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Formaldehyde-fixed arterial allograft as a novel vascular access alternative in end-stage renal disease patients

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Liu and co-workers report on a preliminary study with formaldehyde-fixed arterial allografts. In this way they provide a novel alternative for solving the problem of failing to achieve vascular access in hemodialysis patients. Formaldehyde fixation offers an effective way of reducing the antigenicity of heterologous arterial allograft. Preliminary clinical experience shows that technical survival of such preserved arterial allograft appears quite promising. Further studies will help to define the place of this allograft material in vascular access management of ESRD patients.

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After three decades of maintenance renal replacement therapy, suboptimal vascular access is a major cause of morbidity in patients with end-stage renal disease (ESRD).[1] It is the first cause of hospitalization due to dysfunction, thrombosis, or infection. Vascular access management represents a significant economic burden to the health-care system, consuming 15%–20% of the budget allocated to ESRD treatment in the US (Medicare).[2] Despite significant progress, including presurgery vascular mapping,[3–5] microvascular surgery, and early interventional radiology for correcting dysfunction,[6] many ESRD patients experience failure of primary autogenous arteriovenous fistula.[7] Moreover, creation of new fistulae exhausts native veins, and this has led to innovative approaches in using natural and synthetic material in creating vascular access (Figure 1).[8–10]

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Liu and co-workers[11] (this issue) introduce a new vascular access option based on the use of formaldehyde-fixed arterial allografts. Faced both with multiple native arteriovenous fistula failure and with the excessive cost of polytetrafluoroethylene material in China, they hypothesized that arterial allografts collected from young brain-death subjects would provide an interesting vascular graft alternative. On the basis of this hypothesis, the authors launched a study in two parts. The first phase of the study consisted of collecting femoral arteries (about 20 cm in length) in young brain-dead subjects. Briefly, femoral arteries were subsequently fixed and denatured in formaldehyde solution, then washed and stored in preservative solution. Immunogenicity of this fixed material was tested *ex vivo* by means of specific antibodies produced after rabbit immunization, exposed to unfixed donor material. In this preclinical phase, it was consistently shown that formaldehyde-fixed material was non-immunogenic. The second phase of the study was a clinical trial in which 68 fixed and preserved arterial allografts were implanted in 43 hemodialysis patients. Viral safety was monitored in the donors. Implantation was performed by trained vascular surgeons, mostly on the forearm and rarely on the groin. Blood flow achieved in the artery allografts was 696 ± 282 ml/min. The median primary patency was 28 months, and the median secondary patency was 141 months. Use of preserved artery allografts was simple and identical to use of native arteriovenous fistulae. No acute or subacute allograft rejection was noted. Stenosis and thrombosis occurred in 37.3% (25/68) of patients. Pseudoaneurysm was rarely observed in the clinical phase (2.9%; 2/68). Interestingly, intimal hyperplasia with preserved structure of the media layer and smooth muscle cell architecture and no sign of rejection were noted on removed material after thrombosis.

Technical survival of formaldehyde-fixed arterial allografts is not inferior to that of synthetic polytetrafluoroethylene grafts. Primary patency survival was 28 months, a value close to that for polytetrafluoroethylene, and secondary patency survival was 141 months, a value close to that for native arteriovenous fistulae. Accordingly, arterial allograft survival may be considered as a long-term vascular access offering median survival expectancy close to that seen with polytetrafluoroethylene grafts and native fistulae. These data require further prospective studies to be confirmed.

What do we learn from this study?

The femoral artery provides an excellent graft for vascular access in hemodialysis patients, confirming previous study.[12] It is a straight, well-calibrated, and relatively resistant vessel that could be easily handled and sutured by a vascular surgeon. Interestingly, arteries, contrary to veins, have no valves or collateral branches, meaning that they require specific preparation before being implanted. Constant diameter and relatively low compliance of the artery structure as opposed to vein grafts are quite interesting physical characteristics that guarantee relatively high and constant flow (more than 600 ml/min) over time.

Formaldehyde-fixed arterial allografts provide a simple, safe, and effective way of reducing the antigenicity of heterogenous graft material. In that sense, formaldehyde fixation seems to be safer than cryopreservation technique, which does not

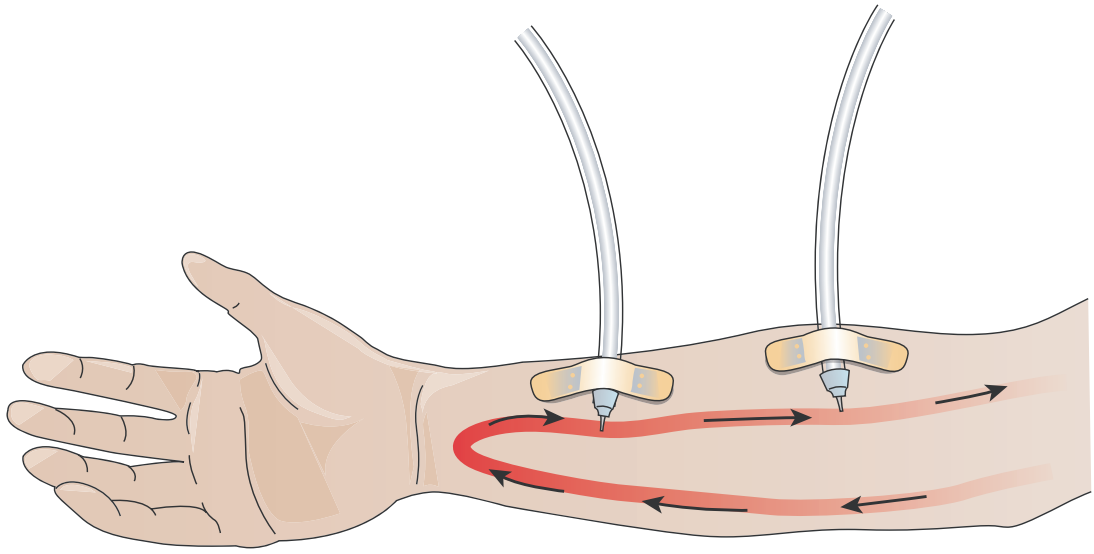

Figure 1 | Vascular access, lifeline of chronic kidney disease patients.

preclude immunization. The fixed arterial allograft did not bind antibodies against unfixed donor arteries. No immunization was observed over time in patients receiving the arterial allograft. In other words, the use of such allograft material in ESRD patients does not increase the risk of alloimmunization, which has implications for future transplantability.

The physiology of formaldehyde-fixed arterial allografts appears to be superior to that of venous material, because it keeps the structure and functionality of the artery. Rigidity and resistance are ensured by the smooth muscle architecture and fibrous capsule of the artery wall structure. Because of the persistence of the endothelium layer on the arterial graft, thrombotic risk seems to be improved. These biological properties need to be explored and documented more carefully.

Preserved arterial allografts clearly offer a relatively cheap vascular access for hemodialysis patients exposed to multiple failures of native arteriovenous fistulae.

What potential problems can be anticipated from implantation of preserved arterial allografts?

Implantation of allograft material of human origin carries a risk of transmitting a disease from the donor.[13] Therefore, it seems mandatory to screen for infectious disease, including bacteria (mycobacteria), viruses (hepatitis B and C viruses, HIV, and slow viruses), fungi, and parasites.[14] Another concern is that of transmitting prion protein to the recipient.[15] Donors must be screened for Creutzfeldt–Jakob disease. Long-term safety is of paramount importance, and longer studies with larger numbers of patients need to be done. Alloimunization against fixed arterial allografts should be detected over time.[16] This specific follow-up is of particular importance in ESRD patients registered on renal-transplant waiting lists.[17] Searching for anti-HLA antibodies should be performed regularly after arterial allograft implantation for patients awaiting kidney transplantation.

Formaldehyde sensitization is another concern in ESRD patients.[18] Many hemodialysis patients exposed to formaldehyde in the past (hemodialyzer reuse, dialysis machine disinfection) were sensitized and immunized against formaldehyde. It has been reported that specific formaldehyde antibodies may react with erythrocytes, inducing chronic hemolysis.[19] Accordingly, washing and very sensible formaldehyde testing should be performed on arterial allografts in order to prevent such risk.

What are the implications of this preliminary study?

Liu and co-workers[11] report on a preliminary study with preserved fixed arterial allografts. In this way they provide a novel alternative for solving the problem of failing to achieve vascular access in hemodialysis patients. Preliminary results show that technical survival of preserved arterial allografts appears quite promising. However, it is necessary to compare these findings with those achieved with native arteriovenous fistulae and already-used grafts in prospective, randomized trials. Further studies will help to define the place of preserved arterial allografts in vascular access management of ESRD patients.

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Basic science meets clinical medicine: identification of a CD2AP-deficient patient

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Recent years have witnessed an explosion of research into the molecular basis of glomerular disease resulting in nephrotic- range urinary protein leak using both human genetics and animal models. Löwik *et al*. describe the first case report of an early-onset nephrotic syndrome presenting in conjunction with a homozygous CD2AP mutation. These data demonstrate the convergence between basic and clinical approaches and their potential to transform our understanding of the pathogenetic mechanisms underlying human glomerular disease.

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The glomerular filtration barrier is a complex structure composed of three layers: a fenestrated endothelium, glomerular basement membrane, and podocytes, modified epithelial cells with foot processes separated by specialized junctions called slit diaphragms. Breakdown of this barrier is thought to be the common feature underlying proteinuric diseases. During the last decade, there has been enormous progress in our understanding of how the filtration barrier works. Much of this work has focused on the unique properties of the podocyte.

Interest in the podocyte began with the finding that the morphology of these cells is universally abnormal in all types of glomerular disease associated with significant proteinuria. Moreover, the detection of mutations in a number of podocyte genes, such as *NPHS1* in Finnish-type congenital nephrotic syndrome and *NPHS2* in familial focal segmental glomerulosclerosis (FSGS), has compounded the role of podocyte dysfunction in nephrotic-range glomerular proteinuria.[1] More recently, mutations of two other genes expressed in podocytes, α-*actinin-4* (*ACTN4*)[2] and *TRPC6*,[3,4] have been detected in human FSGS (Figure 1).

In parallel with positional cloning approaches to identify human genes linked to nephrotic syndrome, mouse knockout and expression studies have led to the identification of other molecules that may be of equal importance in the maintenance of glomerular permselectivity.[5] Some are podocyte specific, such as *NEPH1* and *synaptopodin*, whereas others, such as *CD2AP*, *Nck*, *P-cadherin*, and *FAT1*, are more ubiquitously expressed. An important immediate goal is to determine whether these genes, identified in mice, are relevant to human disease (Figure 1).

Löwik *et al.*[6] (this issue) present a case report in which the evaluation of a male infant for failure to thrive at the age of 10 months led to a diagnosis of an early-onset nephrotic syndrome. As the child had failed to thrive for some time, it is likely that the onset of the nephrotic syndrome occurred much earlier in life. Salient clinical features at presentation were anemia, hypertension, and hypoalbuminemia in the context of nephrotic-range proteinuria. Renal function was normal, which is perhaps discrepant with the other presenting clinical features. Ten glomeruli were obtained on renal biopsy, of which almost half were globally sclerosed despite the normal creatinine. Mesangial proliferation and matrix expansion were observed in the other half, whereas one glomerulus was reported as having a lesion compatible with collapsing FSGS. No immunohistochemistry is reported, although electron microscopy did demonstrate foot process fusion. The patient's renal function deteriorated over the next 2 years, with an episode of acute collapse secondary to sepsis precipitating end-stage renal failure about 2 years after diagnosis. Subsequent renal transplantation has not been complicated by recurrence of disease.

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