demonstrated a time-dependent fall in proximal tubular sodium transport during insulin infusion in healthy subjects which may represent a counterregulatory mechanism. Moreover, in glucose-clamped dogs, the antinatriuretic effect of insulin is of short duration and, after a decrease in sodium excretion during the first 2–3 days, natriuresis returns to normal suggesting that counterregulatory mechanism(s) must be operative [2]. In order to elucidate by what mechanism(s) insulin-stimulated sodium retention is counteracted we have conducted glucose-clamp studies in healthy subjects. Our studies indicate no contributory counterregulatory role of natriuretic hormones, whereas renal vasodilation may be a mechanism counterregulating the distal antinatriuretic effect of insulin [3]. Indeed, insulin has well-documented vasodilatory actions both in skeletal muscle and the kidney [6]. Recent results have also shown that insulin-resistant humans have impaired vasodilator responses to insulin [6]. A blunted renal vasodilatory action of insulin in insulin resistant states may therefore offset the counterregulatory fall in proximal tubular sodium reabsorption during hyperinsulinaemia and thus predispose to sodium retention [7].

The mechanism(s) by which insulin increases sodium reabsorption are not clear, although a stimulatory effect on renal tubular cation transport systems has been demonstrated [for review, see 5]. It has also been suggested that the antinatriuretic effect of insulin in vivo results from insulin-mediated hypokalaemia [4]. However, others [5] have not confirmed these results and the role of insulin-mediated hypokalaemia needs further experimental clarification. Recent results suggest that the antinatriuretic effect of insulin in vivo are independent of the angiotensin and prostaglandin systems, whereas calcium entry and ADH as a cofactor seem to be important for insulin-stimulated sodium reabsorption [5].

In conclusion, although insulin is a potent antinatriuretic factor, there is today no evidence that chronic insulin infusion cause hypertension in healthy subjects and the precise role of insulin-stimulated sodium reabsorption remains to be determined. It is therefore important to elucidate if factors associated with insulin-resistance per se, such as a blunted vasodilatory response, are necessary for the development of sodium retention during hyperinsulinaemia.

References

How do AV fistulae lose function? The roles of haemodynamics, vascular remodelling, and intimal hyperplasia

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Vascular access continues to be the Achilles heel of haemodialysis in a considerable number of patients. One series from the Brigham and Womens Hospital in Boston reported a 1-year patency rate of Cimino fistulae of 64% and a 2-year patency rate of 50% [1]. Even worse results were reported for PTFE grafts.

What is the mechanism of fistula failure?
Undoubtedly many cases of fistula failure can be explained by (i) thrombosis which may be favoured by haematoma or seroma compressing the shunt, (ii) low flow rates resulting from hypovolaemia or hypotension, and (iii) intrinsically hypercoagulable states, e.g. after surgery, during infection or pancreatitis [2].

Early in the treatment, thrombosis is a major cause of fistula failure. The best way to reduce early thrombosis is to hire a skilled surgeon. Later, the aetiology of thrombosis is different. In the majority of cases
[3,4], late thrombosis of Cimino fistulae and PTFE grafts is related to impaired outflow secondary to a reduction of peripheral flow.

*Are haemodynamic signals involved in graft patency?*

The lumen of arteriovenous fistulae enlarges as a result of persistent increase of blood flow. The opposite, a persistent structural decrease in vessel perimeter and lumen diameter, is induced by a long-term decrease of blood flow. These adaptations are initiated by alterations in vessel-wall shear stress. Shear stress, a tractive force on endothelial cells, is directly proportional to flow velocity and inversely proportional to the cube of the vessel radius [5,6]. The vessel remodels itself to maintain a constant predetermined level of shear stress [7].

**Shear stress—a common denominator of atheromatous plaques, neointima formation, and graft failure?**

In a tube with constant diameter, flow is laminar. At obstacles, for instance at the site of graft anastomosis, turbulence occurs when the Reynold’s number exceeds a critical value. Given the blood viscosity of 0.04 poise and density of 1.0 g/ml, the Reynold’s number is 

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32 \times Q \times V/D, \text{ where } Q \text{ is flow in millilitres per second and } D \text{ is lumen diameter in centimetres. Blood flow remains laminar for a Reynold's number of 2000 or less and becomes turbulent above 2000. In the feeder artery the Reynold’s number is usually in the range of 1700–2000 [8]. Several investigators have documented the correlation between turbulent flow, a fluctuating or low wall shear stress, and atherosclerotic plaque formation [9–11].}
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**What is the role of the endothelium?**

It is accepted that the endothelium senses shear stress [12]. The pathways mediating such haemodynamic stimuli to endothelial cells are unknown, however. The structure of the cytoskeleton of endothelial cells is modulated by flow. This observation illustrates that changes in haemodynamics cause changes of the endothelial cell phenotype [13]. Endothelial cells are vascular transducers that process signals from the environment and induce remodelling of the vessel wall through biological mediators, e.g. growth factors, matrix-degrading proteins such as collagenases and stromelysin [14], and others.

**What is the role of growth factors?**

Since local growth factors are involved in the initial steps of atherosclerotic plaque formation, it is reasonable to look into the growth factor status of the neointimal layer in Cimino fistulae. Given the known role of PDGF in the genesis of atherosclerosis, it was logical that Swedberg et al. advanced the following hypothesis: PDGF is released by repeated microthrombus formation near the puncture site of the AV-shunt, thus leading to a stenosing neointima layer downstream of a PTFE graft [15]. The release of growth factors may occur either from passenger cells or from resident cells. Its effect may be enhanced by a longer ‘dwell’ time of passenger cells. Hofstra et al. recently performed a study showing that a mismatch in elastic properties around graft anastomosis of haemodialysis patients accounts for flow disturbance and subsequently a longer particle dwell time, which causes intimal hyperplasia [16].

Numerous growth-promoting and -inhibiting factors such as PDGF, acidic and basic FGF, TGF β1 and β2, interferon γ, and many others act in a complex interplay to influence vascular remodelling and the reaction to vascular injury [7].

Different hierarchies of growth factor activities have been demonstrated in different pathogenetic contexts. It is therefore not sufficient to demonstrate the activation or blockade of one single growth factor. Interactions between growth factors in the development of neointima formation have not been completely elucidated so far. Nevertheless, the consensus is that neointima formation is a response to injury. What is the primary site of injury? It is the endothelium. However, only lesions to both endothelial and smooth muscle cells, trigger neointima formation [17,18].

**Is there a vicious cycle?**

If low flow causes vessel closure, and if neointimal proliferation causes vessel narrowing after injury, the question arises whether the two features may not be linked. Several years ago we performed a study which addressed this issue. The femoral arteries of dogs were locally injured with a heated laser probe. Localized lesions of the arterial wall were created, including the endothelium and medial smooth muscle cells. We reduced the blood flow at the site of injury by ligating the femoral artery more distally. Under low-flow conditions, neointimal thickening was more pronounced than under normal flow conditions [19]. This is illustrated by Figures 1 and 2. The observed difference was independent of the degree of vascular injury. This point was confirmed by studying less severe balloon injury in the same model. Conversely, Kohler et al. found that an increase in flow decreased neointima formation [20].

We therefore propose that in poorly functioning AV fistulae low flow causes intimal hyperplasia so that a vicious cycle is established; low flow generates obstructive neointimal layers, which in turn further reduce the flow.

**What can be done to prevent intimal hyperplasia?**

It is evident that an early detection of intimal hyperplasia by sonography or assessment of the haemodynamic status of the AV shunt is essential to interrupt the vicious cycle.

To prevent late shunt failure of AV fistulae it may be useful to look beyond nephrology for the analogies that are provided by studies on coronary graft patency.
Fig. 1. Normal dog. Neointima formation in a normal-flow situation. Cross-section of the femoral arteries of a dog 8 weeks after injury with a heated laser probe. Magnification x 75; elastica-van Gieson stain.

Such information is useful for the nephrologist to develop rational intervention strategies. For instance, according to several clinical studies elevated vascular resistance was the most powerful predictor for peripheral and coronary graft failure [21-23].

Perhaps nephrologists can avoid repeating some of the negative experiences that were accumulated by cardiologists. Trials in patients undergoing angioplasty have documented beyond reasonable doubt that neither aspirin nor heparin or coumadine prevent restenosis from intimal hyperplasia [24-26]. Great enthusiasm was generated by animal studies documenting antiproliferative effects of ACE inhibitors. Unfortunately these results were not duplicated in clinical studies on restenosis [27,28]. Vasodilators and calcium antagonists, other logical candidates, were also ineffective in significantly reducing restenosis rates after angioplasty [29-31].

There is some indication that lipid-lowering drugs such as lovastatin or omega-3 fatty acids may have some effect in preventing restenosis, at least according to some clinical trials [32,33]. This was not found in all studies and the mechanism involved is not completely elucidated. On the other hand serum lipids, LDL, and HDL cholesterol levels do not predict the risk of stenosis in prospective trials [34].

Another approach to inhibit restenosis has recently been introduced. Stents injure the vessel wall and cause smooth-muscle cell proliferation. When stents administer low-dose radiation to the vessel wall, however, this proliferative reaction of smooth-muscle cells with subsequent neointima formation is prevented, at least in a rabbit model [35]. Although further studies on the minimal dose requirements and the safety of ionizing radiation are still necessary, this approach may turn out to be clinically useful at least in difficult cases.

Unfortunately there is agreement that safe and effective prevention of intimal hyperplasia continues...
to be a challenge to the nephrologist and to vascular biologists.

References