Blood Flow Response to Cryosurgery on Basal Cell Carcinomas

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Cryosurgery with liquid nitrogen is commonly used to treat benign and malignant skin tumours. One of the crucial factors which influences the freezing and thawing rate of the target cells is the response of the microcirculation to cold stimulus. In our experiment, laser Doppler flowmetry was used to monitor blood flow during cryosurgical treatment of basal cell carcinomas. Outside the frozen tissue hemisphere, blood flow, as measured by laser Doppler flowmetry, increased almost instantaneously and remained on a high level during thawing. Baseline blood flow at the contralateral anatomical site remained stable. Pharmacological or physical modification of the cutaneous microcirculation before therapy may influence freezing and thawing times, and therefore the outcome with regard to healing, cosmetic appearance and the recurrence rate of basal cell carcinomas. ***Key words: Cryobiology; Skin tumour; Treatment; Laser Doppler flowmetry.***

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Cryosurgery is an established therapy for certain skin diseases. It is a simple and rapid treatment for benign disorders such as viral warts and seborrheic keratoses and is an effective therapy for premalignant and malignant tumours such as actinic keratoses and basal cell carcinomas (1).

To obtain a high healing rate, in other words the complete destruction of the target cells, several prerequisites during the cryosurgical procedure must be fulfilled (2–4):

1) homogeneous nucleation (intra- and extracellular ice-crystal formation). This requires a freezing rate of approximately 100°C/min, which can only be obtained with liquid nitrogen.
2) a minimal temperature of −25°C in the target tissue.
3) a thawing rate not exceeding 10°C/min to enhance intra- and extracellular recrystallization processes.
4) two freeze/thaw cycles for malignant tumours.

The long-term evolution of lesions treated with cryosurgery has been extensively documented (3–6). An immediate vascular phase is followed by a longer lasting immunological period and ultimately by a repair phase. Although the vascular phase is crucial with regard to the thaw process (7), few investigations have been concerned with blood flow in the frozen area and little is known about the processes in the surrounding microvasculature. To obtain more insight into the immediate vascular phase of the surrounding tissue during and after cryosurgery, laser Doppler flowmetry (LDF) was employed.

MATERIALS AND METHODS

Seven patients with a histologically confirmed solid basal cell carcinoma were chosen. All gave their informed consent. To exclude other factors which stimulate skin blood flow (SBF), e.g. injections, only cases not requiring local anaesthesia and tissue temperature control by a thermocouple were selected. Five males and 2 females with a mean age of 71 years (range: 54–80 years) were investigated. The tumours were located on the forehead ($n = 3$), on the cheek ($n = 2$) and on the back ($n = 2$). They covered a mean area of 63.5 mm^2 (± 37 mm^2).

Measurements were carried out in autumn and winter in a room with constant temperature (23 ± 0.5°C) and humidity (46 ± 5%). The patients rested comfortably in a supine position. The visible tumour border was outlined with a skin marker pen and a second outline was drawn, giving a 3 mm safety margin. To protect the surrounding area, a cone-shaped plastic device, with a lumen corresponding to the safety border, was carefully placed on the skin and held in place. Two probe holders were fixed to the skin with double-sided adhesive tape: one which was specially cut imme-

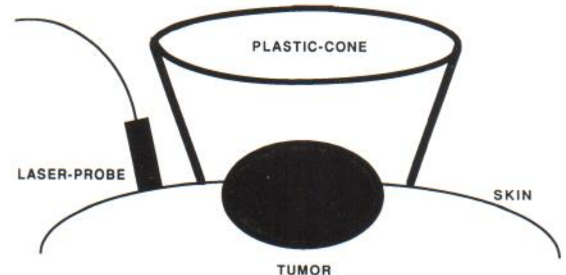

Fig. 1. The tissue beyond the safety margin of 3 mm from the tumour border was protected with a cone-shaped plastic device. The laser Doppler probe was fixed immediately outside, in a specially cut standard plastic probe holder (distance: approximately 5 mm).

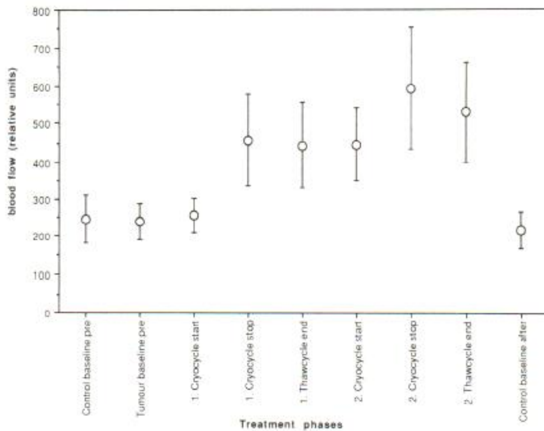

Fig. 2. The control baseline remained stable throughout the cryotherapy procedure. Blood flow increased significantly during the freezing cycle and stabilized on the level reached during thawing. Values given are means ± SEM.

diately outside of the protective cone (Fig. 1), and one to the corresponding contralateral anatomical area. The distance between the cone border and the LDF measuring point was approximately 5 mm.

SBF was measured with a Periflux PF3 laser Doppler flowmeter, which was interfaced to a Yokogawa 4112 LR pen recorder. Baseline SBF was measured at both sites until constant values were obtained (approximately 30 s). The laser probe was then inserted into the probe holder next to the tumour and SBF was continuously monitored throughout the cryosurgical procedure.

Cryosurgery was performed with a Frigitronic CE-8TM unit. Liquid nitrogen was applied to the surface of the tumour for a mean time of 35.3 s (± 10.7 s) using the open spray technique. The frozen lesion was left to thaw spontaneously (133.6 ± 42.1 s). The same procedure was performed a second time to ensure complete destruction of the malignant cells. After the completion of the second thaw cycle and a constant reading, SBF was again recorded at the contralateral control site.

For statistical analysis a paired two-tailed *t*-test was used.

RESULTS

Baseline SBF in the peritumoural area and the contralateral control site were similar. During the first freezing cycle a rapid and steep increase in SBF was observed, with a plateau during thawing. The second freeze cycle induced a further increase in SBF, although it was less pronounced and had a greater standard deviation. During thawing, SBF levelled again and stayed at the SBF value reached for the remaining measuring period (Fig. 2). The increase in SBF was statistically significant ($p = 0.039$) between the pretreatment baseline and the end of the second thaw cycle. SBF remained stable and was not significantly different ($p = 0.453$) at the control baseline before vs. after the freezing procedure.

DISCUSSION

Although the influence of the microcirculation on thawing after a freezing stimulus is one of the crucial events (2), little is known about it. Experimental evidence supports the view that about two–thirds of the capillary circulation ceases between 11° and 3°C, whereas only 35–40% of the blood flow ceases in the arterioles and venules (8). On the other hand, as soon as temperatures fell below 0°C a complete cessation of blood flow measured by ^{133}Xenon clearance (irrespective, of the duration of freezing and the minimal temperature reached) was demonstrated (9). Freezing to −20 to −25°C initially induced vasoconstriction, followed by a sustained vasodilation with shoals of emboli passing through the larger microvessels. Blood flow arrest was immediate and complete in most capillaries (10). Resulting hyperaemia and bleeding in the treated area after thawing was suggested to be due to the opening of arterio-venous anastomoses in the affected tissue (11). In medium and larger vessels (diameter > 0.33 mm) it may take several days for complete cessation of blood flow (11). Cryosurgery of large vessels does not cause complete vascular obstruction and they may retain a normal function (12, 13).

Blood flow in the tissue to be frozen is important with regard to the thawing process and in turn to the extent of the consequent tissue destruction. For example, freezing of rat skin under vasoconstriction induced by epinephrine resulted in a smaller edematous reaction than in uninjected areas (14), and cryodamage was also less pronounced in rats treated during vasoconstriction (induced by bleeding shock) than in control animals with normal perfusion (15). In humans, blockage of blood flow by a tourniquet resulted in a considerably longer thawing time than without a restricted blood flow (7).

It is mainly the surrounding microvasculature which is important for the thawing process, by transporting thermal energy of 37°C from an infinite pool, the body core, to the frozen tissue (9). It appears that the microvasculature around the frozen area is not or is only very briefly impaired, since temperatures outside the periphery of the frozen hemisphere do not fall below 0°C. In the hamster cheek pouch for example, unimpaired flow in the tissue adjacent to the freezing has been observed (10).

Therefore, vasoconstriction in the surrounding microvasculature is transitory or does not occur at all. During freezing this is clinically represented by an almost immediate erythematous response in the peripheral skin, which later extends to the thawed area.

In this investigation a phase-dependent increase in SBF in the tissue immediately around the frozen area was found. Surprisingly, the increase in SBF took place during the two freezing cycles and stabilized at an increased level after the thawing periods. This indicates that the freezing stimulus does not induce vasoconstriction but elicits an almost instantaneous and persisting vasodilatatory response in the unfrozen surrounding vessels. This was clinically clearly visible as an immediate erythema in the surrounding skin. The less pronounced increase in SBF and the larger standard deviation during the second freeze/thaw cycle may indicate that in some individuals the maximum of vasodilation has already been reached during the first freeze/thaw cycle. The stable SBF at the contralateral control site indicates that emotional and physiological factors had no measurable influence on SBF in general.

This increase in blood flow stands in contrast to the perfusion within the frozen tissue, which comes to a complete stop during freezing (2, 7, 10, 11). Our preliminary results suggest that blood flow in the surrounding microvasculature increases rapidly during freezing and persists at a high level thereafter. This early vasodilation and increase in SBF may accelerate the thawing process and in turn influence the resulting tissue damage. It may therefore be possible to influence the intensity and the extent of the cryodamage by pharmacological or physical modulation of the tissue microcirculation before or during cryosurgery. This may ultimately allow better control of the treatment procedure and may result in a shorter healing phase, a satisfying cosmetic appearance and a decrease in the recurrence rate of basal cell carcinomas.

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