HYPOTHESIS

Increased capillary permeability in systemic sclerosis: help or hindrance?

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Systemic sclerosis (SSc) is a connective tissue disease characterised by an increased secretion of normal extracellular matrix proteins in mesenchymal tissue, and by widespread morphofunctional capillary abnormalities. Most of the clinical features of SSc are clearly related to vascular lesions; moreover, a diffuse microangiopathy is a prominent feature in all tissues, regardless of any overt clinical involvement. Diffuse endothelial damage caused by a cytotoxic factor could be the initial lesion. Such damage has been clearly demonstrated by ultrastructural studies and by the finding of increased plasma von Willebrand’s activity, factor VIII/von Willebrand’s factor antigen, and tissue plasminogen activator in patients with SSc. Distinctive microvascular changes in SSc include: dilated and distorted capillary loops, diminished capillary density often culminating in regional avascularity, prolonged phases of reduced or ceased capillary perfusion as a result of cold induced peripheral vasoconstriction, and partial occlusion of the capillary lumen by platelet aggregates. Moreover, it has been well documented that capillary permeability to small solutes such as sodium fluorescein is increased and more rapid in patients with SSc. This functional change has been demonstrated by fluorescence videomicroscopy in the early phases of the disease, and may precede the typical capillaroscopic abnormalities.

The transcapillary diffusion of sodium fluorescein is remarkably uniform both in control subjects and in patients with other rheumatic diseases. The dye accumulates in high concentration in a thin, well delineated extracapillary region (halo region), outside which the concentration remains smaller. Thus it can be hypothesised that a physiological diffusion barrier characterises the normal interstitial space. In contrast, transcapillary diffusion of the dye is dramatically increased in patients with SSc, in whom lack of a uniform pericapillary halo is a typical finding associated with the increased transcapillary diffusion. Halo changes include abnormal shape, increased width, and blurred or abolished margin. The distribution of the dye in the interstitial space is frequently inhomogeneous: ‘ribbon-’ or ‘lake-like’ areas can be observed where sodium fluorescein has accumulated in remote interstitial spaces (fig 1).

Current views of mechanisms

Although the pathophysiology of the increased capillary permeability in SSc is not clearly understood, microvascular lesions are considered a crucial pathogenetic factor in determining the less effective diffusion barrier. It has been hypothesised that widespread endothelial cell damage may be the precursor of small vessel disease, and could lead to increased vascular permeability and the subsequent development of fibrosis. The increased capillary permeability assessed by dynamic fluorescence videomicroscopy has been regarded as the consequence of capillary wall damage, and a link between endothelial injury and increased capillary permeability has also been proposed to explain the pathophysiological mechanisms of vascular disease in diabetes mellitus. However, there are no compelling experimental data demonstrating that increased capillary permeability has a clearly defined pathogenetic role in SSc.

Contradictions

If the increased capillary permeability in SSc is to be regarded as the pathological consequence...
of a damaged diffusion barrier of the capillary loops, and if we accept that it can contribute to the development of fibrosis, then it would be reasonable to antagonise such an increase in permeability and to avoid any sort of influence that could further increase both the transcapillary diffusion and the interstitial distribution of plasma solutes. This is contradicted by two main observations. First, cold induced vasospasm, that causes a dramatic decrease both in peripheral perfusion and in the flow related capillary permeability, has well known negative effects on the disease course; and second, calcium channel blockers, that induce an increase of both capillary flow and permeability, are helpful in treating patients with SSc.

**Hypothesis**

Various observations support the intriguing hypothesis that the increased capillary permeability in SSc could represent a physiological protective mechanism in areas with critical nutritional exchanges.

It has been demonstrated that capillary permeability increases when critical hypoxia occurs. In patients with SSc there occur several abnormalities capable of inducing tissue hypoxia. These include loss of capillaries, decreased diffusion coefficient of oxygen as a result of fibrosis, decreased oxygen supply in the peripheral diffusion zone as a result of both increase in the thickness of vascular layers and fibrin deposition in the perivascular tissues enhanced neutrophil and platelet adherence to damaged endothelium, altered microcirculatory hydrostastics, and impaired vasoemotion. Loss of capillaries, in particular, could be relevant in determining critical tissue hypoxia. A decreased capillary density is an early typical feature of SSc, and it has been estimated that the number of capillaries may be reduced to perhaps only 20% of normal. As a consequence, each single capillary loop would be required to serve for nutritional exchanges over a wider interstitial domain than in normal conditions.

In these dramatic conditions of microvascular impairment in patients with SSc, microvascular dynamics are further worsened by cold induced vasospasm, as demonstrated by the significant decrease in pericapillary and interstitial diffusion of sodium fluorescein in patients with SSc after exposure to cold. Although this decrease occurred within two minutes after the first appearance of dye at the selected capillary loops, the cold induced decrease in capillary permeability should not be assumed to be a temporary phenomenon restricted to the period of vasospasm. The intravenous bolus injection of a single small quantity of sodium fluorescein affords only a quick glimpse of the complex dynamic phenomenon of cold induced changes in capillary permeability akin to looking into a dark room by the light of a single match.

To test the hypothesis that cold induced decrease in capillary permeability is not a temporary phenomenon, we performed a bolus injection of sodium fluorescein 15 minutes after immersion of the hand in cold water, under the same experimental conditions as used in the earlier experiments. We observed a marked decrease in fluorescence light intensity with respect to the baseline value (fig 2), suggesting that a dramatic decrease in capillary permeability is a long lasting phenomenon following cold induced vasospasm.

All these findings support the hypothesis that an increased baseline capillary permeability in SSc could be regarded as an adaptive physiological response to chronic tissue ischemia caused by both the reduced capillary density and the episodic phases of cold induced low capillary perfusion. This view is further supported by the findings of Franz et al., who demonstrated a diffuse leakage of dye from the capillaries into the interstitial space in patients with various conditions characterised by digital artery occlusion and severely ischemic areas.

Additional potential support for the concept that increased capillary permeability in SSc affords nutritional protection arises from the relationship between capillary dilatation and permeability. It has been reported that microvascular dilatation represents a local autoregulatory response to tissue hypoxia. As a dramatic increase in capillary permeability is a prominent characteristic of dilated loops and megacapillaries in patients with SSc, it seems reasonable to consider the resulting increased transcapillary diffusion of solutes as an effective means of achieving better nutritional exchange. It is interesting that the triad 'tissue hypoxia—enlarged loops—increased capillary
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permeability occurs both in SSc and in diabetes mellitus.\textsuperscript{41,42} Transcapillary and interstitial diffusion of sodium fluorescein is increased in diabetes mellitus that is characterised by local tissue hypoxia as a result of impaired oxygen transport.\textsuperscript{23} 40

**Testing the hypothesis**
Experimental support for our hypothesis comes from our previous studies. We have demonstrated that nifedipine significantly antagonises the cold induced decrease in permeability and interstitial concentration of sodium fluorescein in patients with SSc.\textsuperscript{29} If it can be assumed that the significant baseline increase in capillary permeability has some pathogenetic role, then the further increase in transcapillary diffusion of solutes induced by nifedipine may be expected to worsen the disease course in patients with SSc. On the contrary, however, it is well known that calcium channel blockers have several valuable effects—antivasospastic activity,\textsuperscript{30,43} marked improvement in unresponsive skin ulceration,\textsuperscript{44} 45 regression of calcinosis,\textsuperscript{31} and improvement in the diffusing capacity of the lung.\textsuperscript{33} We are currently investigating the influence of nifedipine on capillary permeability. Our preliminary data indicate that the drug induces a significant increase in capillary permeability compared with baseline in patients with SSc (figs 3, 4).

The hypothesis of a protecting role of increased capillary permeability has also been explored by studying the effect of peripheral exposure to warmth on the transcapillary diffusion of sodium fluorescein. It has been reported that placing the hands in warm water can increase resting peripheral perfusion and reduce the reactivity to cold,\textsuperscript{46} and ‘keeping warm’ is a cornerstone of management of patients with Raynaud’s phenomenon in SSc.\textsuperscript{47} 48 We have found in preliminary trials that placing the hands in warm water (42°C) for 10 minutes induces a significant increase in capillary permeability in patients with SSc (fig 5).

While it is necessary to be careful not to overgeneralise our conclusions, these findings offer substantial support to the hypothesis that increased capillary permeability is more of a help than a hindrance in patients with SSc.

**Conclusion**
Microvascular involvement is a predominant finding in SSc that undoubtedly contributes to the pathogenesis of the disease.\textsuperscript{22} One expression of such involvement is the dramatic decrease in capillary density. The consequent widespread and persistent critical tissue hypoxia could be further worsened by several additional mechanisms, including episodes of cold or stress induced vasoconstriction. Another typical feature of the microangiopathy in SSc is the increased transcapillary and interstitial diffusion of low molecular weight tracers such as

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**Figure 3** Scatterplot showing percent variation in fluorescent light intensity induced by nifedipine, with respect to baseline values. Data from six patients in whom a mean 4.5 loops (range 3–7) were examined in the two experimental conditions.

**Figure 4** Representative patterns of pericapillary diffusion and interstitial distribution of sodium fluorescein in a patient with systemic sclerosis. A: Baseline. B: After single oral administration of 10 mg of nifedipine 30 minutes before the examination. Both photographs were taken one minute after the first appearance of the dye at the nail fold.

**Figure 5** Scatterplot showing percent variation in fluorescent light intensity induced by exposure to warmth, with respect to baseline values. Data from three patients in whom a mean 5 loops (range 4–6) were examined in the two experimental conditions.
sodium fluorescein. Current theories indicate that this finding is a consequence of a disrupted physiological barrier as a result of capillary wall damage, but the underlying cause of the mechanisms that determine the increased permeability remains unclear. Although the altered pattern of diffusion could be related to the indurative oedema, no study has demonstrated unequivocally that the increased capillary permeability had a clearly defined role in the pathophysiology of SSc.

Our hypothesis is that the increased baseline capillary permeability in SSc might be regarded as a protective mechanism that allows enhanced nutritive function by single capillary loops to meet the demands resulting from the morphofunctional changes in the microcirculation (overall decrease in capillary density, cold induced peripheral hypoperfusion). This hypothesis does not exclude the possibility of some negative effects of the increased capillary permeability, but these could be regarded as side effects of a protective mechanism.