In Focus

Arteriovenous fistula as a nephroprotective intervention in advanced CKD: scientific discovery and explanation, and the evaluation of interventions

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The story that angiotensin conversion enzyme inhibitors can be nephroprotective started with a small (just nine patients), uncontrolled study by Yoshio Taguma published in the New England Journal of Medicine (NEJM) in 1985 [1]. This case series merely reported repeated measurements of 24-h proteinuria before and after the use of captopril. Today, an exploratory study of this kind would be triaged in most nephrology journals. The editor of NEJM at that time was Dr Arnold Relman, an editor whose tenure at NEJM lasted 14 years, from 1977 to 1990. Relman was a bold editor. An expert in electrolytes and acid–base problems, over the years he became a vocal antagonist of what he called ‘the new medical–industrial complex’, and he is remembered as an indefectible advocate of ethical issues in scientific inquiry. Looking back at those years, the publication of the Taguma paper was proof of Relman’s vision and boldness. He was of course aware of the major limitations of this study, but on the basis of the potential scientific and public health relevance of Taguma’s observations, he decided to publish this study, which literally opened a new era in modern nephrology.

The arteriovenous fistula in dialysis patients is a double-blessing intervention. On the one hand, it has a lower risk of infection than arteriovenous shunts, indwelling central catheters and arteriovenous grafts. On the other hand, arteriovenous fistulas may trigger pulmonary hypertension, which is per se a risk factor for death and cardiovascular events in haemodialysis patients [2]. Yet, it would be reductive to consider the arteriovenous fistula as a purely haemodynamic burden. As it will be discussed below, emerging evidence suggests that the arteriovenous fistula may have unsuspected cardioprotective effects.

Over the past two decades, two novel concepts have been developed that are of major relevance for the interpretation of the potential therapeutic relevance of the arteriovenous fistula. First, there is the concept of ischaemic pre-conditioning, a phenomenon with powerful, emerging implications for cardiovascular and renal protection. Second, it has been demonstrated that implantation of a femoral arteriovenous communication with a minimally invasive technique can substantially lower arterial pressure in patients with resistant hypertension.

In this issue of NDT, we publish a manuscript suggesting that arteriovenous fistula creation may retard chronic kidney disease (CKD) progression, in a Taguma-like study. This study has obvious methodological weaknesses, frankly recognized by the authors, but it brings into the clinical arena a biological phenomenon that may stimulate clinical research in an area that has until now received insufficient attention within the nephrology community. As remarked by Vandebroucke [3], careful, often isolated, inspired clinical observations make the top rank in the pathway to scientific discovery, while the same observations per se remain at the bottom rank of the ladder of scientific evidence.

The concept of ischaemic pre-conditioning is relatively new, dating back to the early 1990s. In November 1991, Karyn Przyklenk and colleagues presented data, at the 64th Scientific Sessions of the American Heart Association, showing that ‘… brief ischaemia in one vascular bed also protects remote, virgin myocardium from subsequent sustained coronary artery occlusion … (and that) this effect may be mediated by factor(s) activated, produced, or transported throughout the heart during brief ischemia/reperfusion …’. These findings were eventually published in Circulation in 1993 [4]. As of 16 June
2015, this paper has been quoted 833 times, setting the stage for landmark advancements in basic and clinical cardiovascular research. A critical passage for the understanding of this phenomenon was the demonstration that organ protection by remote ischaemic conditioning can be produced by brief periods of ischaemia and reperfusion in the upper arms or in the legs (by inflating and deflating blood pressure cuffs). This culminated in a clinical trial showing that short, repeated periods of arm ischaemia before hospital admission in patients with suspected myocardial infarction increase myocardial salvage [5]. The protective effect of pre-conditioning goes beyond the heart and extends to the liver and the kidney. A recent randomized clinical trial has nicely documented that, in high-risk patients undergoing cardiac surgery, remote ischaemic (pre-) conditioning produces a remarkable reduction in the post-operative risk for acute kidney injury (risk reduction: absolute −15%, relative −28%) and need of dialysis (risk reduction: absolute −10%, relative −63%) [6].

Time-honoured experiments in dogs suggest that, as in brief intermittent periods of remote ischaemia, an arteriovenous fistula may precondition the heart and provide protection from the deleterious effects of ischaemia-reperfusion injury. Indeed, animals with femoral arteriovenous fistulas display better left ventricular function, reduced infarct size and limited ATP depletion after ascending coronary artery occlusion and reperfusion when compared with sham-operated control dogs [7].

In mechanical terms, the arteriovenous fistula adds a low-resistance, high-compliance venous compartment to the central arterial system. In long-term hypertensive patients with established arterial hypertrophy and reduced vessel compliance, the application of an arteriovenous shunt attenuates arterial stiffness and reduces arterial pressure [8]. Implantation of an arteriovenous coupler (with a flow similar to that in haemodialysis patients) produced a marked reduction in average 24-h ambulatory systolic pressure (−15 mmHg), in a recent randomized trial in patients with resistant hypertension [9]. Similarly, in a previous uncontrolled series of patients with advanced CKD, the creation of an arteriovenous fistula reduced both arterial stiffness and blood pressure [10]. Apart from its mechanical action on the arterial system, the arteriovenous fistula has complex cardiovascular effects. The increase in venous return augments pulmonary flow, which in turn may recruit underperfused lung areas and increased arterial oxygen content. This phenomenon may in turn raise the oxygen delivery to peripheral organs. Due to severe vasoconstriction, the kidney is underperfused in patients with resistant hypertension, and the resulting ischaemia may trigger a chemoreflex driving central sympathetic overactivity [11]. Thus, increased oxygen delivery to the kidney may in theory reduce arterial pressure also by mitigating the chemoreflex incited by organ underperfusion [8].

As to the kidney, the acute effect of femoral arteriovenous fistula creation in the anaesthetized dog includes renal vasocostriction and a reduction in the glomerular filtration rate (GFR) and in water and sodium excretion [12]. On the other hand, peripheral fistula compression in Korean War veterans with long-standing traumatic arteriovenous shunts in the leg, the arm or in the neck caused a dramatic increase in sodium excretion but did not modify the GFR, renal blood flow and renal venous pressure [13]. Of note, these renal haemodynamic parameters did not change even after the compression was withheld. Overall, such findings point to important long-term haemodynamic adaptations of the renal circulation abolishing the acute renal vasoconstrictive effect of the peripheral arteriovenous fistula. If superimposed to a renal microcirculatory setting, characterized by efferent vasoconstriction and glomerular hypertension, the typical setting of progressive nephropathies, such an adaption may in theory help reduce glomerular hypertension and preserve residual function. Mitigation of a renal chemoreflex triggered by renal underperfusion (see above) may be a relevant mechanism contributing to the putative protective effect of fistula on CKD progression. The potential beneficial effects of the arteriovenous fistula are graphically summarized in Figure 1. Golper et al. now move the issue into the clinical arena and report pilot observations testing the ‘arteriovenous fistula hypothesis’ in a series of 123 patients, with at least two estimated glomerular filtration rate (eGFR) determinations for 2 years before and up to 2 years after functioning fistula creation [14]. Before the intervention, the rate of GFR loss was 5.9 mL/min/year, which dramatically reduced to 0.5 mL/min/year following the same intervention [15].

![Figure 1: Pathways whereby an arteriovenous fistula may slow renal disease progression in patients with advanced CKD. In ischaemic areas (generated by tissue remodelling due to inflammation and fibrosis and powerful afferent vasoconstriction in hypertension-related nephroangiosclerosis, a most common renal disease worldwide), low oxygen triggers a chemoreflex eliciting a rise in central sympathetic drive that results in vasoconstriction (blue arrows and blue characters). In purely theoretical terms, the arteriovenous fistula may favourably influence the evolution of CKD, both by still unknown chronic adaptations (which may be endothelium dependent [15]) or by increasing oxygen delivery to the kidney. Increased venous return and the resulting increase in pulmonary flow may recruit an underperfused lung and augment arterial oxygen content and oxygen delivery to ischaemic areas in the kidney which in turn may interrupt or attenuate the vasoconstrictive renal chemoreflex (light-red arrows and characters). See also the main text.](image-url)
The several limitations in Golper’s study, although transparently listed almost in full in the discussion, must be further emphasized. First, this study is based on a relatively small series of patients. Second, comparative data in patients with non-functioning fistula—which would have helped data interpretation—were not gathered. Third, the assumption of linearity to data analysis adopted by the authors imposes a mathematical constraint that often does not reflect the non-linear nature of GFR loss in a considerable proportion of CKD patients [16]. Fourth, as renal function declines, reduced muscle mass and volume expansion and the ensuing reduced creatinine generation and haemodilution could artificially change the eGFR trajectory dissociating it from the underlying true progression rate. Fifth, ongoing pharmacotherapy, an obvious determinant of CKD progression, could not be controlled for in Golper’s study. Sixth, the progression rate of CKD after fistula creation dropped spectacularly, from −5.9 to −0.5 mL/min/year, making it hardly believable (a plausibility problem) that the observed effect can only be attributed to arteriovenous fistula creation. In the clinical scenario, the arteriovenous fistula is often proactively put in place in rapidly progressing patients with intercurrent diseases or with pharmacologically induced acceleration of CKD progression, which are reversible phenomena coincident with fistula creation. Such confounding may artifically produce GFR time trends simulating a (false) protective effect of arteriovenous fistula [17].

After this ritual, but nevertheless important, listing of limitations, we are left with a hypothesis that has passed the first very large mesh filter of a low-power observational study. The next step is to test the same hypothesis in existing, very large clinical databases by adopting advanced statistical techniques and by performing all of the sensitivity analyses needed to ponder the credibility of the results of such analyses. Ultimately, we should never forget that there are no shortcuts in the assessment of the credibility of the results of such analyses. Thus, the hypothesis is fascinating, and with major public health implications. Herein, NDT provides a landing field to a face-weak but inspirational paper that in the future might well be regarded as a breakthrough in renal research, much like the Taguma study three decades ago.

CONFLICT OF INTEREST STATEMENT

None declared.