doi:10.1016/S0007-1226(03)00012-2

## Developing strategies for therapeutic angiogenesis: vascular endothelial growth factor alone may not be the answer

Sir,

There has been huge development in the understanding of the molecular processes involved in angiogenesis, and identification of many of the growth factors involved in this process. This has inevitably led to attempts to use these factors clinically to manipulate angiogenesis therapeutically. A wide range of clinical applications can be envisaged for increasing blood supply therapeutically in plastic and reconstructive surgery. These include reconstructive applications, such as prefabricating flaps or augmenting blood supply in failing flaps. There are also applications in wound healing. The majority of trials have concentrated on the ligand vascular endothelial growth factor (VEGF). However, VEGF alone may not be enough to encourage the formation of stable patent vessels in the treated tissue.[1]

Angiogenesis can broadly be divided into a stage of initiation and a subsequent stage of vessel stabilisation. Initiation involves a co-ordinated cascade of endothelial-cell activation, migration, proliferation and differentiation to give rise to a new vessel. VEGF is a vascular-specific ligand that is a prime activator of angiogenesis, but there are other important growth factors, such as platelet derived growth factor (PDGF) and fibroblast growth factor, that act on both endothelial cells and non-endothelial cells in the formation of a stable vessel.[2] Blood vessels induced by VEGF alone are primarily leaky and non-patent,[3] as well as being prone to regression on withdrawal of VEGF.[4] However, the acquisition of periendothelial support cells can stabilise the newly formed vessels. Stabilisation and maturation of newly formed vessels requires further angiogenic factors, such as PDGF-β and angiopoietin-1.[2] In order to achieve a meaningful increase in blood supply, newly formed capillaries have to remodel themselves into functional vessels.

Angiopoietin is a vascular-specific ligand that acts upon the Tie-2 receptor. This receptor is essential for the formation of new blood vessels as it is involved in the integrity and stability of newly formed vessels.[5] An increased understanding of pericyte-endothelial-cell interaction and identification of defects in Tie-2 have helped to identify some venous malformations,[6] highlighting the broad potential benefits of increased understanding of the molecular processes of angiogenesis. Angiopoietin-1 can also decrease leakage from vessels,[7] and acts by increasing adhesion between endothelial cells and periendothelial cells, involving activation of the Tie-2 receptor.

When angiopoietin-1 is coadministered with VEGF in a corneal model of angiogenesis, there is a significant increase in neovessel density and the number of patent vessels, compared with administration of VEGF alone.[8] Coadministration of angiopoietin-1 and VEGF in an animal model of hind-limb ischaemia results in increased collateral formation compared with administration of VEGF alone.[9] When angiopoietin-1 and VEGF are administered in viral vectors to cremaster muscle flaps in rats there is a significant increase in functional capillary density, with increased formation of mature vessels. There is an increase in capillary perfusion, with an increase in the number of mature and stable vessels.[10]

Whilst the studies using single agents will undoubtedly be milestones in the development of therapeutic strategies to increase flap survival, it seems likely that the optimal strategy for inducing angiogenesis therapeutically might involve using an initial agent aimed at inducing vessel growth and a subsequent agent to promote stability and function.

Yours faithfully,

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doi:10.1016/S0007-1226(03)00017-1

## A technique for preparing meshed skin grafts with planned expansion ratios

Sir,

A machine-meshed split-skin graft is an effective method of grafting large difficult wounds and burns.[1,2] Sometimes the skin-meshing machine is unavailable. I offer a technique for producing a meshed skin graft with a predetermined expansion ratio. Established calculations are used to discuss how the measurements can be changed to produce various expansion ratios and how the measurements affect healing time. This hand meshing is easy and effective.

The split-skin graft is placed on a wooden skin-graft board, stretched and its corners fixed with staples to an underlying sterile theatre sheet. Rows and columns of uniform cuts in a set pattern are made with a no. 15 surgical blade. The geometric mesh pattern has the following parameters: the cuts have a fixed length, $L$, and fixed vertical, $g$, and horizontal, $d$, separations. First, two rows of cuts are measured and made; the cuts have length $L$, are separated from each other by $2d$ and have a vertical separation of $g$ (Fig. 1(A)). Next, two new

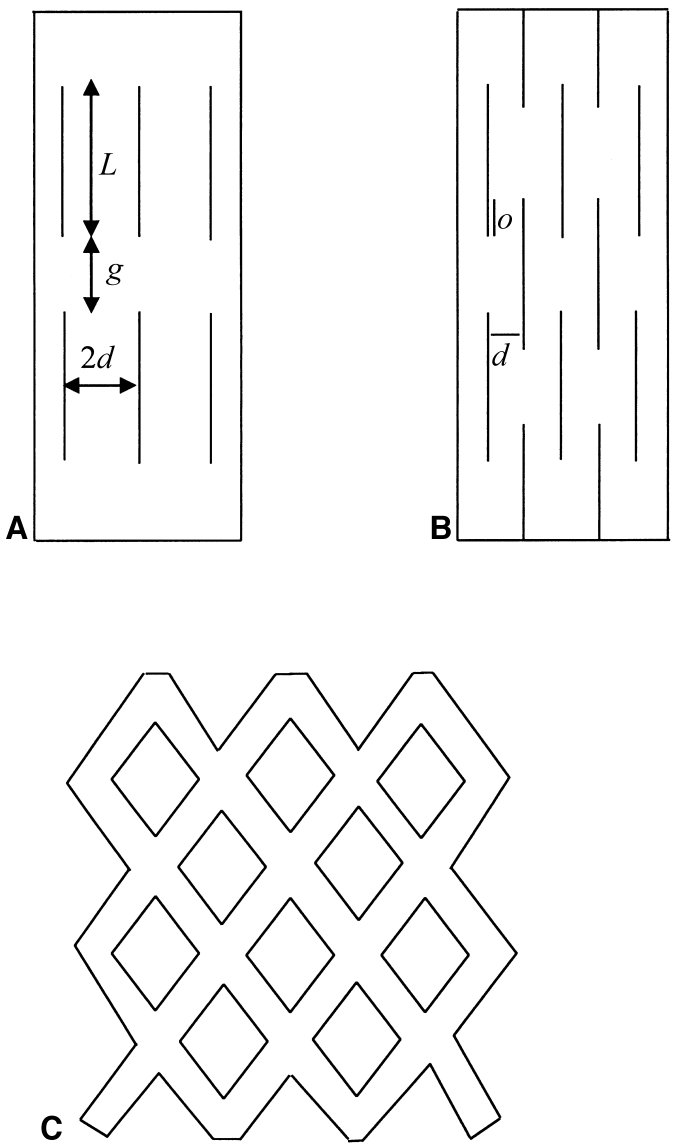


**Figure 1**—Procedure. (A) The first rows of incisions are made, with horizontal spacing $2d$, vertical spacing $g$ and length $L$. (B) Further rows of incisions are made between the initial rows. (C) The meshed pattern now enables the skin graft to be expanded.

rows with the same parameters are placed between the first two rows so that the cuts are equidistant (Fig. 1(B)). The position of the first cut of the new row is determined by the horizontal separation, $d$, between each cut and the overlap, o, of adjacent cuts.

$$o = 1/2(L - g)$$

If there is no overlap, there is very little expansion. This pattern is repeated until it covers the entire area of the skin. Repeated measurements do not need to be made, as the length and spacing of the cuts can be judged by eye. The edges of the graft must be cut, even if only a fraction of the cut can be made, in order to allow expansion at the edge of the graft. When tension is applied to the skin graft to overcome the elasticity, the mesh pattern expands uniformly and the skin covers an increased surface area (Fig. 1C). This process is easy, effective and requires no special equipment. The surgical blade is replaced when it is blunt.

The modified equation published by Vandeput et al can be used to calculate the theoretical expansion ratio for this geometric mesh pattern.[3]

If $R_{exp}$ is the theoretical expansion ratio, $L$ is the length of the cut, $d$ is the distance between the cuts and $g$ is the vertical gap between cuts, then:

$$R_{exp} = 1 + \left[\frac{1}{d} \times \frac{1}{L+g} \times \left(\frac{L}{2}\right)^2\right]$$

When the measurements are $L = 20$ mm, $d = 5$ mm and $g = 10$ mm, the expansion ratio, to two decimal places, is 1.67:1.

$$R_{exp} = 1 + \left[\frac{1}{5} \times \frac{1}{30} \times \left(\frac{20}{2}\right)^2\right] = 1.67$$

The formula for predicting the healing time of the meshed skin graft is based on the assumption that healing by epithelialisation of the mesh interstices occurs at a rate of 1 mm day.[4]

If $t_1$ is the healing time in days and $L$ is the length of the cut

**Table 1** Theoretical expansion ratios for various parameters ($L$ : length of cut; $d$ : distance between cuts; and $g$ : vertical gap between cuts)

| L(mm) | d(mm) | g(mm) | Expansion ratio | Healing time(days) |
|---|---|---|---|---|
| 30 | 10 | 10 | 1.56:1 | 21 |
| 20 | 10 | 10 | 1.33:1 | 14 |
| 20 | 10 | 5 | 1.4:1 | 14 |
| 20 | 5 | 10 | 1.67:1 | 14 |
| 20 | 5 | 5 | 1.8:1 | 14 |
| 10 | 5 | 5 | 1.33:1 | 7 |
| 10 | 4 | 2 | 1.52:1 | 7 |
| 10 | 2 | 2 | 2.04:1 | 7 |
| 10 | 1 | 1 | 3.27:1 | 7 |

in mm, then:

$$t_1 = 0.7L$$

When $L = 20$ mm, the healing time is 14 days.

Table 1 shows how the parameters can be changed to produce different expansion ratios and gives the estimated healing times.

This method of meshing allows the use of relatively large cuts on a moderately sized piece of skin. The technique is limited by the lack of precision of handmade cuts. Previously described methods to be used when a skin-meshing machine is unavailable have not indicated the measurements needed for expansion.[5,6] The geometric mesh pattern I describe is simple, and predetermined measurements can give a predictable expansion ratio.

Yours faithfully,

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doi:10.1016/S0007-1226(03)00016-X

## Painless steroid injections for hypertrophic scars and keloids

Sir,

The recent letter by Azad and Sacks conveyed a simple modification of the steroid-injection technique for hypertrophic scars and keloids.[1] We do appreciate this method of achieving a virtually painless injection. However, we are concerned about the needle prick adjacent to the actual scar because this can give rise to another keloid. The principle of keloid excision is that subsequent injection should always be intralesional in order to avoid a potential hypertrophic or keloid scar in the vicinity. The speed of injection is an important determinant of pain in intralesional chemotherapy.[2] Therefore, we think that slow injection of a lidocaine-mixed preparation of steroid using an electric pump is the best solution.

Yours faithfully,

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