

Pre-Existing Histopathological Changes in the Cephalic Vein of Renal Failure Patients before Arterio-Venous Fistula (AVF) Construction

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Background: Native cephalic vein remains the superior dialysis conduit, even 30 years after it was first described. However, up to 37% of hemodialysis patients develop progressive stenosis in the venous circuit of arterio-venous fistula (AVF), which may later cause thrombosis and occlusion.

Material and Methods: To study the pre-existing morphological changes in the wall of the cephalic vein before AVF construction, we collected 23 cephalic vein specimens from 3 normal, young trauma patients and 20 renal failure patients. The samples were collected at the time of vascular repair in the first group and AVF construction in the second group. Sections were prepared and stained with hematoxylin & eosin (H&E), Masson's trichrome and Verhoff von Gieson's stains.

Results: Compared with normal cephalic veins, all pre-access cephalic veins showed generalized thickening of the wall due to intimal hyperplasia and replacement by collagenous, fibrous tissue. Other changes were disruption or loss of internal elastic lamina in 9 (45%) patients, loss of endothelial cell layer in 6 (30%), atrophy or loss of the muscle layer in 6 (30%), mucoid or myxoid degeneration in 6 (30%), inflammatory cell infiltration of the wall in 5 (25%), mural calcification in 3 (15%) and telangiectasia in 2 (10%). Another important finding was the marked accumulation of spindle-shaped smooth muscle cells (SMCs) on the de-epithelialized intimal surface in areas of intimal hyperplasia.

Conclusion: In conclusion, most of the apparently normal cephalic veins of the renal failure patients showed morphological abnormalities at the time of AVF construction. This may influence the outcome of shunts in terms of future stenosis and failure. (*Ann Thorac Cardiovasc Surg* 2006; 12: 341–8)

Key words: cephalic vein, arterio-venous fistula, renal failure, intimal hyperplasia, stenosis, thrombosis, failure

Introduction

A well-functioning vascular access is the pre-requisite

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for chronic hemodialysis treatment, and the arterio-venous fistula (AVF) is the optimal form of vascular access.¹ The native cephalic vein remains the superior dialysis conduit, and constructing a native fistula in the forearm or upper arm, will serve the patient better in the long term than a prosthetic graft.² The National Kidney Foundation (USA) has issued an appeal for the increased use of native AVFs.³ While complications are less frequent with AVFs than with synthetic grafts, vascular access dysfunction in general is an important cause of morbidity for dialysis patients and a major contributor to hemodialysis cost.^{4,5}

This morbidity accounted for 15% of hospital admissions among USA hemodialysis patients at a cost which exceeded \$1 billion per year in 1996.^{4,6)} The immediate or primary failure rate for various AVFs is 7.7–13% in the first month and the 1- and 5-year patency rates are 56% and 30% respectively.^{7,8)} Thrombosis is a leading cause of vascular access failure and usually results from stenotic lesions in the venous outflow system.⁵⁾ It was responsible for 87.2% of late failures.⁷⁾ In a group of 51 patients with suspected impairment of AVF function, color flow-Doppler ultrasound (CFDU) showed AVF stenoses in 35% and partial or complete AVF thrombosis in 65%.⁹⁾ Only recently have the changes of intimal fibrosis and sclerosis in pre-bypass long saphenous vein (LSV) been documented prior to cardiac and femoro-popliteal bypass surgeries.^{10–18)} It was suggested that the extent of pre-existing disease in vein grafts may affect the outcome of coronary and femoro-popliteal bypasses.¹⁹⁾ However, little attention has been paid to the baseline morphologic characteristics of the cephalic vein of renal failure patients and to the presence of pre-existing vein disease which may contribute to both early and late shunt failures. This study has been conducted to see if similar, preexisting changes are present in the cephalic vein of renal failure patients at the time of AVF construction.

Material and Methods

During the period from June 2000 to October 2001, a total of 23 cephalic vein specimens were collected from 3 young trauma and 20 renal failure patients at Aseer Central Hospital (ACH), in Abha, Kingdom of Saudi Arabia. The trauma patients who underwent repair of their upper limb arterial injuries and acted as normal controls were 3 males with the mean age of 24 years \pm 3.6 (20–27 years). The renal failure patients were 8 males and 12 females with a mean age of 44.3 years \pm 16.2 (16–70 years). Ten of these patients were hypertensive and 5 were diabetics. These patients underwent construction of a primary direct AVF for hemodialysis on the chosen limb. The fistulas were equally distributed between the right and left upper limbs, with 5 done at wrist and 15 at elbow. None of the patients had an existing or a previously documented history of deep vein thrombosis or superficial thrombo-phlebitis on the operated limb. Renal failure patients underwent pre-operative physical examination. If required, they underwent upper limb venography to ascertain the presence of a suitable cephalic vein at either the wrist or elbow. All the patients gave their informed

consent for a cephalic vein biopsy prior to surgery.

At the time of operation, the cephalic veins were digitally palpated for the presence of apparent wall fibrosis or calcification. The veins were routinely irrigated with heparin/saline solution and palpated for transmitted thrill along their course. A 2–3 mm circumferential segment was excised from a non-traumatized part of the cephalic vein in every patient. The specimen was collected in a small, labeled test tube containing 10% formalin for light microscopy examination. In the pathology laboratory, paraffin sections were prepared and semithin sections were stained with hematoxylin & eosin (H&E), Masson's trichrome and Verhoff von Gieson's stains. Slides were examined under the light microscope and representative sections were photographed using Olympus® PM 10 SP automatic micrographic system (Japan). A perfusion technique as described by Milroy et al. was not used, because only a small segment of the vein was available.¹⁷⁾ Qualitative assessment of the different cephalic vein sections was done by looking for certain morphological changes in the vein wall. These changes included: generalized thickening of the wall, fibrous tissue infiltration, intimal hyperplasia, loss of the endothelial cell layer, disruption or loss of the internal elastic lamina, atrophy or loss of the medial smooth muscle cells (SMCs), mucoid or myxoid degeneration, presence of telangiectasia, mural calcification and inflammatory reaction in the wall with infiltration by erythrocytes and/or histiocytes. Intimal hyperplasia was simply defined as a thickening or increase in the size of the intimal layer as compared to that in the "normal" vein.

Results

Intra-operative digital examination of the cephalic veins showed no apparent fibrosis or calcification in any of the patients in the study.

Sections of the normal cephalic vein were stained with H&E. These showed regular wall and intimal surface with an intact endothelial cell layer. The normal ratio of intima to media was in the range of 1:5, with normal content and arrangement of intimal and medial SMCs (Fig. 1A). In renal failure patients, sections of the cephalic vein showed irregularity of the wall and the lumen with marked focal or diffuse hypertrophy. This was mainly due to intimal thickening or hypertrophy and thinning of the medial SMC layer with reversal of the normal intima: media ratio to be in the range of 5:1. There was also partial or complete loss of the endothelial cell layer and disruption

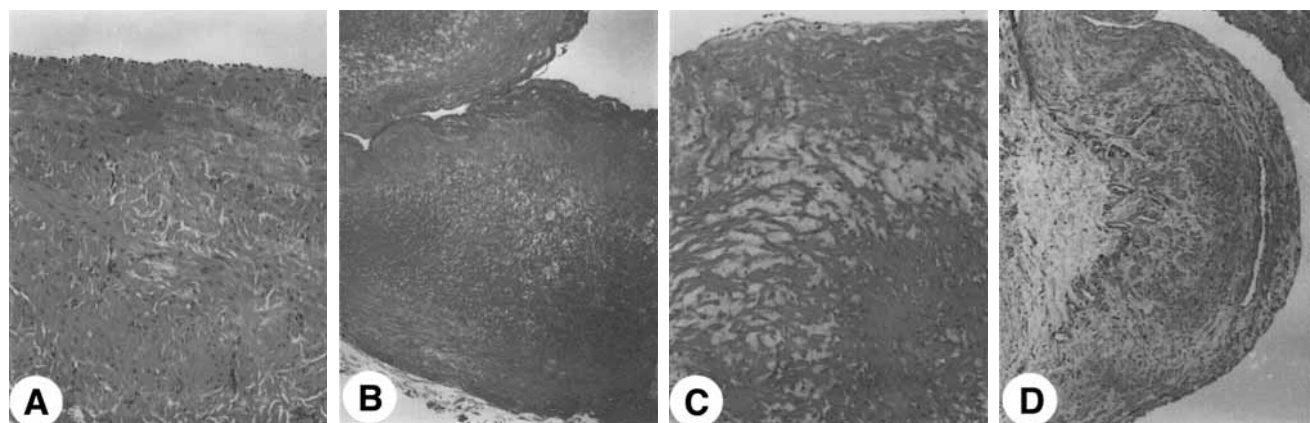


Fig. 1. Cross sections of normal and pre-access cephalic veins.

- A:** Section of a normal vein showing the normal proportion of intima and media and the intact endothelial cell layer. Note the normal content and arrangement of the intimal and medial smooth muscle cells (SMCs). (H&E stain: $\times 1,030$)
- B:** Cephalic vein of renal failure patient showing thickening of the wall due to marked intimal hyperplasia. Note the irregular intimal surface and the thin media. (H&E stain: $\times 515$)
- C:** High power magnification of an area of intimal hyperplasia showing the fibrous tissue infiltration with few scattered SMCs. Note the partial loss of the endothelial cell layer. (H&E stain: $\times 1,030$)
- D:** Cephalic vein of renal failure patient showing focal intimal hyperplasia with marked telangiectasia. (H&E stain: $\times 515$)

of the normal palisade arrangement of the intimal SMCs (Fig. 1B). These changes were more apparent at higher magnification. They also showed loose arrangement of the intimal hyperplastic tissue and appearance of myxoid or mucoid degeneration. This was more apparent in sections stained with Alcian blue. Intimal hyperplasia appeared to consist of loosely laid fibrous tissue with few, scattered SMCs (Fig. 1C). Intimal hyperplastic lesions also showed marked telangiectatic changes (Fig. 1D).

Sections stained with Masson's trichrome stain showed that the areas of diffuse and focal intimal hyperplasia were almost completely replaced by fibrous, collagenous tissue, with very little smooth muscle content. The few remaining, scattered intimal and medial SMCs had hardly any apparent arrangement (Fig. 2A). At higher magnification, intimal hyperplastic lesions were seen to consist of collagenous tissue with marked accumulation of spindle-shaped SMCs on the de-epithelialized intimal, "luminal" surface (Fig. 2B). Sections stained with Verhoff von Gieson's stain showed disruption or, in some areas, total loss of the internal elastic lamina with scattering or dispersion of the fragmented elastic fibers among the different layers of the wall (Fig. 2C). At higher magnification, irregular fragments of elastic fibers were scattered among the coarse collagen fibers and the scattered SMCs

of the media and also in the adventitia (Fig. 2D).

In general, all the specimens showed focal or diffuse intimal hyperplasia and collagenosis of the wall. The other changes which we described earlier were present in 10–45% of the renal failure patients, as shown in Table 1. Individual histopathology reports of the changes in the cephalic veins of different renal failure patients are shown in Table 2.

Discussion

There have been many studies of the morphological changes that occur in veins that have been used for arterial grafting.¹⁹⁾ The initial changes that have been classically described are those of endothelial cell damage, followed by intimal hyperplasia with elastic tissue reduplication.^{20–27)} Areas of graft stenoses demonstrate the features of intimal hyperplasia and muscle hypertrophy.^{20,22,25)} Some of these features were previously attributed to exposure to high pressure with arterialization, trauma or mural ischemia.^{20–24)} Only in the last 25 years has the pre-bypass vein structure been investigated, despite the use of vein grafts for over half a century.^{10–14)} Waller and Roberts who analyzed 3,394 cm of vein taken randomly from 402 patients at the time of coronary bypass surgery, dem-

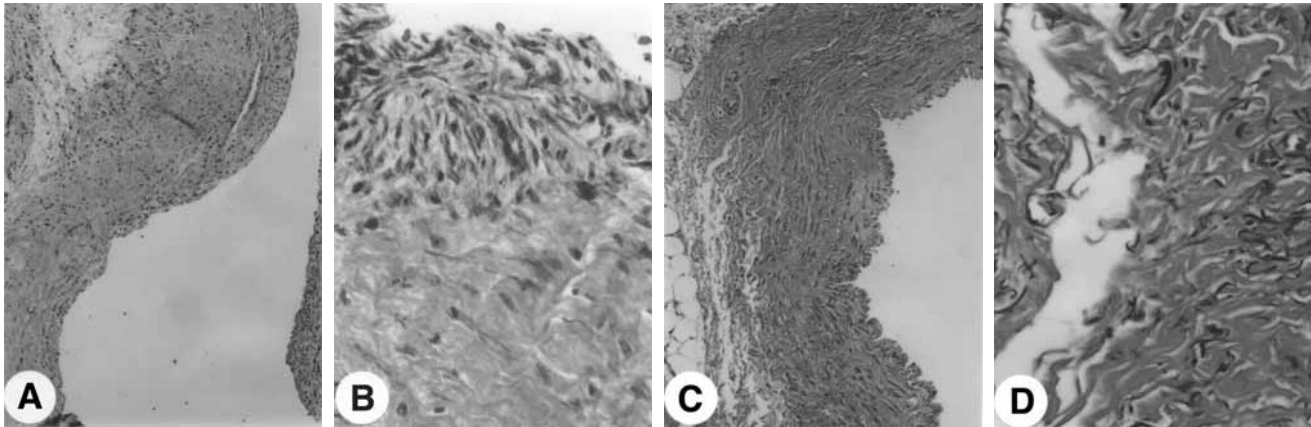


Fig. 2. Special stains of pre-access cephalic veins.

- A:** Focal intimal hyperplastic lesion of a pre-access cephalic vein showing severe infiltration by collagenous, fibrous tissue. Note the marked decrease in the content and loss of the normal arrangement of both intimal and medial SMCs, which are sparsely scattered in the wall. (Masson's trichrome stain: $\times 515$)
- B:** High power magnification of the previous section showing accumulation of spindle-shaped intimal SMCs towards the intimal, "luminal" surface. (Masson's trichrome stain: $\times 1,160$)
- C:** Pre-access cephalic vein showing disruption of the internal elastic lamina with scattering of fragments of elastic fibers in the different layers of the wall. (Verhoff von Gieson's stain: $\times 515$)
- D:** High power section of pre-access cephalic vein showing the fragmented elastic fibers lying among coarsely laid collagen fibers. Note the distortion of the normal collagen/elastin lattice. (Verhoff von Gieson's stain: $\times 1,160$)

Table 1. Incidence of different wall changes in the cephalic veins of renal failure patients

Change	Number	%
Intimal hyperplasia	20	100
Wall collagenosis	20	100
Disruption or loss of internal elastic lamina	9	45
Loss or disruption of endothelial cell layer	6	30
Muscle loss or atrophy	6	30
Mucoid or myxoid degeneration	6	30
Inflammatory reaction — Infiltration by erythrocytes/histiocytes	5	25
Mural calcification	3	15
Telangiectasia	2	10

onstrated the previous findings and showed no difference for age and sex.¹²⁾ Similar changes have been shown in veins used for femoro-popliteal bypass surgery, where random specimens of the LSV below the knee were studied.^{16–18)} The study by Davies et al. confirmed the findings of previous studies and showed that these changes occur throughout the vein and similar changes are also present in the arm cephalic vein.¹⁹⁾ According to Panetta et al., early graft failures occurred in 20% of cases with pre-existing SV disease. These were the result of unrecognized or minimal vein disease, in veins with normal external appearance and adequate luminal diameter. The

cumulative primary patency rate for diseased veins was significantly less than that for non-diseased ones.²⁸⁾ Histopathologically, intimal hyperplasia (focal or diffuse) was present in 73–87% of specimens, while muscle hypertrophy (circular and/or longitudinal) was present in 68–88% of specimens. In addition, 75% of arm cephalic vein samples showed intimal hyperplasia and muscle layer changes, which compare well with our present data (Table 1).¹⁹⁾ In our previous work, we demonstrated degenerative changes in the medial SMCs which were widely separated by an increased amount of extracellular collagen fibers.²⁹⁾ In agreement with our findings, Thiene et al.,

Table 2. Individual histopathology reports of different cephalic vein samples

Patient no.	Changes
1	Mucoid degeneration of the intima and media. Muscle bundles destroyed and reduced to a small amount/atrophied.
2	Endothelial cells focally distorted. Loose fibro-connective tissue enhanced beneath endothelium and splitting muscle bundles. Internal elastic lamina disrupted. Few histiocytes and erythrocytes seen in the media.
3	Internal elastic lamina focally continuous and prominent — destroyed at places — sparse histiocytes and erythrocytes in loose connective tissue giving myxoid pattern in-between muscle bundles. Focal mucoid degeneration of the wall. Granulation tissue, hemorrhage and inflammation (not predominant) observed on the luminal surface.
4	Endothelium disrupted.
5	Intimal thickening — collagenosis and myxoid changes of intima and media.
6	Intima and media replaced by fibrous, connective tissue. Focal areas of mucoid degeneration. Elastic fibers disrupted. Erythrocytes noticed amongst fibro-connective tissue in the media.
7	Marked collagenosis of the wall. Apparent telangiectatic vessels noticed. No histiocytes. Looks like neo-vascularization process.
8	Loss of endothelial layer. Intima destroyed at areas.
9	Loss of internal elastic lamina. Dispersion of elastic fibers in the wall.
10	Internal elastic lamina present. Degeneration of muscle bundles with increased amount of collagen fibers.
11	Intimal thickening. Wall fibrosis.
12	Thickening of the wall. Internal elastic lamina lost. Some elastic fibers present in the wall. Degeneration of muscle bundles with increased collagenosis.
13	Intimal thickening. Wall fibrosis.
14	Dilatation of the lumen. Focal intimal thickening with myxoid degeneration. Focal calcification. Loss of internal elastic lamina. Few scattered, disrupted elastic fibers in the wall. Destruction of muscle bundles, replaced by fibro-connective tissue.
15	Intimal thickening. Focal disruption of the endothelial cell layer. Loss of internal elastic lamina. Few, disrupted, scattered elastic fibers in the wall. Areas of mural inflammatory reaction with focal areas of calcification. Few histiocytes seen in the wall. Destruction of muscle bundles. Atherosclerotic-like changes. Luminal thrombus with fibrin, eosinophilic material.
16	Intimal thickening. Wall fibrosis (early).
17	Intimal hyperplasia, focal. Collagenosis of the wall. Atrophy of smooth muscles.
18	Intimal thickening. Wall fibrosis.
19	Intimal thickening. Marked collagenosis of the wall. Disrupted, fragmented, scattered elastic fibers. Telangiectatic changes.
20	Intima and media partially replaced by fibrous, connective tissue. Areas of mucoid/myxoid degeneration.

found that sclerosis of the inner medial layer appeared as a replacement process of the muscle elements.¹¹⁾ The intimal fibrosis consisted of acellular connective tissue proliferation, causing luminal narrowing. However, the intimal fibrosis was not severe enough to significantly reduce the lumen of the vein. Although these lesions were widely regarded as an aging process, statistical analysis revealed that neither the intimal fibrosis nor the medial sclerosis correlated with the age or the sex of the patients.¹¹⁾ In another study, there was no significant difference in age, sex, presence of hypertension, coronary artery disease, history of smoking, hypercholesterolemia,

or renal insufficiency between patients whose grafts either developed significant lesions or failed and those whose grafts remained patent and normally functioning for an 18–30 months period.³⁰⁾

Decreased patency of vein bypass grafts has been reported when adequate, ipsilateral greater saphenous veins were not available and smaller diameter veins were used.^{31–34)} An operator-curve analysis showed that a cutpoint of 2.6 mm for minimum forearm cephalic vein diameter (CVD) had the greatest predictive value for fistula failure.³⁵⁾ Therefore, increased size and capacitance of native arm veins before the formation of vascular ac-

cess surgery through incremental resistance, exercise training program has been considered an important variable in the success rate of AVF operation.³⁾

Recent work by Davies et al. has shown that pre-operative assessment of vein wall compliance can be used to predict vein grafts at risk of failure.¹⁸⁾ Correlative histologic analysis of veins with decreased compliance showed that such veins had increased fibrosis at the time of insertion and a subsequent increased failure rate. Thick-walled veins can occur as a result of intimal, medial and/or adventitial fibrosis, as a result of trauma, aging, increased vein pressure and possible superficial thrombophlebitis. According to Marin et al. occult vein wall calcification was an uncommon finding that occurred with increased frequency in vein remnants from grafts that failed or developed hemodynamically significant lesions. This finding was frequently associated with increased intimal thickness, which also correlated positively with the risk of developing a lesion.³⁰⁾ According to the same authors, the most significant vein biopsy finding was the presence of increased intimal cellularity greater than 5 cell layers thick (Fig. 2), which increased the risk of failure almost 30 times. Seventy percent of grafts that contained these cells began to fail. This was significantly greater than the 7.5% incidence in grafts that did not fail.³⁰⁾ These cells had a distinct spindle or stellate shape and contained the morphologic appearance of SMCs. Electron microscopic examination of these cells demonstrated poorly differentiated SMCs with few contractile fibers and abundant cytoplasmic vacuoles and secretory granules.³⁶⁾ The presence of hyperplastic-appearing cells in the intima has also recently been noted by Davies et al., who found a similar adverse effect of intimal cellularity on graft patency.¹⁹⁾ These cells showed a similar resemblance to the cells present in the mature lesions of intimal hyperplastic stenoses.³⁷⁾ As has been noted in previous studies, a stenotic lesion in the venous outflow system is the leading cause of AVF thrombosis and subsequent failure.^{5,38)} It is possible that these abnormal cells in the sub-endothelial area are likely candidates to produce or respond to growth stimuli.³⁰⁾

It is surprising that such serious changes are seen in apparently normal veins. Current theories in the presence of a defective endothelium have been suggested to explain the development of these changes, as demonstrated in the present study. The first possibility is that repeated episodes of thrombophlebitis cause endothelial damage and transmural injury. The second one suggests that these veins have an inherently defective endothelium. Both

mechanisms involve platelet activation.¹⁹⁾ Release of platelet-derived factors may then cause either migration or activation of the pre-existing SMCs as their precursor.³⁹⁻⁴¹⁾ An alternative hypothesis is that the endothelium remains intact and that the SMCs and lymphocytes secrete cell mediators for the SMCs following a stimulus.^{42,43)} However, in the experimental model of Boerboom et al., platelet inhibition did not decrease the extent of intimal hyperplasia. The prevalence of adherent platelets and the amount of fibrin correlated inversely with the amount of intact endothelium present during the first 14 days after arterio-venous shunt.¹⁾ This may indicate that the primary problem is in the endothelial cell loss and that platelet adherence is a secondary problem, as suggested in our present study.

The need to predict prior to or during an operation which veins are at risk of failure, so that the operation can be modified accordingly, remains an unsolved problem.³⁰⁾ The pre-operative diagnosis of diseased veins or vein segments is possible in some cases by physical examination, and the use of duplex ultrasonography or venography. However, vein wall thickness is often difficult to assess with current technology.²⁸⁾ Intra-operative measures are required to supplement pre-operative screening tests for diagnosis. These include visual inspection, gentle palpation of the vein, routine irrigation with heparin-saline solution and palpation of transmitted thrill over the course of the native arm (cephalic) vein. If pre-existing vein disease is suspected, biopsy of the remnant vein segment should be performed. If cephalic vein disease is identified, an increased risk of shunt failure should be expected. If another native vein that is free of disease is not available, consideration of a synthetic graft may be warranted, based on the type of AVF being performed.⁴⁴⁾

Conclusion

In conclusion, at the time of AVF construction, most of the apparently "normal" cephalic veins have been shown to have morphological abnormalities, especially in the form of intimal hyperplasia, mural collagenosis and partial or complete loss of the endothelial cell layer. This may influence the outcome of shunts in terms of future stenosis and failure due to thickening of the wall, adherence of platelets to the bare intima and activation of intimal SMCs. It seems likely that stenosis development may be the result of pre-existing disease rather than as a direct result of arterialization insult. We recommend

good clinical examination of the arm veins before operation and digital examination at the time of the shunt procedure.

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