Haemodialysis access without thrombosis: is it possible?

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Introduction

Sustaining patency of the permanent vascular access remains an important challenge in the management of haemodialysis patients. Re-establishing flow in a thrombosed access requires invasive techniques and often placement of a temporary catheter. These procedures carry a definite risk for morbidity and mortality, are expensive, and increase the risk of underdialysis. The care of haemodialysis patients must include maximal efforts to prevent thrombosis. In this Comment we focus on the strategies employed to maintain patency of arteriovenous bridge grafts.

Arteriovenous fistula

A fully developed radiocephalic arteriovenous fistula (AVF) seldom clots. Numerous studies have documented their excellent long-term function [1,2], making them the optimal access modality in haemodialysis patients. Results of brachiocephalic AVF are less well known, although a primary patency identical to that of radiocephalic AVF has been reported [3]. Unfortunately, native veins are often considered unsuitable for the creation of a radiocephalic AVF, or show insufficient dilatation and arterIALIZATION after construction of an AVF. Little is known about specific surgical or comorbidity factors predicting favourable fistula development. Because of their superior long-term function, construction of an AVF should be attempted whenever judged feasible.

Arteriovenous bridge graft

In patients with AV grafts, thrombosis is an important cause of access dysfunction [4]. Although in an occasional case this may be caused by too occlusive a bandage or by arm malpositioning during sleep, it is almost always associated with the presence of one or more stenotic areas [5-7]. These are typically located near the venous anastomosis, but possibly occur anywhere in the graft flow tract from the arterial anastomosis up to the venous system [5-7]. Evidently the optimal strategy for graft maintenance is prevention of stenosis. Effective means to accomplish this are not yet defined. Early detection and correction of stenoses is the next best approach.

Stenosis detection

Angiography, Doppler ultrasonography, and magnetic resonance imaging provide information concerning the anatomy. Angiography, which should always include the arterial anastomosis, the graft, and the venous system up to the subclavian vein, is considered to be the gold standard for confirmation and localization of stenotic areas, and is indispensable before correction can be considered. However, these techniques are unsuitable as routine screening tests to detect stenoses because they are expensive, invasive, and/or highly operator dependent. The indication for such anamnestic studies should follow from more readily available data on graft function.

Information about the functional status of the graft can be obtained from flow and pressure. Obviously, in the (non-autoregulating) graft the flow is determined by the blood pressure difference and the resistance over the vascular access tract. Resistance is determined by the anatomy of the graft and venous outflow tract. Therefore both flow and pressure can be used as an index of resistance.

Venous pressure measured by the dialyser has been convincingly validated in clinical trials, whereas there are only limited data on access flow measurements. Venous pressures increase when resistance in the venous outflow tract increases as a result of a stenosis. However, venous pressure will also be determined by the dialyser blood flow, the resistance in the tubing set and needle, recirculation, and the height difference between the graft and the measuring device. Therefore measurement of venous pressure needs to be standardized carefully and ‘normal’ values need to be established for a given dialyser blood flow for each combination of needles and tubing set. Despite these limitations, Schwab et al. [8] and Besarab et al. [9] showed that patients who during follow-up developed a predetermined level of venous pressure measured at a fixed blood flow or at zero blood flow were very likely to have a graft stenosis. Subsequent systematic correction reduces venous pressures and, importantly, also thrombosis rate from 0.50–1.00 to 0.17–0.20 events per patient year. Although not formally investigated, it is not unlikely that access surveillance and repeated angiography with stenosis correction produces less overall costs for access maintenance than an ‘act only if thrombosed’ approach.

Even in patients with ‘normal’ venous pressures thrombosis still occurs at a rate of approximately 0.15

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per patient year [8]. Such patients may have stenoses upstream from the venous needle, which will result in low instead of high venous pressures. This methodological problem of pressure-based assessment of the graft function can be overcome by measurement of volume flow. Volume flow is affected by stenoses irrespective of its localization. A limited number of studies over the past 20 years, using constant infusion of $^{99m}$Tc, dye-dilution, electromagnetic flow meters, Doppler imaging, or magnetic resonance angiography (references summarized in [10]) have indicated that access volume flow below a certain level ($\approx 500 \text{ ml/min}$), predicts thrombosis in the near future. None of these methods has gained widespread acceptance, because of their invasiveness, low reliability, intrinsic difficulty, operator dependency, and costs. Recently a newly developed device for access volume flow measurement was introduced, based on the Fick principle. With this technique, dilution of blood in the extracorporeal circuit by isotonic saline is measured by ultrasound [11]. We have compared this easily applicable method with flow assessments by magnetic resonance angiography and with a technique based on ultrasound-dilution device correlated well with both other techniques over a wide range of flows. It is likely that such flow measurements, especially if obtained at regular time intervals and related to (changes in) pressure, will prove to be of great help in long-term graft surveillance.

**Stenosis correction**

Once stenoses have been diagnosed, they may be corrected by surgical or radiological techniques. Percutaneous transluminal angioplasty (PTA) is now widely practised. Primary patency after PTA of the venous anastomosis at 6 months ranges from 50 to 70%, and at 1 year from 40 to 60% [5–7,12,13]. Angioplasty of veins central to the grafts usually show a lower patency rate [12]. Comparisons of surgical treatment and PTA indicate no convincing difference in primary patency [14,15]. This makes PTA the primary choice of treatment for stenoses, as it is less traumatizing to the venous system. Moreover, PTA can be done repeatedly, without compromising patency rates. Beathard [12] found similar results with no relation to the first, second, or third PTA performed. Also, PTA can be carried out without general or regional anaesthesia and is usually done as an outpatient procedure, which may reduce costs.

Nonetheless, restenosis is an always imminent danger after PTA, which has prompted the use of stents. In a randomized comparison, no significant difference was noted in patency after the treatment of venous anastomosis stenoses with PTA with or without stent implantation [16]. In contrast, patency of central venous stenoses with stents is better than without [17]. In addition, stents are helpful in kinking and collapsing stenoses or for sealing off dissections [18].

PTA typically injures the vessel wall. The proliferative response to this injury is implicated as cause for restenosis. Recently the hypothesis was tested that increasing the luminal diameter by sharp and regular endovascular surgical incisions instead of circular dilatation by a conventional balloon, may enhance the success of angioplasty [19]. A balloon with 3–4 metal blades (‘cutting balloon’) may induce less vessel injury, expression of growth factors, and subsequent proliferative response than a conventional PTA balloon. Indeed, in an animal model the cutting balloon produced less intimal proliferation than a standard balloon [19]. Expression of platelet-derived growth factor, which is a powerful smooth-muscle mitogen, was localized to the vicinity of the incisions, whereas it was circular after conventional balloon dilatation [20]. This new device is now being tested in clinical trials for coronary angioplasty. No systematic evaluation has been done in haemodialysis grafts.

**Prevention of stenosis**

If we could, we would of course prevent stenosis. For that we need to understand more about its pathogenesis. The stenotic areas show the characteristic morphology of intimal hyperplasia [21]. Intimal thickening is a feature of the normal healing response of blood vessels at graft anastomoses. However, in many (but not all) cases this normal response progresses over time to a hyperplastic lesion causing luminal narrowing. Endothelial cells suffering from surgical injury and adhered platelets can produce a variety of growth factors, which can drive vascular smooth muscle cell proliferation, extracellular matrix production and angiogenesis. Several haemodynamic factors may be of importance in determining this response. These factors include flow velocity, wall shear stress, and mechanical compliance mismatch. Some experimental studies indicate that intimal thickening preferentially occurs in areas with the highest flow velocities; also differences in elastic properties around the anastomosis (‘compliance mismatch’) may favour intimal growth (references summarized in [22]). In a clinical study, development of stenosis at the venous anastomosis was associated with high flow velocity at the anastomosis soon after implantation and not with compliance mismatch [22].

In contrast, other experimental evidence indicates that intimal hyperplasia preferentially develops in grafts with low or normal flow [23–25], and that it does not occur, or can even regress, when the grafts are subjected to higher than normal flows [26,27].

Several features of the graft, all in some way affecting haemodynamics, have been implicated, at least in experimental settings, to contribute to the development of intimal hyperplasia. End-to-side anastomosis, untapered grafts, and grafts with diameter of 4 mm appeared to offer more favourable conditions for development of intimal hyperplasia than grafts with end-to-end anastomosis, 4–7 mm taper grafts, and grafts with diameter of 6 or 8 mm [28–30]. Also the dialysis procedure itself may be involved. Repeated cannulations induce injury and flow disturbances, which
may enhance the release of biological mediators. Over the last decade the frequency of dialysis treatment has increased, and may further increase if daily home dialysis becomes accepted. No studies have attempted to delineate the relative contribution of these ‘hemo-
dynamic’ factors to intimal hyperplasia development.

Irrespective of the exact mechanical mechanisms underlying intimal hyperplasia, it is now well accepted that many biological mediators are involved. Several pharmacological treatments which affect these biological mediators have been shown to be more or less effective in experimental models of intimal hyperplasia. These therapies include ACE inhibitors, calcium-channel blockers, heparin, inhibitors of platelet aggregation, and specific inhibitors of growth factors [31]. Only a limited number of studies tested some of these strategies systematically in haemodialysis patients. Dipyridamol reduced the risk of the clinical end-point of thrombosis in patients with new PTFE grafts [32]. This beneficial effect was not seen in patients with prior thrombosis. In a recent study, patients receiving a PTFE graft were postoperatively treated with heparin subcutaneously for 4 days or low-molecular-weight dextran intravenously for 16 h. Neither treatment influenced the radiologically evaluated development of stenosis after 3 months [33]. Regression analysis, however, indicated that older patients and patients on a calcium-channel blocker were less likely to develop a stenosis.

Alternative techniques which may be tested in haemodialysis patients include heparin-coated stents, which in a recent study showed a low incidence of restenosis in coronary arteries [34]. An unselective way of growth inhibition can be accomplished by radiotherapy. Studies in an animal model of intimal hyperplasia and preliminary clinical results show virtually complete prevention of the development of intimal hyperplasia by local irradiation [35,36].

**Conclusion**

An AVF, radiocephalic or brachiocephalic, is the primary choice for vascular access in haemodialysis patients, because of the superior patency as compared to bridge grafts. In patients with a bridge graft development of stenoses is the most important, potentially curable, cause for graft failure. Today, early detection and treatment of stenotic areas remain the cornerstone of graft maintenance. In this regard, recently developed methodology for functional graft surveillance is promising. Future studies have to show whether medical treatment is helpful in stenosis prevention.

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