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The modulation of smooth muscle cell phenotype is an early event in human aorto-coronary saphenous vein grafts

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Summary. The morphological changes in human vein grafts occurring in the first days after a coronary bypass operation (CBP) are rarely reported in the literature. Sections of aorto-coronary vein grafts from 11 patients who died during the first 10 days after a CBP were obtained at autopsy. The number of vein grafts per patient ranged from 1 to 4, yielding a total of 28 vein grafts. The early changes in the vein grafts have been studied by light microscopy, immunohistochemistry, transmission and scanning electron microscopy. The study demonstrates that soon after grafting, the vein wall is infiltrated by polymorphonuclear leucocytes (PMN). At 24 h the endothelium shows extensive desquamation. The massive migration of PMN through the venous wall occurs simultaneously with the endothelial damage. The circular layer of the media is severely damaged, resulting in a loss of smooth muscle cells (SMC). The remaining SMC in this layer show a change toward the synthetic phenotype and a reduced expression of α-smooth muscle actin. These early changes in the SMC function may initiate the process of fibrosis in the intima and the media of the vein grafts.

Key words: Coronary artery bypass – Saphenous vein – Smooth muscle cells – Synthetic phenotype

Introduction

Despite the widespread use of saphenous veins to bypass narrowed coronary arteries, morphological changes in human vein grafts occurring in the first days after the operation are reported only briefly in vein graft literature (Dilley et al. 1988; Jones et al. 1973; Marti et al. 1971; Titus 1988; Unni et al. 1974). Late histopathological changes are well documented (Barboriak et al. 1976, 1978; Bulkley and Hutchins 1977; Fuchs et al. 1978; Unni et al. 1974; Vlodaver and Edwards 1971). In most of these studies it is assumed that no significant lesions can be found in the grafts which have been in place for less than 2 weeks (Campeau et al. 1975; Kern et al. 1972; Vlodaver and Edwards 1971). However, they focus on intima formation or hyperplasia of the persisting intima and on thrombotic events followed by organization (Smith and Geer 1983).

Early sequential changes in the media of vein grafts have only been studied in animals (Brody et al. 1972; Ramos et al. 1976; Stewart et al. 1974). The early changes of the cytoskeletal proteins in medial SMC of vein grafts have not been described.

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Materials and methods

Sections of aorto-coronary vein grafts from 11 patients who died during the first 10 days after a coronary bypass (CBP) operation were obtained at autopsy (Table 1). This group included all patients who died in our hospital after a CBP in the early post-operative period during the last 4 years. The CBP included a flushing and preservation of the vein segment with heparinized blood and a perfusion under normal pressure with saline to check for leaks. The number of vein grafts per patient ranged from 1 to 4, yielding a total of 28 vein grafts. In 4 patients, control segments of the contralateral non-implanted saphenous veins were obtained at autopsy. The time interval between the operation and the decease ranged from 12 h to 10 days.

At autopsy the vein grafts were removed together with an adjacent portion of the aorta and of the distal coronary artery and fixed in toto in 4% formalin.

In 3 patients additional implanted vein segments were also processed for transmission (TEM) and scanning electron microscopy (SEM). Non-implanted saphenous veins used as controls for the EM studies included: (a) non-flushed, non-perfused saphenous vein segments obtained during CBP, (b) flushed and perfused saphenous vein segments obtained during CBP, (c) non-flushed and non-perfused saphenous vein segments removed at autopsy.

After fixation for 24 h, blocks of the proximal, mid and distal segment of the vein graft starting from the aorta were selected and paraffin embedded. All sections were stained with haematoxylin and eosin. Additional stains were Masson's trichrome, Verhoeff elastic and sirius (B) haematoxylin.

After selection in the Masson's trichrome stained material an immunohistochemical stain for α-smooth muscle cell (SMC) actin

Table 1. Details of patients, number of venous grafts and cause of death

Patient no.	Age (years)	Time interval between CBP and death	Number of venous grafts examined	Cause of death
1	74	6–7 days	2	Cholesterol emboli; colon and small intestine infarction
2	66	<24 h	1	Transmural myocardial infarction
3	59	24 h	3	Myocardial ischaemia; recent myocardial infarction
4	65	24 h	4 +1 control	Aortic dissection; cholesterol emboli in myocardium
5	72	10 days	1	Right heart failure
6	71	7 days	3 +2 controls	Acute renal failure; shock kidney
7	70	5 days	4 +1 control	Aortic aneurysm with rupture
8	79	12 h	3	Aortic dissection
9	70	24 h	1	Aortic dissection
10	71	4 days	3	Peritonitis
11	76	7 days	3 +1 control	Small bowel infarction

was done. The antibody (Sigma, St. Louis, Mo.) was used at a dilution of 1/1000. It was detected by an indirect peroxidase antibody conjugate technique. The antibody directed against vimentin (Biogenex, San Ramon, Calif.) was used at dilution of 1/200. This antibody was detected by a streptavidin biotin complex technique (Biogenex). Amino-ethyl-carbazole was used as a chromogen.

The fragments for TEM were fixed for 2 h in 1% (v/v) glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4). They were post-fixed for 30 min in 1% (v/v) osmium tetroxide in 0.1 M sodium cacodylate buffer (pH 7.4). After dehydration in an ethanol gradient they were embedded in LX-112 (Ladd Research Industries, Burlington, Vt.). Selection of the zones most representative for the lesions was made on 2-µm sections orientated in a transverse plane (perpendicular to the bloodstream) and stained with toluidine blue. Sections, 50 nm thick, were cut on an Ultratome Nova (Reichert-Jung, Vienna, Austria). They were stained during 30 min at 40° C with uranyl acetate and during 15 min at 20° C with lead citrate in an Ultrostainer 2168 (LKB, Bromma, Sweden). The sections were examined in a Jeol-100B transmission electron microscope at 80 kV. Photographs were made with electron microscopy film 4489 Estar Thick Base (Kodak).

For SEM fixation was carried out as for TEM. The sections were then dehydrated in an ethanol gradient up to 70% ethanol and further dehydrated in acetone. They were dried in a critical point dryer (Balzers CPD 030, Liechtenstein, Fla.) with CO_2 as transition fluid. The specimens were mounted on an aluminium stub with silverprint (Silver Print, GC Electronics, Rockford, Ill.) and coated with a 20-nm gold layer in an E5000 sputter coater (Polaron, Biorad House, Watford, UK). They were photographed in a MSI SR-50 scanning electron microscope at 10 kV with 5-TMX 120 film (Kodak).

Results

The contralateral control non-implanted saphenous veins were lined by flat endothelial cells whose nuclei were often clustered. In the sub-endothelial region segmental or circumferential accumulations of few SMC surrounded by a loose meshwork of collagen fibres were present. The nuclei of the SMC were generally orientated in a circular direction. This circular direction and the looseness of the collagen fibre network allowed these structures, which for convenience will be referred to as intima, to be distinguished from the media. The media consisted of two distinct layers: an inner longitudinal SMC layer and an outer circular layer. In the longitudinal layer the SMC were separated by a dense network of thick collagen fibres, clearly distinct from the intimal network. The circular layer consisted almost exclusively of SMC of identical shape, separated by collagen fibres. Longitudinal SMC bundles in the adventitia were often found.

In grafts in place less than 12 h, the luminal surface was sometimes covered with a narrow rim of fibrin and

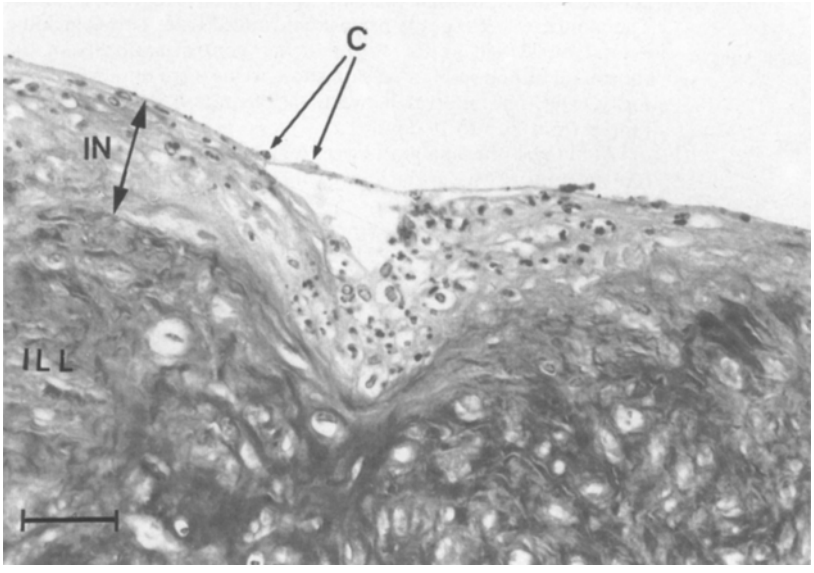

Fig. 1. At 12 h after grafting polymorphonuclear leucocytes (PMN) accumulate in the intima. Most of the endothelial cells are absent. A few flattened cells are still present, covering the PMN infiltrate (*C*). The *double arrow* indicates the intima (*IN*). The inner longitudinal layer of the media (*ILL*) is well preserved. Scale bar, 50 µm; sirius (B) haematoxylin stain, ×270

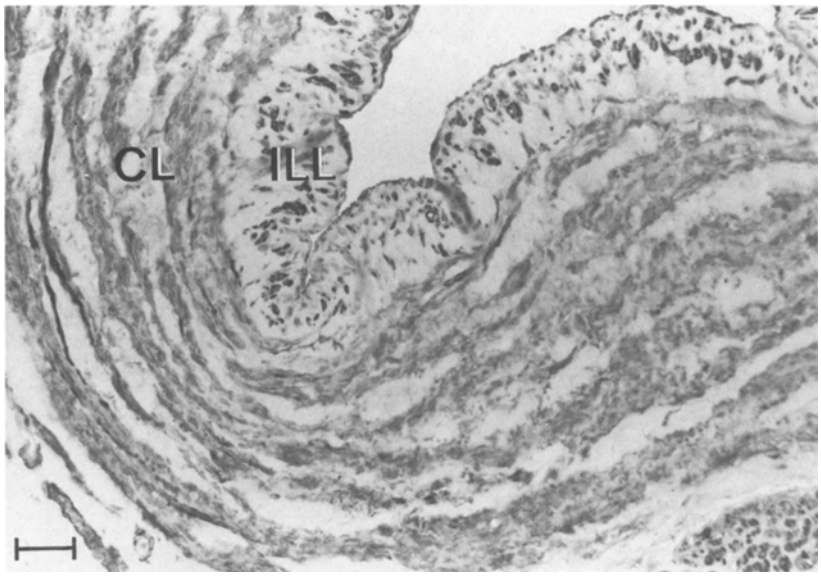

Fig. 2. Non-implanted saphenous vein (contralateral side) stained for α-smooth muscle cell (SMC) actin. In the media the inner longitudinal (*ILL*) and the outer circular (*CL*) layer can be clearly distinguished. Scale bar, 50 μm; ×170

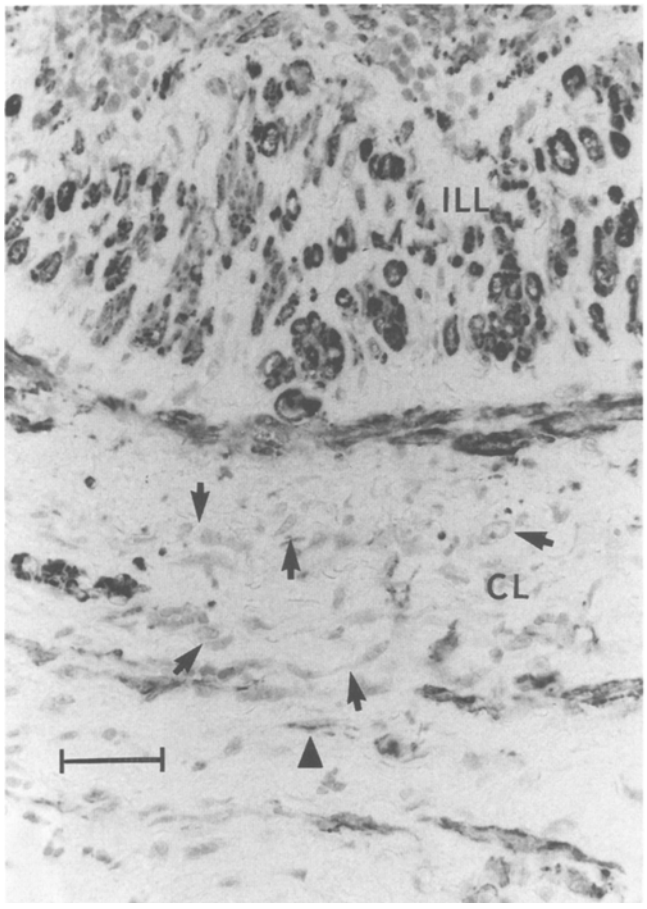

Fig. 3. Saphenous vein, 7 days after grafting stained for α-SMC actin. The SMC in the inner longitudinal layer (*ILL*) are immunoreactive. The circular layer (*CL*) has almost completely lost cells immunoreactive for α-SMC actin. Numerous spindle-shaped cells persist in this layer (*arrows*). These cells often have large nuclei with prominent nucleoli and are often not immunoreactive for α-SMC actin. Few of these cells show a weak staining for α-SMC actin (*arrowhead*). Scale bar, 50 μm; ×270

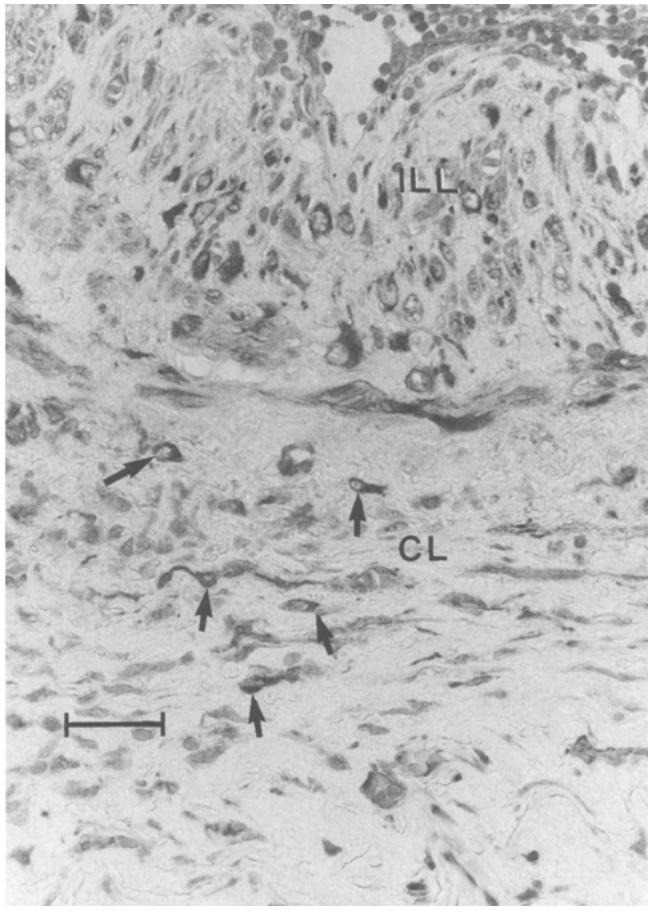

Fig. 4. Same vein graft as Fig. 3, stained for vimentin. The α-SMC actin-negative spindle-shaped cells in the circular layer (*CL*) of the media are immunoreactive (*arrows*). Scale bar, 50 μm; ×270

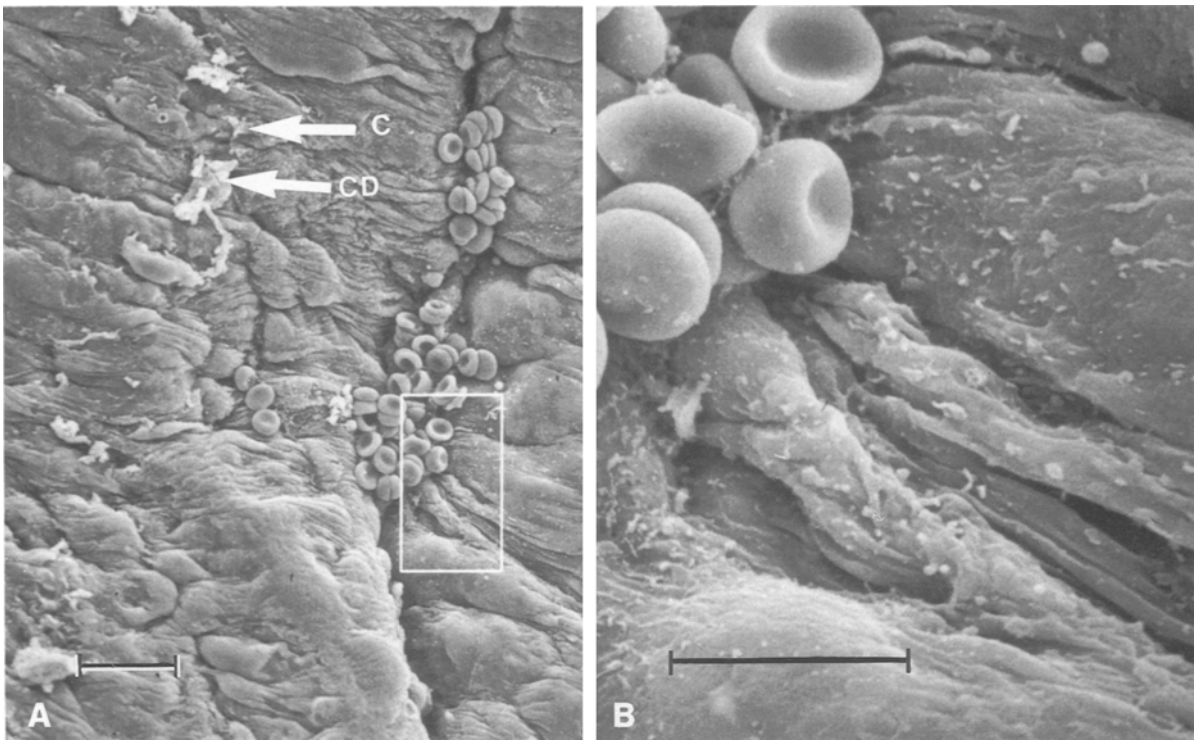

Fig. 5. A SEM of a non-implanted flushed and perfused saphenous vein. The endothelial cells are present. Few endothelial cells are desquamated leaving small craters (*C*), surrounded by cellular debris (*CD*) on the inner surface of the vein. The corrugated aspect of the surface is due to a tissue-constrictive effect. Scale bar, 20 μm. **B** Higher magnification of the boxed area of **A**. The endothelial cell surface is covered with microvilli. Scale bar, 10 μm

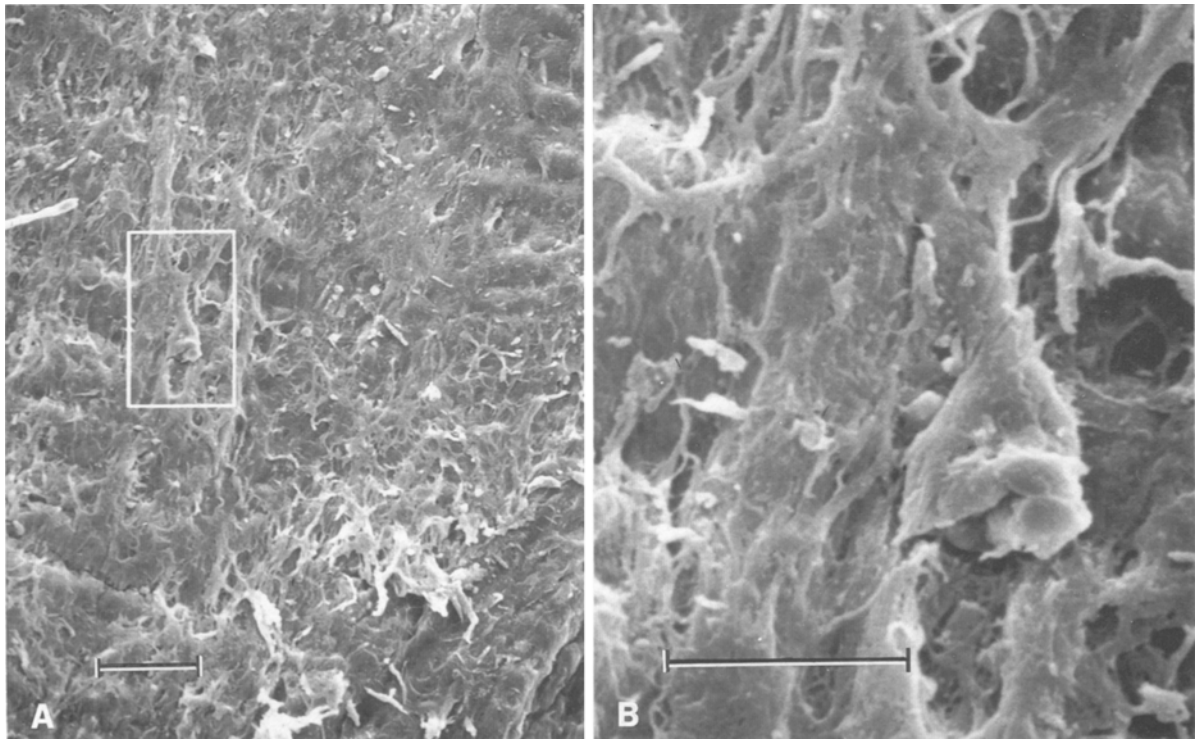

Fig. 6. A SEM of a saphenous vein 24 h after grafting. There is an extensive desquamation of the endothelium, exposing the collagen fibre network. Scale bar, 20 μm. **B** Higher magnification of the boxed area of **A**. Scale bar, 10 μm

platelets. Focal adhesion of polymorphonuclear cells (PMN) to the endothelium was conspicuous. Some PMN were located between the remaining endothelium and the underlying collagen fibres, resulting in an uplifting of the endothelial cells (Fig. 1). Most of the endothelial cells were desquamated. In a few segments valves showed infiltration by PMN. PMN infiltration was variable between the different vein grafts and between the proximal and distal sections of the graft. There was a slight predilection for the proximal and the mid portion.

In vein grafts in place for 24 h the PMN infiltration was more pronounced, reaching the circular layer of the media. The circular layer of the media displayed foci of blurred SMC, showing a narrowing of the cytoplasm.

In grafts at 4–10 days, the endothelial cells showed local desquamation. The naked luminal surface was covered with a fibrin layer. Two grafts contained small adherent fibrin and platelet thrombi. A few PMN persisted beneath the endothelium. In two grafts spindle-shaped cells were found beneath the endothelium, with morphological characteristics suggestive of fibroblasts. The media was free of PMN. However, small foci of nuclear dust (karyorrhexis) could be detected. The circular SMC layer of the media showed a segmental and sometimes a circular loss of SMC in almost every vein. Some of the SMC were recognizable with a Masson's trichrome stain as narrow undulating ribbons. Foci of enlarged and somewhat modified irregularly spindle-shaped SMC were frequently present in the circular layer. The nuclei of these cells were enlarged and contained nucleoli.

In the non-implanted veins all SMC showed immunoreactivity (Fig. 2) for α-SMC actin. In both layers of the media scattered cells, negative for α-SMC actin, were detected. Endothelial cells were negative. The vasa vasorum in the adventitia and in the media demonstrated a constant reactivity. The peri-adventitia (fibroblastic) cells were negative. In the vein grafts which were in place for 24 h the circular layer of the media showed a wavy appearance of the SMC, which were still α-SMC actin positive. The inner longitudinal layer of the media was intact.

At 7 days the vein grafts showed a significant loss of SMC in the media. In some grafts the circular layer had completely disappeared. The remaining spindle-shaped cells were non-reactive for α-SMC actin, although the nuclei and the cytoplasm were intact (Fig. 3).

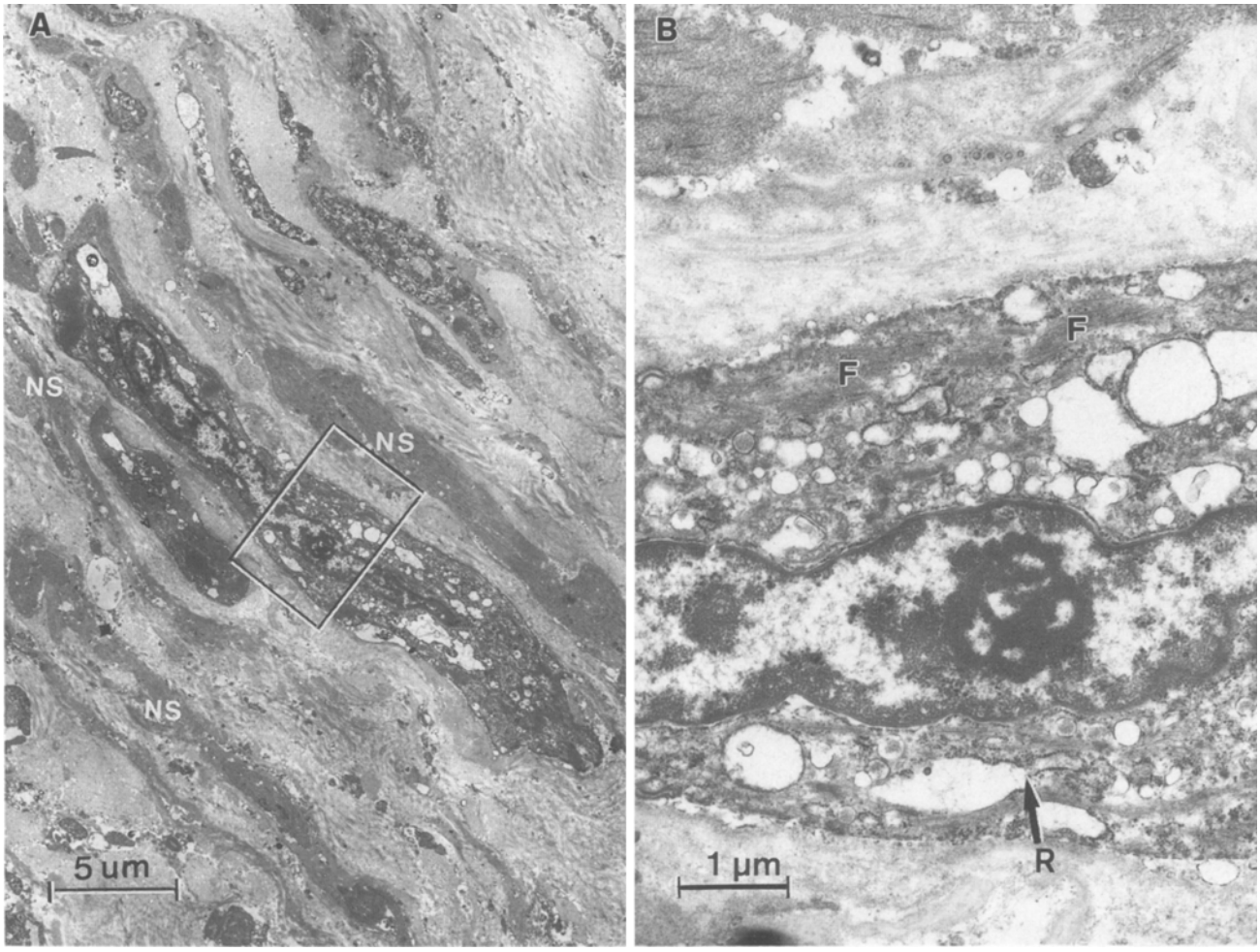

Fig. 7. A TEM of the circular layer of a saphenous vein 24 h after grafting. Numerous SMC are necrotic (*NS*). Spindle-shaped cells containing numerous vacuoles persist. ×3400. **B** Higher magnification of the boxed area of **A**. The persisting cells demonstrate a remarkable dilatation and vesiculation of the rough endoplasmic reticulum (*R*). Tracts of myofilaments (*F*) are present. ×15000

These actin-negative spindle-shaped cells were not confined to the damaged media but were also present underneath remaining endothelial cells.

In the non-implanted veins the staining pattern of vimentin in the SMC was comparable to that of α-SMC actin. Moreover the endothelial cells showed a clear reactivity. The peri-adventitial cells were positive. In the vein grafts all the SMC of the inner longitudinal and of the circular layer showed a positive immunoreactivity. At 7 days the spindle-shaped cells in the circular layer of the media were immunoreactive (Fig. 4). In the inner vein wall foci of reactive cells with rounded nuclei were detected.

SEM and TEM of non-implanted non-manipulated saphenous veins showed that the endothelial cells were preserved. There was no difference between the saphenous veins prepared during CBP or at autopsy.

TEM of the vein wall demonstrated the different layers in the total vein wall using a montage of adjacent low-power photomicrographs. The intima consisted of circularly orientated SMC and sparse collagen fibres. The media contained an inner longitudinal and an outer circular SMC layer as already described at the light microscopic level. Between the SMC collagen fibres were interposed oriented in different directions.

In non-implanted saphenous veins flushed and perfused most of the endothelium was preserved, as demonstrated by SEM. A few endothelial cells were desquamated and rolled up, leaving small craters on the inner surface. The endothelial cell surface was covered with microvilli (Fig. 5A, B). SEM of the vein media showed SMC and collagen fibres, which displayed a cross-linking pattern spanning the gaps between the SMC. The aspect of the vein wall with TEM was identical to that of the non-manipulated veins.

In the vein grafts examined with SEM, almost all endothelial cells were desquamated (Fig. 6). A few islands of persisting endothelial cells could be identified. This denuded surface was present at 24 h and at 7 days after grafting. With TEM the different layers of the vein, as in the controls, could be identified on a montage of low-power photomicrographs.

At 24 h after grafting the intima contained a few circulatory directed SMC which were damaged. The cytoplasm of some contained granulo-fibrillar material; others were necrotic. The media displayed a remarkable difference between its inner longitudinal layer and its outer circular layer. The inner layer was intact and contained bundles of longitudinal SMC separated by densely packed collagen fibres. The cytoplasm of these cells contained numerous myofilaments and showed a slight dilatation of the rough endoplasmic reticulum (RER). The circular layer, in contrast, was severely damaged (Fig. 7), most SMC being necrotic. Between the necrotic SMC, viable SMC showing a dilatation and vesiculation of the RER were seen (Fig. 7A, B).

At 7 days the circular layer of the media contained numerous SMC of the synthetic phenotype. In comparison with SMC of the non-implanted veins (Fig. 8), these cells had a prominent RER and Golgi apparatus. The intracytoplasmic filaments still displayed focal densities along their course (Fig. 9). These modified SMC con-

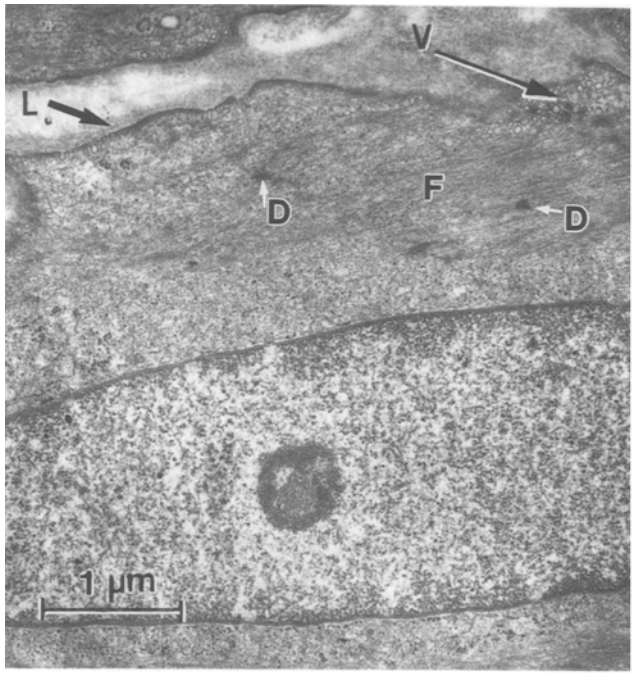

Fig. 8. TEM of a SMC of a non-implanted saphenous vein. The cytoplasm contains numerous filaments (*F*) with focal densities (*D*) along their course. There is a scarcity of rough endoplasmic reticulum (*R*). Numerous plasmalemma (pinocytotic) vesicles (*V*) are present. An external (basal) lamina ensheaths the SMC (*L*). ×19000

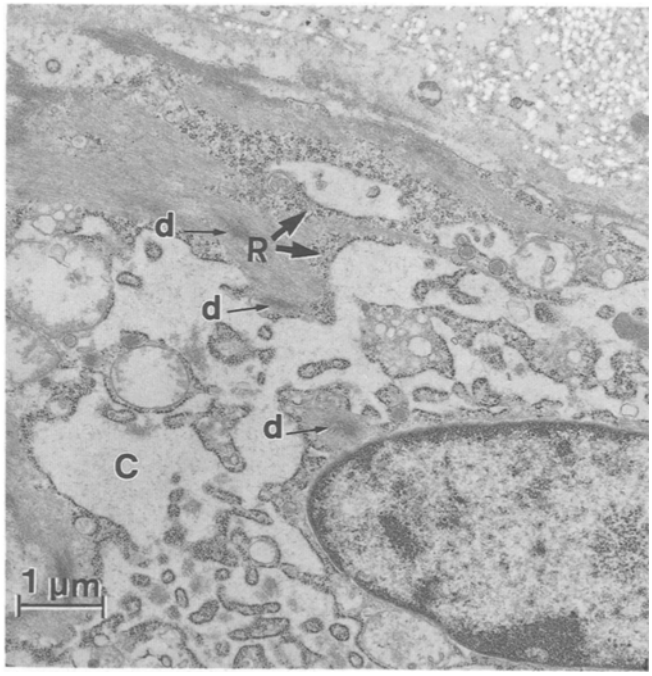

Fig. 9. TEM of a SMC of the circular layer of a saphenous vein, 7 days after grafting (same graft as Figs. 3, 4). There is a prominent rough endoplasmic reticulum, often with cisternae (*C*). The surface of the dilated cisternae is studded with ribosomal granules (*R*). The filaments still contain densities (*d*) along their course. Note the absence of pinocytotic vesicles. ×11000

tained far less pinocytotic (plasmalemmal) vesicles than those with the contractile phenotype. The basal (external) lamina was often interrupted.

Discussion

The present study demonstrates that PMN adhere to and infiltrate into the saphenous vein wall over its total thickness very soon after the bypass operation. The passage of PMN into the intima with time is associated with the endothelial damage. In the control veins which were left intact after removal the endothelial cells were well preserved.

Preparation of the veins before implantation is associated with a limited loss of endothelial cells, in contrast with the findings of Angelini et al. (1987, 1989), who reported a much higher endothelial cell loss. However, they estimated the endothelial cell loss after a pharmacological experiment and used a different preparation technique.

At 24 h after grafting, most endothelial cells were desquamated. This study is the first to show an early extensive endothelial denudation in implanted human saphenous vein grafts even when our surgical preparation technique causes little endothelial damage, as demonstrated by SEM. It confirms the findings of animal studies (Bush et al. 1986) and demonstrates the necessity of immediate post-operative anti-platelet aggregation therapy and anti-coagulation as soon as possible.

The PMN infiltration is an early phenomenon because PMN are virtually absent in the vein segments after 4–10 days, suggesting a short initial infiltration period. A massive infiltration of PMN in vein segments has been reported by Stewart et al. (1974) in canine jugular and femoral veins. It was caused by a surgical trauma consisting of exposure of a vessel segment, followed by 1–7 min occlusion by externally applied pressure just below the areas of exposure. In their study the PMN were considered responsible for the endothelial cell damage. It is known that denudation of the endothelium is followed by adhesion of PMN to the free accessible collagen or elastic fibres and to SMC, which are often damaged by the experimental procedure (Reidy 1985). Whether this adhesion is the factor which allows or promotes migration of PMN into the vessel wall is hard to determine because of the multitude of factors involved. An obvious candidate for a chemotactic attractant is the damaged SMC population. However, PMN also appear in zones of the media where no damage of SMC is detectable by morphological methods. Damaged endothelial cells may also produce chemotactic factors, and degeneration products of the coagulation cascade may diffuse into the vessel wall, both paving the way for PMN infiltration.

Theoretically the early disappearance of the endothelium, as observed, could set up a cascade mechanism for the intima formation. The assumption is supported by a study of Shiokawa et al. (1989), who reported that early re-endothelialization inhibits subsequent intimal thickening in vein grafts.

In the present study the SMC of the media of grafted veins often show severe damage. This results in a significant decrease of the SMC in the circular layer of the media. The inner longitudinal SMC layer of the media is less affected. In a study of aorto-coronary vein grafts in dogs, Brody et al. (1972) noted these changes in the media. They suggested that the changes were due to an ischaemic state of the media as a consequence of the interruption of the vasa vasora. In the present study the persisting spindle-shaped cells in the damaged media are vimentin positive but show a loss of α-SMC actin expression. These cells have the ultrastructural features of SMC of the synthetic phenotype. In the control saphenous veins the medial SMC all demonstrate the contractile phenotype. This phenotype change may be important since it has been suggested by Thyberg and Fredholm (1987), Chamley-Campbell et al. (1981) and Campbell et al. (1988) that SMC will only respond to mitogens after they have acquired the synthetic phenotype, (Schwartz et al. 1990). This modulation includes a loss of expression of contractile filaments and the appearance of large amounts of endoplasmic reticulum. It has been shown that α-SMC actin expression in SMC is modulated during various experimental and pathological conditions (Sappino et al. 1990). During experimental arterial thickening after endothelial denudation, as well as in human atheromatosis, SMC show a decreased content of α-SMC actin and predominantly express the β-isoform (Gabbiani et al. 1984; Kocher et al. 1985).

The histopathological changes of saphenous vein grafts at later periods consist of a remarkable intimal thickening with fat accumulation. Electron microscopic studies of the thickened intima demonstrate SMC and macrophages. In the newly formed intima there is a prominence of modified SMC, consistent with previous phase of proliferation (Kern et al. 1972; Unni et al. 1974). The ultrastructural aspects of these cells are similar to that of the modified SMC described in the media. The media of vein grafts which were in place for 1 month shows fibrosis (Barboriak 1976, 1978; Bergeur et al. 1980; Brody et al. 1972; Dilley et al. 1988; Ramos et al. 1976; Spray and Roberts 1976). In these studies fibroblasts and collagen fibres were found in increasing amounts in the vein graft media in the 1st month after grafting.

Our study demonstrates that in the days following grafting the SMC of the saphenous veins acquire a secretory phenotype and constitute the cell population which is capable of initiating the fibrotic transformation of the intima and of the media. The significance of the PMN infiltration is difficult to evaluate. It is associated with endothelial cell desquamation and of short duration, which suggests that it is an epiphenomenon which has no influence on the phenotypic modulation of intimal and medial SMC.

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