38 months following transplantation as compared to two months, but the delayed time to peak during hyperemia was even more impaired at 38 months. This is probably due to a disturbed function of the smooth muscle cells of the vessel wall and might indicate a progress of structural changes in spite of an improved metabolism. The venoarteriolar reflex was also impaired at both time points, probably due to neuropathy, since this reflex depends on an intact sympathetic nerve function. A trend for improvement in four out of five patients with the most impaired reflex was observed, but it did not reach statistical significance, but still may indicate that diabetic neuropathy can improve after transplantation (23). Laser Doppler perfusion imaging of patients with diabetic neuropathy showed skin vasodilation following topical application of methyl nicotinate at the forearm and foot levels, suggesting a potential of methyl nicotinate to increase blood flow and to prevent diabetic foot problems (166).

These and other studies indicate that LDF can be useful in the investigation of some diabetes pathophysiological mechanisms, disease severity, and the efficacy of its control.

54.4.2.10 Raynaud Phenomenon

The intermittent blanching that occurs in Raynaud phenomenon is believed to result from an active microvascular vasoconstriction and emptying. Therefore, LDF is useful for the investigation of the pathophysiological mechanisms underlying Raynaud phenomenon and for evaluating treatments.

To clarify the etiology of Raynaud phenomenon, three vasodilators were intravenously administered, and the response of CGRP was compared with that of endothelium-dependent adenosine triphosphate and the endothelium-independent prostacyclin (167). The first vasodilator induced an increase in blood flow in the hands of patients but not in healthy controls, which may reflect a deficiency of endogenous CGRP release in Raynaud phenomenon.

The role of the histaminergic and peptidergic axes in primary Raynaud phenomenon was also studied (29, 30). Digital blood flow response to intradermal injections of saline, histamine, histamine-releasing agent (compound 48/80), substance P, and CGRP was measured. No evidence of local deficiency in histamine release or in the response to histamine was found (30), even at low temperatures (29), and the patients reacted normally to the neuropeptides substance P (29, 30) and CGRP (30), providing a rationale for treating Raynaud phenomenon with vasoactive peptides.

Digital skin blood flow of both hands was measured during local heating of only one hand. Patients with Raynaud phenomenon showed a decreased digital blood flow during stepwise cooling in both hands, but the reaction in the cooled hand was more pronounced and more consistent (168). Patients with Raynaud phenomenon had an abnormal vascular response to temperature change (32). Studying the hyperemic response to local skin warming, the patients showed vasodilatation at lower skin temperatures than normal, independent of central sympathetic control. Knowledge of skin temperature is therefore important for the interpretation of blood flow studies in Raynaud phenomenon. Provocative testing (occlusion) under different degrees of finger and body cooling detected an increase in the number of fingers of patients exhibiting vasospasm as the severity of cooling increased (169).

Occupational exposure to vibrations causes Raynaud phenomenon. For prevention and treatment of vibration syndrome, an objective test was developed, combining LDF with finger cooling (170). It enabled the demonstration of significant differences among four groups: subjects without vibration exposure, subjects with exposure but with no signs of white fingers, subjects with few attacks, and subjects with frequent attacks.

In patients with Raynaud phenomenon suffering from scleroderma, blood flow decrease during cooling was similar to healthy controls, but the patients had a longer rewarming period (171). In such patients, when resting blood flow was very low, the postischemic reactive hyperemia response was absent (172). After warming the hand in warm water, the hyperemic response was restored and its magnitude corrected, but its time course was longer, with a delay to achieving maximum flow