

figure 3, A–C in ref. 5 are clathrin-coated vesicles (CCVs). Indeed, in the discussion we caveat our findings, noting that plasma membrane-bound structures could mimic virus. Similar structures, presumably representing CCVs, are occasionally seen in renal tubular epithelial cells in kidney biopsies from patients without coronavirus disease 2019 (COVID-19).

There are features of the structures we report that are not typical for CCVs. CCVs are not usually seen in array-like clusters, as we have observed in several COVID-19 autopsies. The structures in figure 3 in ref. 5 are uniform in size, and CCVs can show a greater heterogeneity in sizes depending on cargo and number of clathrin triskelions, with diameters of 30–200 nm.<sup>6</sup> There is also some heterogeneity in the reported morphology of SARS-CoV-2, and our observed structures (65- to 91-nm diameter) are closer in size to the 60- to 81-nm diameter initially reported for SARS-CoV-2 grown in Vero cells than the 80- to 140-nm diameter reported by Miller.<sup>7,8</sup> Nonetheless, it is possible that uniform CCVs could accumulate in epithelial cells in unusual clusters due to cytokine storm or perimortem injury.<sup>9</sup>

Since publication, other investigators have detected SARS-CoV-2 RNA in the kidney using *in situ* hybridization, although ultrastructural localization was not performed.<sup>10</sup> To adequately address the question of direct renal infection, a comprehensive and sufficiently powered autopsy case series, using multiple modalities of detection and with adequate non-COVID-19 controls, is needed.

## DISCLOSURES

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See related Letters to the Editor, “Caution in Identifying Coronaviruses by Electron Microscopy,” and “Kidney Involvement in COVID-19: Need for Better Definitions,” on pages 2223–2224 and 2224–2225, respectively.

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## Early Predictors of Arteriovenous Fistula Maturation: Preoperative Arterial Diameter Alone Is Not Enough

Given the lack of high-quality evidence, the use to date of preoperative ultrasound for vascular access planning has not improved the maturation rates of the arteriovenous fistula (AVF).

Recently in *JASN*, Farrington *et al.*<sup>1</sup> in their retrospective analysis involving 300 catheter-dependent patients receiving a new AVF proved a linear association between preoperative vascular diameter and AVF maturation not corresponding to a single threshold value. They also found that the preoperative

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arterial diameter, not venous diameter as generally believed, was the most significant predictor of AVF maturation.

These findings suggest the idea that AVFs created with larger vessels (in particular, larger arterial diameters) might be associated with superior maturation rates.

Such an idea would evidently imply a rise in placement of AVFs preferentially in the upper arm rather than in the forearm.

Although the authors carefully emphasize the possible negative implications of this message, such as limiting future vascular access sites to younger patients on hemodialysis with longer life expectancy and a greater risk of heart failure, they appear to be convinced that it also has important positive implications, such as the greater probability of obtaining a mature and functional AVF and the reduction of dependence on central venous catheters.

All of this is strongly supported by the dramatic evolution of clinical practice over the past decade: in the United States, above all, there has been a steady increase in AVF positioning preferably in the upper arm rather than in the forearm, which represents a substantial departure from the 2006 Kidney Disease Outcomes Quality Initiative vascular access guidelines.<sup>2,3</sup>

On closer inspection, when preoperative vascular mapping is performed, the evaluation of the arterial diameter alone is not enough to establish the optimal site of AVF placement, but it should be routinely implemented by sonographic markers of arterial function (in particular, by arterial ability to vasodilate).<sup>4–6</sup> In fact, arterial diameter is only one of the factors that affect the probability of successful AVF creation and maturation, and it has to be evaluated in conjunction with the functional status of the artery. After surgery, the adequate fistula maturation is associated with dilation of the artery that feeds the AVF, and the artery's ability to increase its caliber (distensibility) can be estimated preoperatively on the basis of variations in the artery Doppler spectrum during functional test, the "reactive hyperemia test."<sup>7</sup> Distensibility test provides an excellent index of the functional status of the artery and therefore, is particularly useful for selecting the artery (radial or brachial) and the surgical site (wrist, forearm, or upper arm) for AVF construction.

The functional quality of the artery is an important determinant of AVF success, and it is not necessarily related to the internal diameter of the vessel as shown, for example, by experience with AVF creation in pediatric patients; if only artery diameter was assessed, probably almost all patients would be precluded from receiving any AVF.

It is likely that the choice of increasing the threshold of minimal arterial diameter for fistula creation (e.g., minimal

arterial diameter  $\geq 4$  mm) might be associated with improved AVF maturation rates and the accompanying benefits of shorter catheter dependence, greater secondary AVF patency, and fewer interventions to maintain long-term patency for hemodialysis; however, if larger minimal arterial diameters were to be adopted as the threshold for AVF creation, AVF achievement might be precluded in patients not meeting such a threshold (even in the brachial artery), or more patients might receive an arteriovenous graft rather than a native fistula.

If such risk is acceptable in patients on hemodialysis with reduced life expectancy (elderly patients and patients with cancer), it is instead totally unacceptable for younger patients because it could limit the number of potential vascular access sites, and of consequence, it may reduce their life expectancy on dialysis. Therefore, we recommend choosing different minimal arterial diameter threshold criteria for fistula placement on the basis of the age of the patient, life expectancy, and functional status of the artery.

In younger patients, we choose lower-minimal arterial diameter criteria (1.5–2 mm for radial artery and 2.5–3 mm for brachial artery) on the condition that the arterial wall shows a good distensibility (presence of arterial response at the reactive hyperemia test); if the artery's distensibility is poor (absence of arterial response at the reactive hyperemia test), we choose higher-minimal arterial diameter criteria ( $>2$  mm for radial artery and  $>3$  mm for brachial artery) for fistula placement (Table 1).

In elderly patients, we choose in the first instance higher-minimal arterial diameter criteria ( $\geq 2$  mm for radial artery and  $\geq 3$  mm for brachial artery) independently of the ability of the artery to vasodilate (Table 1).

In the same way, as it has long been known that the surgeon's training and experience can affect AVF maturation and survival,<sup>8,9</sup> it is possible to choose different minimal arterial diameter threshold criteria on the basis of the "know-how" of the surgeon; in our opinion, it is advisable that only skilled and experienced surgeons operate on smaller arteries (artery diameter  $\leq 2.5$  mm).

Finally, in our opinion, preoperative vascular mapping should be performed by the operating surgeon because in this way, it yields the most useful information. In the transfer of writing information from the sonographers/radiologists to the surgeons, it is probable that some practical information is lost, such as, for example, the distance between the artery and the vein, the course of the vessels (difficult to manually perceive when the vessels are deep), the possible presence of arteriovenous crossings or anatomic relationships with muscular or nervous structures that can make surgical isolation of the artery or vein

**Table 1.** Preoperative vascular mapping: Minimal arterial requirements for fistula placement

Artery	Younger Patients (Long Life Expectancy)		Older Patients (Medium or Short Life Expectancy)
Radial artery	1.5–2.0 mm (if RH+)	$>2.0$ mm (if RH–)	$\geq 2.0$ mm
Brachial artery	2.5–3.0 mm (if RH+)	$>3.0$ mm (if RH–)	$\geq 3.0$ mm

RH+, presence of arterial response at the reactive hyperemia test; RH–, absence of arterial response at the reactive hyperemia test.

difficult, the real depth of the vessels with respect to the skin plane, and the presence/diameter of large collateral veins near the site chosen for the anastomosis. Such information is difficult to deduce from a report, but it is instead easy to acquire if the surgeon himself carries out the preoperative evaluation, and this information can influence the selection of blood vessels (AVF location) and the intervention planning by the surgeon. Therefore, the surgeon who wants to devote himself to the creation of vascular accesses for hemodialysis should acquire specific skills in order to carry out the preoperative ultrasound evaluation firsthand.

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See related Letters to the Editor, “Authors’ Reply,” on pages 2228–2229.

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## Authors’ Reply

In our paper<sup>1</sup> “Early predictors of arteriovenous fistula maturation: A novel perspective on an enduring problem,” we demonstrated a linear relationship between the preoperative arterial diameter and arteriovenous fistula (AVF) maturation. Our finding is novel given that, in much of the previously published literature, the preoperative venous diameter has been deemed the primary determinant of AVF maturation in adult patients with advanced stage kidney disease, and little attention has been paid to the role of the artery in the process of AVF maturation. However, we recognize that successful AVF maturation is influenced by additional factors, including patient comorbidities, surgeon experience, and the quality of the native blood vessels.

Zamboli *et al.*<sup>2</sup> raise two important issues for consideration. The first is the ability of the native artery to dilate and accommodate higher blood flow rates following AVF creation. Measurement of brachial arterial function by flow-mediated dilation or nitroglycerin-mediated dilation has been associated with AVF maturation.<sup>3,4</sup> However, in our experience, vascular function studies are time consuming and highly operator dependent, which may pose significant challenges to their widespread use outside of the research setting.

We also agree with the authors’ second point that having a skilled surgeon who performs his or her own preoperative vascular mapping is ideal. In practice, however, many surgeons may need to rely upon the expertise of their radiology colleagues to assist with access planning. Provided that AVF maturation is a challenging, multifaceted process, developing a collaborative approach using the skills and resources of a comprehensive vascular access team offers a reasonable solution for clinicians seeking to optimize vascular access care for their patients on hemodialysis.<sup>5</sup>

Kidney Disease Outcomes Quality Initiative guidelines on vascular access have recently been updated to reflect the complexities involved in choosing an appropriate vascular access on the basis of the individual needs and wishes of patients, projected life expectancy, social support, and other contributing factors outside of preoperative vessel size or quality.<sup>6</sup> In

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