Local regulation of blood flow in subcutaneous tissue in patients with acute myocardial infarction

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Summary

1. Local regulation of subcutaneous blood flow in the forearm was studied in the acute phase of myocardial infarction. Blood flow was measured by the local $^{133}$Xe-washout technique.

2. Plasma concentrations of noradrenaline and adrenaline were increased on day 1, suggesting an increase in sympathetic neuronal activity, but gradually returned to normal thereafter.

3. Subcutaneous blood flow on day 1 was far below normal (38%) and steadily increased to reach normal at day 7 after coronary occlusion. The sympathetic vasoconstrictor activity that caused the initial reduction in flow could be blocked by proximal nervous blockade, increasing the subcutaneous blood flow by 130, 63 and 14% on days 1, 3 and 7 respectively after coronary occlusion. A normal response to decrease in arterial perfusion pressure was observed, suggesting that intrinsic vascular reactions responsible for autoregulation of blood flow were not affected by the increase in sympathetic vasoconstrictor activity. The vasoconstrictor response to increase in venous transmural pressure could not be demonstrated on day 1 after coronary occlusion but gradually reappeared during the following days.

4. Abolition of the vasoconstrictor response is most likely to be due to a centrally elicited increase in sympathetic activity, as a normal vasoconstrictor response was obtained after proximal nervous blockade. Thus the local sympathetic reflex mechanism underlying the vasoconstrictor response appears to be suppressed by a centrally elicited increase in sympathetic discharge rate.

Key words: acute myocardial infarction, autoregulation, catecholamines, subcutaneous blood flow, vasoconstrictor response.

Introduction

Studies in man indicate that local mechanisms seem to play an important part in regulation of vascular tone in subcutaneous tissue during orthostatic changes of vascular transmural pressure.

Autoregulation of blood flow, defined as maintenance of constant blood flow during changes in arterial perfusion pressure (Johnson, 1964), has been studied in human forearm subcutaneous and cutaneous tissue by elevating the area under study various distances above heart level. Under these circumstances, when arterial pressure decreases by about 15 mmHg whereas venous transmural pressure remains almost constant owing to collapse of the veins, there is no change in blood flow, indicating that autoregulation of blood flow is present. The observed autoregulatory changes persisted years after sympathectomy (Henriksen, 1976a) and were not affected by local nervous blockade induced by local infiltration of lignocaine or phentolamine (Henriksen, 1976b). These observations indicate, in agreement with the findings in cat skeletal muscle (Folkow, 1949), that intrinsic vascular mechanisms are responsible for the autoregulatory changes in vascular resistance. Possible mechanisms include a myogenic response to stretch of the vascular wall (Bayliss,
local changes in concentration of vasoactive metabolites liberated from the tissue (Anrep, 1912; Berne, 1964; Hilton, 1971) or variation in local oxygen tension (Duling & Pittman, 1975).

A second local mechanism controlling subcutaneous blood flow can be demonstrated by lowering the forearm (corresponding to an increase in arterial and venous transmural pressure of about 25 mmHg or more). This causes a decrease in subcutaneous blood flow of about 50%, implying an increase in total vascular resistance of about 100% (Henriksen, Nielsen & Paaske, 1973; Levick & Michel, 1978). This increase in vascular resistance is referred to as the 'vasoconstrictor response' to increase in vascular transmural pressure, and a number of observations indicate that it is due to a local venoarteriolar sympathetic axon reflex elicited by venous distension (Henriksen, 1977).

Vascular tone in subcutaneous tissue is also influenced by centrally elicited sympathetic vasoconstrictor activity as shown by the decrease in vascular resistance that follows acute spinal sympathetic blockade and cervico-dorsal sympathectomy (Henriksen & Alsner, 1975; Henriksen, 1976a).

However, it is not known whether or not an increase in centrally elicited sympathetic vasoconstrictor activity influences the local blood flow control systems in human subcutaneous tissue. In the acute phase of myocardial infarction sympathetic block and cervico-dorsal sympathectomy (Henriksen & Alsner, 1975; Henriksen, 1976a).

Materials and methods

Patients

Eleven males (mean age 53 years, range 40–71 years) and four females (mean age 68 years, range 64–70 years) with electrocardiographic signs of acute transmural myocardial infarction were examined as soon as possible after admission to the Coronary Care Unit. The localization of the myocardial infarction was anterior in nine patients and inferior in six patients. On arrival, duration of chest pain was less than 6 h in all patients. None of them received antiarrhythmic drugs before admission or during the period of investigation. Only one of the patients showed clinical signs of congestive heart failure during the period of investigation. None of the patients had increased peripheral venous pressure. Eight patients were studied on days 1, 2, 3 and 7 of hospitalization. Seven patients were only studied on day 1. Before the investigation informed consent was obtained from all patients.

Experimental procedure

Subcutaneous blood flow was measured by the local 133Xe-washout technique (Sejrsen, 1971). The measurements were carried out with the patients in a supine position. Room temperature was about 22°C and remained constant during the investigations. 133Xe in sodium chloride solution (150 mmol/l) (0.1–0.2 ml, 3 mCi/ml) was injected slowly subcutaneously into the distal, dorsal part of the forearm 5 cm proximal to the wrist. To avoid the influence of the injection trauma (Nielsen, 1972a) measurements were started 30 min after the injections. To minimize day-to-day variation in the tissue-to-blood partition coefficient, λ, all measurements were made in the same area in each of the patients. A single investigation consisted of a triad of measurements each lasting 5–8 min with the labelled area of the forearm moved passively between the following levels: (1) reference level (jugular notch), (2) a test level 20 cm above or more than 40 cm below the jugular notch, and (3) reference level.

The γ-emission of 133Xe was detected by a sodium iodide (TI) scintillation detector connected to a universal printing gamma-spectrometer (Meditronic, Denmark) with a window set around the 81 keV photopeak of 133Xe.

The effect of proximal nervous blockade on the local vascular response to lowering the forearm was studied on day 1 in ten patients. In four of the patients additional studies were performed on days 3 and 7. Nervous blockade was induced by lignocaine infiltrated subcutaneously 5 cm proximally, laterally and medially to the area under study. The influence of pethidine in doses used in the acute phase for chest pain was tested on day 7. No influence upon reference blood flow and the vasoconstrictor response was observed.

Methodological considerations and calculations

When the washout of a tracer from a homogeneous tissue with homogeneous perfusion is entirely perfusion limited, then the perfusion coefficient, \( f \), can be calculated by the Kety formula:

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 f (\text{ml min}^{-1} 100 \text{ g}^{-1}) = \lambda \cdot k \cdot 100 \text{(Kety,}
\]

1951), where $\lambda$ is the tissue-to-blood partition coefficient (ml/g) and $k$ is the fractional washout rate constant (min$^{-1}$).

Studies performed on the isolated inguinal fat pad of rabbits showed good agreement between blood flow measured directly and flow calculated from $^{133}$Xe-washout curves (Nielsen, 1972b), indicating that the $^{133}$Xe-washout technique is valid for determination of subcutaneous blood flow if $\lambda$ is known. $\lambda$ was not determined in the present study but as the studies on a particular day were performed in the same radioactive depot, $\lambda$ was assumed to remain constant during the different experimental conditions. Relative blood flow was then calculated as $f_{\text{test}}/f_{\text{ref.}} = k_{\text{test}}/k_{\text{ref.}}$, where $k_{\text{test}}$ is the washout rate constant obtained during elevation or lowering and $k_{\text{ref.}}$ is the average washout rate obtained just before and after the test. $k$ was obtained as the slope of the regression line calculated by the 'least-squares' method with logarithmically transformed count rates corrected for background activity. To avoid variations caused by changes in subcutaneous blood flow due to other mechanisms than the test, data were only analysed when the reference washout rate obtained just before and after the test did not differ more than 50%, which is about twice the relative standard deviation.

Relative vascular resistance, $R_{\text{test}}/R_{\text{ref.}}$, was calculated from the obtained relative blood flow and arterial and venous mean pressures. Venous pressure was measured directly in a superficial vein on the back of the hand. Arterial pressure was measured by using a cuff and a sphygmonanometer. Mean arterial pressure was calculated as diastolic pressure $+$ $\frac{1}{3}$ (pulse pressure). It was assumed that changes in position caused a change in arterial mean pressure that corresponded to the hydrostatic pressure of a blood column of a similar height from heart level to the test level (Henriksen & Søjrse, 1977; Levick & Michel, 1978).

Statistics

$k_{\text{test}}$ and $k_{\text{ref.}}$ were compared by Student's $t$-test for paired samples; $P = 0.05$ was chosen as level of significance.

Determination of plasma concentrations of noradrenaline and adrenaline

Plasma concentrations of noradrenaline and adrenaline were determined by an enzymic double-isotope derivative technique as described by Engelman & Portnoy (1970). Normal values of noradrenaline and adrenaline were 0.36 ± 0.09 and 0.09 ± 0.02 µg/l (mean ± SD) respectively.

Results

Mean arterial pressure ± SEM was 97 ± 2, 91 ± 3, 93 ± 1 and 92 ± 3 mmHg, and heart rate ± SEM was 80 ± 4, 88 ± 5, 92 ± 4 and 74 ± 3 beats/min on days 1, 2, 3 and 7 respectively. On day 1 venous pressure on the back of the hand at reference level was 2 ± 0.2 mmHg ($n = 5$). During elevation venous pressure remained almost constant at 0 ± 0.5 mmHg. Lowering the hand 40 cm below reference level caused an increase in venous pressure of 32 ± 3 mmHg that corresponded to the hydrostatic pressure of a blood column of similar height. Similar findings were obtained on the other days.

Plasma concentrations of noradrenaline and adrenaline plotted against time after coronary occlusion are shown in Fig. 1. On day 1 the mean plasma concentrations (±SEM) of noradrenaline and adrenaline were 0.80 ± 0.07 and 0.19 ± 0.02 µg/l respectively. On the following days both concentrations declined to reach approximately normal values on day 3. As indicated by the standard error in Fig. 1, plasma noradrenaline was still high in some of the patients on day 2.

![Fig. 1. Plasma concentrations of noradrenaline and adrenaline (±SEM) during the course of acute myocardial infarction. Figures in parentheses denote the number of measurements. ●, Noradrenaline; ○, adrenaline.](image-url)
The plasma noradrenaline concentrations were significantly different at days 1, 2 and 3 from those at day 7 ($P < 0.005$ and $<0.02$ respectively).

An example of the $^{133}$Xe-washout curves obtained in one patient is shown in Fig. 2, and the compiled data of the $^{133}$Xe studies are shown in Fig. 3. The effect of postural changes upon blood flow is shown in the top panel and the corresponding relative vascular resistance is shown in the middle panel. In all investigations blood flow remained constant when the area under study was raised 20 cm, corresponding to a decrease in vascular resistance of about 25%, indicating that autoregulation of blood flow was present.

On day 1 after coronary occlusion, blood flow and vascular resistance remained constant when the area under study was lowered 40 cm or more below the jugular notch level ($P > 0.7$). On day 2 blood flow decreased about 25% during lowering ($P < 0.01$), corresponding to an increase in
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vascular resistance of about 40%. On days 3 and 7 blood flow decreased by about 40% ($P < 0.001$) and vascular resistance increased by 100%. Thus on day 1 after coronary occlusion the local vasoconstrictor response could not be demonstrated, but started to appear on day 2 and was normal by day 3. In the bottom panel of Fig. 3 the mean reference washout rate obtained on a particular day is expressed relative to the mean value obtained on day 7 ($f_{\text{ref, re}}/f_{\text{ref, ref}}$) in the eight patients that were studied on all four days. The mean ratio after coronary occlusion was $0.38 \pm 0.05$ on day 1 and then increased to $0.72 \pm 0.03$ and $0.66 \pm 0.11$ on days 2 and 3 respectively.

The effect of proximal nervous blockade on reference blood flow and the vasoconstrictor response on days 1, 3 and 7 after myocardial infarction is shown in Fig. 4. About 10 min after injection of lignocaine anaesthesia and analgesia corresponding to the labelled field was present,
indicating that proximal nervous blockade was present.

The effect of proximal blockade upon the vasoconstrictor response is shown in the top panel of Fig. 4. On day 1 no vasoconstrictor response could be demonstrated before blockade, but afterwards a normal vasoconstrictor response was obtained, with blood flow decreasing by 42% during arm lowering \((P < 0.02)\). On days 3 and 7 blood flow decreased 24 and 43% before, and 41 and 46% after blockade \((P < 0.05)\). In the bottom panel reference washout rates are normalized to the mean value obtained after blockade on day 1. The blockade induced an average increase in reference blood flow of about 130, 63 and 14% on days 1, 3 and 7 respectively.

**Discussion**

A main result of the present study is that the local vasoconstrictor response to increase in venous transmural pressure was abolished on day 1 after coronary occlusion but reappeared during the following days (Fig. 3).

Furthermore the observations indicate that the sympathetic discharge rate from the central nervous system was probably increased in the acute phase of myocardial infarction and then gradually decreased during the following days: plasma concentration of noradrenaline, which presumably mainly reflects activity in sympathetic fibres (Lake, Ziegler & Kopin, 1976), was increased on day 1 after coronary occlusion and then decreased to normal levels during the following days (Fig. 1). This finding is in agreement with other studies (Hansen, Hesse & Christensen, 1978). Although the changes in plasma concentration of noradrenaline may not reflect sympathetic vasoconstrictor activity in the area under study, relative reference washout rate increased by 130% on day 1, which is about four times higher than the increase obtained in subcutaneous tissue at lateral malleolus in normal subjects after spinal sympathetic blockade (Henriksen & Alsner, 1975). The relative increase in reference washout rate induced by proximal nervous blockade diminished during the course of acute myocardial infarction (Henriksen & Alsner, 1975). The relative increase in reference washout rate induced by proximal sympathetic blockade diminished during the course of acute myocardial infarction (Fig. 4). This, taken together with the finding that reference washout rate increased to the same level after proximal blockade (Fig. 4), indicates that sympathetic vasoconstrictor activity in the investigated area was in fact increased on day 1 after coronary occlusion and then gradually decreased during the following days.

The observations indicate that centrally augmented sympathetic activity suppresses the local vasoconstrictor response responsible for the vasoconstrictor response. First, the vasoconstrictor response reappeared after proximal sympathetic blockade on day 1 after coronary occlusion (Fig. 4). Secondly, there was a significant correlation between the magnitude of relative blood flow during arm lowering and plasma concentration of noradrenaline \((r = 0.56; P < 0.01)\) (Fig. 5).

The abolition of the vasoconstrictor response on day 1 might be ascribed to an increase in venous tone mediated by an increase in sympathetic vasoconstrictor activity giving a diminished distensibility of the veins. Thus the difference in response to increase in venous transmural pressure before and after proximal nervous blockade could then be due to differences in distensibility of the veins. However, this seems less likely for the following reason: further increase in venous distension beyond the threshold level, which corresponds to an increase in venous transmural pressure of about 25 mmHg, does not cause an additional increase in vascular resistance (Henriksen et al., 1973). The vasoconstrictor response was still abolished when the area under study was lowered 60 cm (corres-
responding to an increase in venous transmural pressure that, during normal conditions, is about twice the amount needed to elicit the vasoconstrictor response). Wood, Litter & Wilkins (1956) observed that the distensibility of the veins in the forearm of patients with manifest congestive heart failure was on average reduced by about 30%, indicating that an increase in venous transmural pressure of 45 mmHg could cause an amount of venous distension sufficient to elicit the vasoconstrictor response.

Hyperactivity in sympathetic fibres might abolish the local vasoconstrictor response because prolonged neurally mediated vasocostriction tends to impair removal of vasodilating metabolites liberated in the tissue and to induce tissue acidosis. This will counteract a further increase in vasoconstrictor activity of the vascular smooth muscle cells (autoregulatory escape) (Cobbold, Folkow, Kjellmer & Mellander, 1963; Ballard & Rossell, 1971; Henriksen, 1974; Dusting & Rand, 1975; Henriksen & Wisborg, 1975; Belfrage, 1978). However, autoregulation of blood flow was not significantly affected as blood flow remained constant when the area under study was elevated 20 cm. This suggests that intrinsic vascular reactions to changes in arterial transmural pressure were not affected by increase in sympathetic activity and the possible subsequent accumulation of vasoactive metabolites liberated in the tissue.

Other possible mechanisms by which augmented activity in sympathetic fibres might abolish the local vasoconstrictor response are: (a) centrally elicited impulse frequency in sympathetic fibres has reached a maximum level and cannot be increased further; (b) blockade of orthodromically conducted action potentials in sympathetic fibres by antidromically conducted action potentials elicited by venous distension; (c) diminished responsiveness of vascular smooth muscle cells to sympathetic stimuli and/or catecholamines due to increased vascular tone (Sivertsson, 1970).

Studies with passive head-up tilt during the course of myocardial infarction (Skagen, 1981) suggest that the suppression of the local venoarteriolar reflex mechanism is probably due to antidromic impulse inhibition and/or diminished sensitivity of the receptors located in small veins.

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References