

The Arteriovenous Fistula and Progression of Kidney Disease

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In 1978, Bill Bennett hired me to “do academic dialysis.” As part of the first National Kidney Foundation Dialysis Outcome Quality Initiative Clinical Practice Guideline leadership team, I became more interested in hemodialysis vascular access. I designed and placed “save the vessels” bracelets for our patients to wear protecting vessels. When I considered hemodialysis to be likely within 12 months, I strongly encouraged creation of arteriovenous fistulae (AVFs). I delayed arteriovenous graft (AVG) placement until much closer to the expected hemodialysis initiation date. Over 35 years I noticed that a significant fraction of patients with functioning AVFs seemed to slow the decline in their rate of eGFR. In a simple proof-of-concept retrospective observational study, it appeared that eGFR decline did display a slowing after AVF creation (1). Subsequent better-designed studies corroborated our findings (2–5). Although fraught with methodological problems, one study suggested that even placing a peritoneal dialysis catheter slowed progression (4). This did not make physiologic sense to me. In this issue of *Kidney360*, another study from Montreal dispels the notion that placing of a peritoneal dialysis catheter affects eGFR decline (5).

Sumida *et al.* utilized a Veterans Administration database, which included AVGs and AVFs with over 3000 patients, not limited by AVF maturation, and used central venous catheter recipients as propensity-matched controls (2). AVF and AVG recipients showed eGFR deceleration after surgical creation, independent of maturation, whereas our study only evaluated maturing AVFs. The first Montreal paper precisely defined the cohort, its clinical characteristics, tried to adjust for known confounders, and used maturation for inclusion (3). Attenuation of eGFR decline over time was again noted after AVF creation. At about the same time, Lundström *et al.* (4) were utilizing a Swedish national database and used patients with peritoneal dialysis catheters as comparators trying to equate eGFRs at the time of fistula placement to matched patients with peritoneal dialysis catheters, looking retroactively to when eGFRs were the same. Both the patients with peritoneal dialysis catheters and AVFs showed decreases in eGFR trajectories after the surgeries. These findings raised two important issues, namely that the observations are merely a regression toward the mean and/or that some behavioral change

affected both groups and similarly altered subsequent eGFR declines.

A second study by Annie-Claire Nadeau-Fredette’s Montreal group published in this issue of *Kidney360* looks at AVF recipients and compares their outcomes with peritoneal dialysis catheter recipients (5). Unlike the Swedish study, the “time zero” for the peritoneal dialysis catheter cohort was defined by the eGFR of the propensity-matched recipients with AVF. This strategy provides a better comparison. The AVF cohort had a slower decline in postaccess eGFR and the peritoneal dialysis cohort did not. These findings reinforce my initial concerns about the Swedish study peritoneal dialysis results.

Possible Mechanisms

The study designs of the Veterans Administration and Montreal papers argue against regression toward the mean. To that end, Francesca Tentori and I designed database input parameters for a prospective observational study to be conducted by Chronic Kidney Disease Outcome and Practice Patterns. Another mechanism is that some compliance/adherence or other behavioral changes accompany the access creation and consequently slow progression. I cannot identify what this could be, considering that my patients who agree to timely access creation are already overall highly adherent. I am open-minded as to a behavioral change explanation, but not seeking a basic physiologic explanation misses an opportunity to identify factors that might protect kidney function for all patients with CKD. This is part of the basis for the editorial comments by Locatelli and Zoccali (6) that accompanied our 2015 paper (1).

Locatelli and Zoccali suggested several potential physiologic mechanisms as to how an AVF might affect progression. Increased venous return to the heart through the fistula increases pulmonary blood flow, which may recruit underperfused lung. This would increase arterial oxygenation and oxygen delivery to the kidney. If the kidney is underperfused due to resistant hypertension or a chemoreflex driving central sympathetic overactivity, it might be ameliorated by improved oxygenation. I will return to renal oxygenation below. Whereas the macrovascular effects of AVF creation are well known because they relate to general

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hemodynamics, specific renal effects are not known. The editorialists speculate on this, but center on the argument of arterial stiffness. Arterial stiffness is known to be associated with kidney function decline (7,8) and is reduced after AVF formation (9).

The editorial also proposes that remote ischemic preconditioning (RIPC) might be a possible mechanism for renal protection (6). The origin of the ischemic stimulus may be twofold. First is the surgical procedure itself with the artery clamped for a few minutes while the anastomosis is created. Second, after AVF creation, there may be persistent subclinical distal arm ischemia. Bonventre (10) informs me that in rodent models there can be a protracted time effect of RIPC. However, I am skeptical about the RIPC theory. First, 10 minutes of clamping of the radial artery with normal ulnar arterial flow does not lead to much ischemia, if any. This provocation of ischemia is much less aggressive than that used in human RIPC models. Furthermore, years of subclinical distal arm ischemia are infrequently recognized, may not even be present, and have not been described in RIPC models.

Are endocrine or immunologic factors involved, possibly even secondary to RIPC? Do we consider vascular endothelium as endocrine tissue? Working on his doctoral thesis with Chris McIntyre in Nottingham, United Kingdom, Korsheed *et al.* (11) first suggested this by studying subcutaneous dermal capillaries in the ipsilateral and contralateral forearms of patients with CKD after AVF creation. Patients with functioning AVFs were compared with patients post-AVF-creation whose AVFs were not functional. Both local and remote microcirculatory changes were attributed in part to vascular endothelial-derived vasoactive substances. The vascular shear stress in the post anastomotic vein induces arterIALIZATION and this endothelium may be the site of endocrine activity. Additionally, systemic vascular changes may alter endothelia elsewhere. The net result is vasoactive endothelial-derived substances that may affect renal vasculature. These substances may be the mechanisms of decreased vascular stiffness described above (9) but may also be functioning to recruit renal reserve, as described decades ago by Bosch *et al.* (12). Systemic vascular changes may affect skeletal muscle vascular beds, which can interact with renal function in a positive manner (13).

Locatelli and Zoccali (6) suggested that renal oxygenation may improve because of AVF lung effects. I hypothesize that the endothelial-derived substance(s) mentioned by Korsheed *et al.* (9) may have direct effects on renal vasculature, recruiting renal functional reserve, and that these effects culminate in improved renal oxygenation, slowing renal scarring and progressive loss of GFR. To ascertain if renal oxygenation is immediately affected by an AVF, Rachele Crencenzi, Stuart Sprague, Pottumarthi Prasad, Bhupinder Singh, and I will be looking at blood oxygen level-dependent magnetic resonance imaging (14) of the kidneys, along with biomarkers of renal viability, a few days before and 3 weeks after the creation of an AVF.

Implications

The slowing of renal functional decline after AVF creation appears to be real and the mechanism(s) must be elucidated. The discovery of specific substances that may be associated

with the slowing could be applied in many CKD settings and might delay or obviate hemodialysis. The consequence of that on the quality of life of our patients is immeasurable. Financial implications can be measured. There would be a reduction in the financial burden in all components of late-stage CKD. First, preserved kidney function may slow comorbidities and lower related drug expenditure and hospitalizations. Second would be the delayed or avoided direct costs of hemodialysis treatments, transportation, time away from work, and much more.

Even if the benefits just described are minimal, they help serve as an incentive for timely creation of what most consider the best and safest hemodialysis access. Clinicians understand the difficulty in persuading some patients to agree to timely AVF creation. The possibility that this maneuver might delay hemodialysis may be the persuasive tip-over rationale for the reluctant patient to have an AVF created in a timely manner. If we are not ready to make this argument now, we are quite close to it.

Disclosures

T. Golper is course director for Home Dialysis University; Dialysis Coeditor for *Up To Date*; is on the Medical Advisory Board for NxStage; reports consultancy agreements with Akebia and NxStage; honoraria from Akebia, Home Dialysis University, Mallinkrodt, NxStage, Reata, the Renal Research Institute, and *Up To Date*; and scientific advisor or membership of Akebia, Reata, Mallinkrodt, and NxStage.

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Author Contributions

T. Golper was responsible for project administration, wrote the original draft, and reviewed and edited the manuscript.

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See related article, “Arteriovenous Fistula Creation and Estimated Glomerular Filtration Rate Decline in Advanced CKD: A Matched Cohort Study,” on pages 42–49.