Rarefaction of skin capillaries in patients with anginal chest pain and normal coronary arteriograms

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Aims Patients with arterial hypertension often have a reduction in capillary density (rarefaction) and a reduction in coronary flow reserve because of functional and structural alterations of the coronary microcirculation. Patients with chest pain and normal coronary arteriograms may have coronary microvascular dysfunction, but it is not known whether capillary rarefaction plays a role in the pathogenesis of this syndrome. The aim of this study was to compare capillary density in hypertensive and normotensive subjects with anginal chest pain and normal coronary arteriograms vs asymptomatic hypertensives and healthy controls.

Methods and Results We studied 49 patients with typical anginal chest pain, positive exercise testing and normal coronary arteriograms; 22 were hypertensive and 27 were normotensive. We used intra-vital video-microscopy to examine the skin of the dorsum of the middle finger of the non-dominant hand before and after maximization of perfused capillaries with venous congestion. Mean capillary density was significantly lower in patients with chest pain and normal coronary arteriograms independent of their blood pressure level, compared to normotensive healthy controls. Differences were found both at baseline [51 ± 2 (hypertensive) and 52 ± 2 (normotensive) vs 65 ± 2 (controls) per 0.56 mm² respectively] (P<0.0001) and after maximization [57 ± 3 (hypertensive) and 59 ± 2 (normotensive) versus 75 ± 3 (controls) respectively] (P<0.0001).

Conclusions Skin capillary density is significantly lower in patients with chest pain and normal coronary arteriograms compared to normotensive controls. The pathophysiological importance of capillary rarefaction in patients with chest pain and normal coronary arteriograms remains unknown. Further studies are needed to determine whether the abnormality is associated with myocardial flow disturbances such that the findings can be extended to the heart.


Key Words: Chest pain and normal coronary arteries, essential hypertension, microcirculation, capillary rarefaction.

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not known whether capillary rarefaction is associated with microvascular angina in hypertensive and normotensive patients with chest pain and normal coronary arteriograms.

The aim of this study was to compare skin capillary density in normotensive and hypertensive patients with typical exertional chest pain, positive responses to exercise testing and normal coronary arteriograms, and in healthy volunteers.

**Methods**

**Subjects**

Forty nine patients with typical exertional anginal chest pain, a positive response to exercise stress testing (>1 mm down-sloping or rectilinear ST-segment depression in ≥2 leads) and normal coronary arteriograms were studied; 22 of these patients had treated essential hypertension (mean sitting blood pressure 138/80 mmHg) and 27 patients were normotensive (syndrome X) (mean blood pressure 125/73 mmHg). We also studied 29 age- and weight-matched normotensive controls (mean blood pressure 122/75 mmHg) and 21 asymptomatic patients with essential hypertension who had not received any previous treatment for their hypertension (mean blood pressure 156/97 mmHg). Subjects with chest pain and normal coronary arteriograms were recruited from consecutive patients attending the Coronary Artery Disease Research Unit outpatient clinic at St George’s Hospital Medical School. Other subjects were recruited by local posters and by notices in local and national media. Patients were defined as having hypertension if they had systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg. Only Caucasian and light-skinned Asian patients were eligible to be included in the study because of the technical difficulty in performing capillaroscopy in Afro-Caribbean subjects. Patients with a history of connective tissue disease, diabetes mellitus, skin diseases or with cold hands or Raynaud’s phenomenon were excluded from the study. The protocol was approved by the local Research Ethics Committee of St George’s Hospital. Written informed consent was obtained from each patient.

**Intravital capillaroscopy**

Subjects were studied in the morning between 0900 and 1100 h after an overnight fast. All subjects were non-smokers except for one normotensive patient with chest pain and normal coronary arteriograms who was asked to refrain from smoking on the day of the study. One hypertensive patient with a history of Raynaud’s disease was excluded from the study. All syndrome X patients were treated with diltiazem. Hypertensive subjects with chest pain and normal coronary arteriograms were treated with diltiazem alone or with an angiotensin converting enzyme inhibitor. All subjects were symptomatic at entry to the study and all found their medications helpful. Hence it was considered unethical to discontinue their medication except on the day of the study only. The capillaroscopy studies were performed in a temperature-controlled laboratory (21 °C–24 °C), after the study subjects had at least a 20-min rest. They were seated comfortably with the left forearm and hand supported at heart level. Intra-vital microscopy was carried out according to a standardized, well-validated methodology[49]. The operator was blind to the clinical characteristics of the patients. Microscopic images were obtained with a CCD camera (Sony model XC-75CE) and were stored using a video recorder (Panasonic model NV-FS88). The skin of the dorsum of middle phalanx of the non-dominant (left) hand was examined. Four microscopic fields (0.56 mm² each) centred around an ink spot were recorded continuously for 5 min so as to detect intermittently perfused capillaries. The number of capillaries per field was counted on-line using computer software (KK-Technology, England). A miniature blood pressure cuff was applied to the base of the left middle finger and the cuff was then inflated and maintained at 60 mmHg for 2 min and further images were recorded using one of the four microscopic fields chosen at random. The enhancing effect of venous congestion on the visualization of skin capillaries by videomicroscopy has been previously reported[40]. Blood pressure was measured with an automatic oscilometric device (OMRON HEM705CP)[31] with appropriate cuff size. Sitting blood pressure was taken as the mean of three readings obtained at 1- to 2-min intervals.

**Statistical analysis**

All results are given as means ± SEM. Data were processed by use of StatView 5.0 software (SAS Institute, U.S.A). ANOVA was used to compare groups and when ANOVA yielded statistically significant differences between groups, post hoc pair-wise comparison was done using Bonferroni’s test.

**Results**

Table 1 shows baseline characteristics and capillaroscopic measurements in the study subjects before and during 2 min of venous congestion. Mean capillary density was significantly lower (17%) in patients with asymptomatic essential hypertension than in normotensive healthy controls both at baseline (54 ± 2 vs 65 ± 2 capillaries per 0.56 mm² respectively, P=0.001) and after maximization with venous congestion (62 ± 2 vs 75 ± 3 capillaries per field, P=0.0005) confirming structural rarefaction of skin capillaries in patients with essential hypertension[31]. Patients with chest pain and normal coronary arteriograms and hypertension also had a significantly lower capillary density than healthy
controls both at baseline (51 ± 2 per field; \( P = 0.0001 \)) and after maximization (57 ± 3 per field; \( P < 0.0001 \)). Normotensive patients with chest pain and normal coronary arteriograms (syndrome X) also had a lower mean baseline capillary density (52 ± 2 per field; \( P = 0.0001 \)) and a lower maximal capillary density (59 ± 2 per field; \( P = 0.0001 \)) than healthy controls (Fig. 1). There were no statistically significant differences between subjects with chest pain and normal coronary arteriograms and asymptomatic patients with hypertension.

**Discussion**

The main finding of this study was that patients with anginal chest pain and normal coronary arteriograms had significantly lower skin capillary density than
matched healthy volunteers. Both normotensive and hypertensive chest pain and normal coronary arteriograms patients showed rarefaction of their skin capillaries both at baseline and after maximization with venous congestion, indicating that rarefaction is likely to be due to the structural (anatomical) absence of capillaries. Arterial hypertension is known to affect the coronary circulation through several mechanisms including coronary artery disease, left ventricular hypertrophy, and microvascular disease. Experimental and clinical data indicate that coronary microvascular disease exists in patients with essential hypertension in whom it can cause both a reduction of coronary flow reserve and a shift to the right of the coronary flow autoregulation curve\[4\]. Previous studies have demonstrated a reduced peripheral dilator capacity in patients with essential hypertension\[12,13\] and several structural changes have also been described in the vessel walls of these patients\[14\] as well as in those with a family history of hypertension\[15\]. We have recently shown that rarefaction of skin capillaries in essential hypertension is likely to be a primary or a very early abnormality that antedates the onset of sustained hypertension\[8,9\]. A proportion of patients with syndrome X are known to develop systemic hypertension during long-term follow-up\[16\] and this may be one possible explanation for the finding of capillary rarefaction in patients with syndrome X. It has been recently suggested that patients with microvascular angina may have insulin resistance\[17–19\]. Insulin resistance has also been observed in patients with essential hypertension, diabetes mellitus and in obese individuals\[20\]. Reduction in microvascular density may be a possible pathogenic link between these entities\[21–23\]. In our study, patients with chest pain and normal coronary arteriograms and successfully treated hypertension had a level of capillary density similar to that of untreated asymptomatic hypertensives and significantly lower than that of healthy volunteers. This suggests that capillary rarefaction in hypertensive patients is not necessarily reversed by normalization of blood pressure. However, because these patients were already on treatment when studied, the impact of hypertension medication on capillary density is not known. It can also be argued that treatment may have improved capillary density and therefore our results may have over-estimated capillary density in untreated hypertensive patients with chest pain and normal coronary arteriograms. This argument, however, reinforces our finding of reduced capillary density in these subjects.

The pathophysiological importance of capillary rarefaction in patients with chest pain and normal coronary arteriograms remains unknown. Further studies are needed to determine whether the abnormality is associated with myocardial flow disturbances, such that the findings can be extended to the heart. Capillary rarefaction cannot per se entirely explain the mechanism of chest pain in hypertensive patients with chest pain and normal coronary arteriograms as these patients had a similar reduction in skin capillary density compared to asymptomatic hypertensive patients. It is intriguing that for a similar degree of capillary rarefaction, some hypertensive patients have chest pain whilst others do not. It has been shown that patients with syndrome X have abnormal pain perception\[23,24\] and this may explain the decreased pain threshold in these patients. It is also possible that hypertensive patients with chest pain and normal coronary arteriograms have more severe microvascular rarefaction in the myocardium than at skin sites. There are few reports of structural small vessel abnormalities in patients with chest pain and normal coronary arteriograms. Suzuki et al.\[25\] in a study of 10 patients with microvascular angina using electron microscopy of myocardial biopsies found that the capillaries of these patients were irregular in shape with chromatoin margination of the endothelial nuclei and basal lamina thickening. Mosseri et al.\[26\] found that during coronary angiography, patients with chest pain and normal coronary arteriograms had significantly reduced flow velocity of angiographic contrast medium compared with that in the control group. Right ventricular endomycocardial biopsy revealed pathological small coronary arteries with fibromuscular hyperplasia, hypertrophy of the media, myo-intimal proliferation, and endothelial degeneration and capillaries with swollen endothelial cells encroaching on the lumen\[26\]. Very recently Buchthal et al.\[27\] studied 35 women with chest pain and normal coronary arteriograms and 12 age- and weight-matched control women with no evidence of heart disease. They used Phosphorus-31 nuclear magnetic resonance spectroscopy to identify metabolic evidence of myocardial ischaemia. They found that 20% of their patients with chest pain and normal coronary arteriograms had evidence of an abnormal metabolic response to handgrip exercise consistent with the occurrence of myocardial ischaemia suggesting that microvascular coronary artery disease is the most likely cause of their chest pain. Studies have also suggested that patients with microvascular angina and syndrome X may not only have abnormalities of the coronary microvasculature, but rather a more generalized systemic vascular involvement\[28\]. Sax et al.\[29\] found that patients with syndrome X had a significantly higher minimal forearm vascular resistance than normal controls indicating impaired vasodilator capacity. Of particular interest is their observation that the magnitude of the vasodilator impairment of the peripheral bed correlated closely with that of the coronary bed, indicating a relationship between central and peripheral vascular abnormalities. \[29\]. Pedrinelli et al.\[30\] also measured minimal forearm vascular resistance during maximal post-ischaemic vasodilation in patients with syndrome X. They found that syndrome X patients had a significantly higher minimal forearm vascular resistance than the normals, indicating a structural vasodilatory abnormality. Similar findings were reported by Buus et al.\[31\] and Botker et al.\[32\]. These results indicate that a substantial proportion of patients with syndrome X has a systemic microvascular abnormality resulting in decreased coronary and peripheral vasodilator capacity.
In conclusion, skin capillary density in patients with anginal chest pain and normal coronary arteriograms is lower than in matched normotensive controls. Structural rarefaction of capillaries in these patients suggests a generalized microvascular abnormality that may play a role in the pathogenesis of this syndrome. New therapeutic approaches for patients with chest pain and normal coronary arteriograms targeting capillary angiogenesis and improving capillary reserve warrant future investigation.

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References


