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 morpho-functional capillary abnormalities.^{1,2} 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.³⁻⁵ Diffuse endothelial damage caused by a cytotoxic factor could be the initial lesion^{6,7}; such damage has been clearly demonstrated by ultrastructural studies⁸ and by the finding of increased plasma von Willebrand's activity, factor VIII/von Willebrand's factor antigen,⁹ and tissue plasminogen activator¹⁰ in patients with SSc. Distinctive microvascular changes in SSc include: dilated and distorted capillary loops,¹¹ diminished capillary density often culminating in regional avascularity,¹² prolonged phases of reduced or ceased capillary perfusion as a result of cold induced peripheral vasospasm, and partial occlusion of the capillary lumen by platelet aggregates.¹³⁻¹⁵ 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.¹⁶ This functional change has been demonstrated by fluorescence videomicroscopy in the early phases of the disease, and may precede the typical capillaroscopic abnormalities.¹⁶

The transcapillary diffusion of sodium fluorescein is remarkably uniform both in control subjects and in patients with other rheumatic diseases.¹⁷⁻¹⁹ 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.²⁰ 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).^{16,21}

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 permeability¹³ and the subsequent development of fibrosis.²² The increased capillary permeability assessed by dynamic fluorescence videomicroscopy has been regarded as the consequence of capillary wall damage,¹⁶ 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.²³ 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

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Figure 1 Fluorescence videomicroscopy. **A:** Homogeneous pericapillary distribution of sodium fluorescein in a control subject. **B:** Increased inhomogeneous transcapillary diffusion of sodium fluorescein in a normal shaped loop in a patient with systemic sclerosis (SSc). **C:** Marked increase in capillary permeability along the whole profile of a megacapillary in a patient with SSc. **D:** Definite loss of diffusion barrier around a cluster of newly formed capillaries in a patient with SSc.

of a damaged diffusion barrier of the capillary loops, and if we accept that it can contribute to the development of fibrosis,²² 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^{5 20 24} and in the flow related capillary permeability,²⁵ has well known negative effects²⁶⁻²⁸ on the disease course; and second, calcium channel blockers, that induce an increase of both capillary flow and permeability,²⁹ are helpful in treating patients with SSc.³⁰⁻³³

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.³⁴ In patients with SSc there occur several abnormalities capable of inducing tissue hypoxia. These include loss of capillaries,³⁵ decreased diffusion coefficient of oxygen as a result of fibrosis,³⁴ decreased oxygen supply in the peripheral diffusion zone as a result of both increase in the thickness of vascular layers^{36 37} and fibrin deposition in the perivascular tissues³⁸ enhanced neutrophil and platelet adherence to damaged endothelium, altered microcirculatory hydrostatics, and impaired vasomotion.¹⁴ Loss of capillaries, in particular, could be relevant in determining critical tissue hypoxia. A decreased capillary density is an early typical feature of SSc,¹² and it has been estimated that the number of capillaries may be reduced to perhaps only 20% of normal.²² 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.²⁵ 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.²⁵ 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 ischaemia 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 Franzeck *et al*,³⁹ 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 ischaemic 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.²³ As a dramatic increase in capillary permeability is a prominent characteristic of dilated loops and megacapillaries in patients with SSc,¹⁶ 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

Figure 2 Fluorescent light intensity (FLI) measured at different times after the first appearance of sodium fluorescein in selected capillary loops of two patients with systemic sclerosis. Capillary permeability was assessed 15 minutes after peripheral cold exposure (hands covered with plastic gloves and immersed for three minutes in water at 5°C). ♦ = Basal condition; ■ = after cold test.

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.

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