relative reduction in normals and patients, which meant that blood flow in the patients was decreased to levels lower than in normals $0.15 (V) \pm 0.1 \text{ SEM}$ vis-à-vis $0.60 (V) \pm 0.2 \text{ SEM}$ ($p < 0.001$). The period until blood flow tended to increase was prolonged in the patients (Fig. 2) and was $5.4 \text{ min} \pm 1.0 \text{ SEM}$ vis-à-vis a value of $2.9 \text{ min} \pm 1.1 \text{ SEM}$ in normals ($p < 0.001$). After 5 min of rewarming, the blood flow had increased to 85% in normals and 33% in the patients (Fig. 2).

In 2 patients with primary Raynaud's phenomenon and persistently cold hands, the rewarming period after direct cooling was very prolonged as compared with results in normals. During an observation period of 20 min, no tendency to return to previous blood flow levels was observed. After indirect cooling in these patients, relative blood flow was reduced to 20%. This response was more pronounced than in normals (46%) as well as in scleroderma patients (57%) (cf. Fig. 2).

In the sympathectomized patient, the reaction to indirect cooling was almost non-existent. The re-

sponse to direct cooling was very pronounced as in non-sympathectomized patients with primary or secondary Raynaud's phenomenon and the rewarming period was prolonged as compared with normals, as only 14% of resting blood flow was regained after 5 min.

From Figs. 3 and 4 it appears that the reaction to venous stasis of 40 mmHg, the Valsalva maneuver and a deep inspiration is almost equal in arm cutaneous tissue, while in the pulp the reactions to the Valsalva maneuver and to venous stasis are revealed only when the finger is cooled.

From Fig. 3 it is apparent that in arm cutaneous tissue the reaction to the various maneuvers is very pronounced, while in the pulp the Valsalva maneuvers elicit only a brief reaction, as does a deep breath, whereas venous stasis of 40 mmHg is without effect.

2a, 2b, and 2c. From Table 1 it can be seen that the Valsalva maneuver caused no blood flow reduction in normal fingertips, whereas it caused a significant reduction in a cooled finger, dorsally on the finger, in arm cutaneous tissue, in scleroderma patients and also in a patient with primary Raynaud's phenomenon. The reaction to a deep breath was present except in an anesthetized finger. In scleroderma patients, who were severely affected by the disease process, the response was decreased. In moderate scleroderma and in a patient with primary Raynaud's phenomenon a normal reaction to a deep breath could be observed.

DISCUSSION

In contrast to isotope washout techniques the present technique for blood flow measurement can be applied for continuous measurement during various

Table 1. Relative blood flow during maneuvers, based on five experiments or more

	Valsalva	Deep breath
Pulp normal ($N=5$)	0.97 ± 0.02	0.43 ± 0.06
Pulp cooled ($N=1$)	0.77 ± 0.06	0.34 ± 0.06
Pulp anesthetized ($N=1$)	0.93 ± 0.02	0.99 ± 0.03
Dorsal finger ($N=1$)	0.47 ± 0.10	0.49 ± 0.02
Dorsal finger anesthetized ($N=1$)	0.95 ± 0.02	0.99 ± 0.03
Arm ($N=2$)	0.37 ± 0.05	0.35 ± 0.13
Scleroderma ($N=5$)	0.43 ± 0.06	0.87 ± 0.04
Scleroderma moderate ($N=1$)	0.36 ± 0.01	0.40 ± 0.02
Primary Raynaud ($N=1$)	0.70 ± 0.03	0.38 ± 0.02

maneuvers. A further advantage is that it can be applied to all areas of the skin. It has been substantiated that an expression of total skin blood flow (i.e. nutritional and non-nutritional) is measured, which is in contrast to the extensively used ^{133}Xe -washout technique (6). The capillary circulation may be regulated differently from the rest of the skin circulation, whose main purpose is body temperature regulation (7). Since the capillary flow is only a small part of the whole, this explains why assessment of this parameter hardly distinguishes between normals and scleroderma patients with regard to amount of blood flow in all areas investigated, except the fingertips (13). Estimation of total fingertip blood flow by plethysmography has failed to identify hypersensitive, cold-induced microvascular reflexes in patients with Raynaud's phenomenon (3). This is consistent with the present observations showing the same relative reduction in finger blood flow during indirect cooling. The main difference between normals and patients seems not to be a more irritable sympathetic nervous system, but rather a near-normal or subnormal activity in the sympathetic nerves superimposed on an altered vascular bed (15). The striking difference in response to direct cooling probably reflects the local fault in the blood vessels in patients with generalized scleroderma (9, 11, 12, 14), but in the patients with primary Raynaud's phenomenon the abnormal reaction observed might well be due partly to an altered response of the sympathetic nervous system, as indirect cooling was an effective stimulus. Sympathectomy in a patient with secondary Raynaud's phenomenon did not alleviate an abnormal response to direct cooling, although the response to indirect cooling was absent, a finding which again underlines the importance of the local fault in the blood vessels (12).

The theory of defective function of the arteriovenous anastomosis in patients with Raynaud's phenomenon was further evaluated, as the finding of severely decreased resting blood flow and the very slow rewarming after direct cooling suggest such a defect.

In normal fingertips of warm-handed individuals a reaction to a deep breath was seen, whereas no reaction to the Valsalva maneuver or to venous stasis occurred. In an anesthetized fingertip, the reaction to a deep breath was absent (showing its nervous origin), while a fingertip cooled to about 20°C did react to both the Valsalva maneuver and to

a deep breath. These findings might be interpreted as evidence of a dual innervation or a dual circulation in fingertips. Only the capillary circulation seems to participate in baroreflex-mediated regulation, while both capillary and shunt flow seem to react to a deep breath. In skin areas devoid of arteriovenous anastomoses (the dorsum of the finger and arm cutaneous tissue), both the Valsalva and the deep breath reaction were present. Pulp blood flow in moderate scleroderma and in primary Raynaud's phenomenon reacted like skin devoid of shunts, while in late scleroderma the pulp still reacted to the Valsalva maneuver though the response to a deep breath was diminished. These findings suggest that in primary Raynaud's phenomenon and moderate scleroderma the shunts are closed at normal ambient temperatures, whereas in late scleroderma the shunts are closed or may have disappeared.

These investigations need to be extended as it seems that a classification of patients with Raynaud's phenomenon might be possible on the basis of these fairly simple function studies providing a more logical approach in future therapeutic trials (17). In this connection it might be suggested to combine these measurements with strain-gauge plethysmography (9, 16).

The optimal set-up might be registration of sympathetic nervous activity by microneurography and simultaneous recording of effector organ response (blood flow and pressure) during various provocation tests (20).

ACKNOWLEDGEMENT

We would like to thank Perimed, Stockholm, Sweden, for placing the laser-Dropller apparatus at our disposal.

REFERENCES

1. Bini, G., Hagbarth, K.-E., Hynninen, P. & Wallin, B. G.: Regional similarities and differences in thermoregulatory vaso- and sudomotor tone. *J Physiol* 306: 553-565, 1980.
2. Burch, G. E., Harb, J. M. & Sun, C. S.: Fine structure of digital vascular lesions in Raynaud's phenomenon and disease. *Angiology* 27: 361-376, 1981.
3. Coffman, J. D. & Tudor Davies, W.: Vasospastic diseases: A review. *Progr Cardiovasc Dis* 18: 123-146, 1975.
4. Delius, W., Hagbarth, K.-E., Hongell, A. & Wallin, B. G.: Manoeuvres affecting sympathetic outflow in human skin nerves. *Acta Physiol Scand* 84: 177-186, 1972.
5. Delius, W., Wallin, G. & Hagbarth, K.-E.: Role of

- sympathetic nerve impulses in regulation of peripheral circulation. *Scand J Clin Lab Invest Suppl.* 128: 47-50, 1973.
6. Engelhart, M. & Kristensen, J. K.: Cutaneous blood flow responses measured by ¹³³Xenon washout and a laser-Doppler flowmeter. *J Invest Dermatol.* In press.
 7. Folkow, B. & Neil, E.: *Circulation*, pp. 449-465. Oxford University Press, 1971.
 8. Folkow, B., Fox, R. H., Krog, J., Odelram, H. & Thorén, ●.: Studies on the reactions of the cutaneous vessels to cold exposure. *Acta Physiol Scand* 58: 342-354, 1963.
 9. Henriksen, O. & Kristensen, J. K.: Reduced systolic blood pressure in fingers of patients with generalized scleroderma. *Acta Dermatovener (Stockholm)* 61: 531-534, 1981.
 10. Holloway, G. A.: Cutaneous blood flow responses to injection trauma measured by laser Doppler velocimetry. *J Invest Dermatol* 74: 1-4, 1980.
 11. Kristensen, J. K.: Finger skin perfusion pressure in generalized scleroderma. *Acta Dermatovener (Stockholm)* 58: 491-493, 1978.
 12. — Blood flow in fingers in generalized scleroderma with Raynaud's phenomenon: Influence of arterial blood pressure reduction and proximal vasodilation. *J Invest Dermatol* 77: 373-376, 1981.
 13. — Local regulation of blood flow in cutaneous and subcutaneous tissue in generalized scleroderma. *Acta Dermatovener (Stockholm), Suppl.* 90, pp. 1-39, 1980.
 14. Lassen, N. A. & Westling, H.: Blood flow in the low-pressure vascular bed distal to an arterial occlusion. *Scand J Clin Lab Invest* 24: 97-100, 1969.
 15. Mendlowitz, M. & Naftchi, N.: Digital circulation in Raynaud's disease. *Am J Cardiol* 4: 580-584, 1959.
 16. Nielsen, S. L.: Raynaud phenomena and finger systolic pressure during cooling. *Scand J Clin Lab Invest* 38: 765-770, 1978.
 17. Nilsen, K. H.: Pathophysiological classification of Raynaud's phenomenon. *Br J Dermatol* 102: 1-5, 1980.
 18. Nilsson, G. E., Tenland, T. & Øberg, P. Å.: Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. *IEEE Trans Biomed Eng* 27: 597-604, 1980.
 19. Rowell, L. B.: Reflex control of the cutaneous vasculature. *J Invest Dermatol* 69: 154-166, 1977.
 20. Wallin, B. G.: New aspects of sympathetic function in man. *In* Butterworths Int Med Rev Clinical Neurophysiology (ed. E. Stålberg & R. R. Young). Butterworths, London, 1981.

Received April 7, 1982

J. K. Kristensen, M.D.
 Department of Dermatology
 Rigshospital
 9 Blegdamsvej
 DK-2100 Copenhagen
 Denmark