HEMODIALYSIS ACCESS SURVEILLANCE

FUNDAMENTAL FLAWS IN SCIENTIFIC STUDIES THAT JEOPARDIZE CARE

An interview with Dr. Nikolai Krivitski in response to the ongoing controversy: "Vascular Access Surveillance in Mature Fistulas: Is It Worthwhile?" [NDT (2019)]

A link to a timeline of vascular access surveillance studies is featured at the end of the article.

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Susan Eymann

As Dr. Nikolai Krivitski sits at his desk crunching patient measurements for his latest project to improve ECMO outcomes, I ask him about the ongoing controversy behind hemodialysis access surveillance.

Dr. Nikolai Krivitski

It's interesting. If you look at the overall history of publications on the Krivitski method of indicator dilution for measuring AV access flow, **there are 28 positive original studies** showing the usefulness of the measurement. There are actually **only a few negative original articles**. The really shocking thing is that there are over 20 more "literature reviews and meta-analysis" that repeatedly reference three of these negative studies which all have issues that have not been addressed by the authors. Think about that for a minute: 20+ review articles that are summarizing prior work with fundamental flaws without bringing anything new to light! As a scientist, I'm interested in the actual original clinical studies and their findings, not the reviews of those studies. The independent studies overwhelmingly underscore the value of AV access flow measurements, if the technology is used for its intended purpose.

That is interesting! So these review articles point back to just a few RCTs?

Yes, most of the "controversy" and negative "review or meta-analyses" reference two RCTs that used Transonic as the surveillance method, but which point to intervention as the primary issue, and one original publication by Dr. W.D. Paulson. These three papers were then leveraged for multiple review articles. In my opinion, this is somewhat of a manufactured controversy. By using trigger words like "controversy" in the titles of some of the articles, the concern is kept alive, but the reviews, in fact, do not offer any new scientific data or insights and miss the key errors in the studies."

Tell me more about your statement on using the technology for its intended purpose. What do you mean by that?

Well, the use of the technology is very simple. A hemodialysis access is created to carry enough blood flow to sustain dialysis. The Transonic technology is a way to measure that access flow during dialysis in true mL/min. Its intended purpose is to provide the dialysis care team with a tool to objectively answer access flow-related questions:

1) Is access flow too small to facilitate full dialysis dose delivery?

2) Is access flow so high that it may lead to cardiac failure?

3) Does reported access flow or its trending indicate that the access may be heading for a hemodynamically significant stenosis? Per KDOQI, this follows specific guidelines for flow thresholds and/or for percentage flow decreases over time.

And guess what? The sensitivity of predicting hemodynamically significant stenosis was confirmed as 92 to 100 percent. This is the intended use of surveillance! This is very important because not all stenoses limit flow or require intervention. The measurements are simply factual data that can be relayed to the nephrologist who needs to decide on how to act on the information. The physician should always be involved and should always take the patient's entire clinical status under advisement.

When the goal of a study becomes whether the technology can decrease thrombosis rates or prolong the lifetime of the access or send people to intervention without a nephrologist being involved, it is no longer about the quality or value of access flow measurements for predicting hemodynamically significant stenosis. You then have other important factors coming into play such as:

- were best practice guidelines (KDOQI) being fully applied?
- was the PTA effective?
- has access flow increased significantly?
- what is the delta flow after the patient returns after PTA?

Without a significant increase in access flow after PTA, at least 300-400 mL per minute, all your surveillance is meaningless. This is a known issue. In fact, we developed a technology at the request of Dr. T. Vesely to guide intervention with flow measurement, as we wanted to help radiologists achieve good outcomes. This technology is now in use at many leading U.S. universities.

Can you fill us in on the issues you found in these studies?

I examined those studies in great detail for accuracy and even communicated with the authors to get clarification when their papers suggested serious flaws in the science. The thing that disturbs me the most is when basic scientific principles are disregarded, and then misunderstandings and conclusions are drawn that don't follow from the data. These erroneous conclusions will ultimately impact patient care.

Three studies are referenced repeatedly in meta-analyses and reviews about the value of vascular access surveillance. They include either a wrong basic theoretical assumption, or they do not follow KDOQI guidelines and/or indicate failed angioplasty.

The first is Moist *et al.*, **"Regular Monitoring of Access Flow Compared with Monitoring of Venous Pressure Fails to Improve Graft Survival"** [J Am Soc Nephrol, 2003]. For this study, our software engineers customized the software so that access blood flow measurements could not be read by the nurses, thus making the study a double-blind prospective randomized controlled trial. It included 112 patients over two years.

The patients were divided into two groups: In the first group, patients were sent for angiography as a result of clinical observations plus increased dynamic venous pressure. In the second "flow" group, patients were sent for angiography due to clinical observations and increased dynamic venous pressure and Transonic flow (with static and dynamic thresholds analogous to KDOQI). This was where the study became immediately flawed. In the "flow" group, patients were sent for intervention, not only due to flow, but also due to increased dynamic venous pressure. Venous pressure is known to send patients with good flows for intervention, and there's a study that clearly outlines this: **"Venous Pressure Ratio Does Not Correlate with Access Blood Flow"** (Spergel LM *et al*, Kid Intíl 2004; 66(4): 1512-1516.) As Dr. Spergel's study shows, patients with the best access flows have the largest venous pressures. This study by Dr. L.M. Moist sent patients with excellent blood flow for angiogram/PTA because of high venous pressure. This increased unnecessary interventions and effectively delegitimized the performance of the flow surveillance group, and consequently, the entire study.

Did any of these 23 review/meta-analysis publications address this issue?

No, they did not! The second, and even most important thing to understand about the Moist study at the outset is that its very title "Regular Monitoring of Access Flow…Fails to Improve Graft Survival" is inconsistent with the authors' stated conclusion in the paper itself which was:

> "The observation that there is no significant difference in thrombosis rate or graft patency between groups, ***in spite of an improvement in detection of graft stenosis, calls into question not the monitoring technique but the success of the PTA intervention"***

When Dr. Moist first presented this study at the ASN meeting, I asked her if she had looked into the results of intervention and she promised to me that she would. To my understanding, the PTA interventions were the failure in this study, not the access flow surveillance. The interventions not only failed, there were more of them as they also used venous pressure to send patients to PTA in the flow group despite KDOQI guidelines. There are multiple studies which were addressed in a publication (Krivitski N, **"Why vascular access trials on flow surveillance failed."** J Vasc Access. 2014;15 Suppl 7:S15-9) that show that upon the patients' return to the hemodialysis unit, more than half of their flows remained below the threshold that they had been sent to PTA to fix. [Linden *et al*, **"Short- and Long-Term Functional Effects of PTA in Hemodialysis Vascular Access"** J Am Soc, Nephrol, 2002 , 13 (3) 715-720.] Despite this, many reviews or meta-analyses that examine this publication state again and again "failed flow surveillance," rather than "failed PTA." **This slanted summary thus becomes an invitation to the reader and reviewer to kill the messenger (surveillance) rather than act on the message (institute better means to control PTA and correct onset of stenosis).**

There was another paper that you also submitted a response via a Letter to the Editor about: Paulson's "Accuracy of Decrease in Blood Flow in Predicting Hemodialysis Graft Thrombosis." [Am J Kidney Dis. 2000] Can you speak to this?

This was an interesting study, and chronologically one of the first with an unusual back story. Dr. Paulson has had a long-standing position that Transonic surveillance is unneeded and has published extensively to support his opinion. He also repeatedly references his own publications to support his position. This study was well designed (83 synthetic grafts only) and had a very thoughtful protocol which, in my opinion, presents a very strong case for flow surveillance of the access. The idea was simple: Just measure monthly blood flow, do nothing and wait to see if the access thromboses or not. In order to evaluate the success of access blood flow to predict thrombosis, Dr. Paulson postulated that clinically useful technology should have a sensitivity of 80 percent or better and false positive rate of 20 percent or less to predict thrombosis. After data was collected, Dr. Paulson examined the flow data to see if there was any prediction of thrombus at various flow thresholds and/or flow change with time that met his criteria. The paper presents some raw data and multiple tables. This was definitely a unique study to evaluate the predictive power of different static thresholds (<600, <900; <1200; <1800 mL/min) and dynamic thresholds like flow decrease (≥10%; ≥20%; ≥50%;) and their combination. Dr. Paulson found that the best predictive combination from his data was:

"Qa less than 600 mL/min or ΔQa of 20% or greater with a sensitivity of 77% with an FPR of 23%"

However, these findings did not reach Dr. Paulson's self-devised 80 percent and 20 percent criteria for useful clinical technology, so his conclusion was negative. A lengthy discussion followed about why access flow failed to reach his criteria but unfortunately, Dr. Paulson did not explain how he arrived at his 80/20 percent criteria. There are text books that teach how to scientifically define sensitivity and FPR rates for such studies, so in our paper, **"Access Flow Measurement as a Predictor of Hemodialysis Graft Thrombosis: Making Clinical Decisions,"** (N. Krivitski, S. Gantela (Seminars in Dialysis 2001; 14(3) 181-185), I applied the universally accepted statistical approach, based on prevalence of disease and cost benefit analysis, to Paulson's study.

Access Flow Measurement as a Predictor of Hemodialysis Graft Thrombosis: Making Clinical Decisions

by N. Krivitski, S. Gantela
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> Quote from Sackett DL, Haynes RB, Tugwell P: Clinical Epidemiology: A Basic Science for Clinical Medicine. Boston: Little Brown, 1985, 19:
> ***"Clinicians should take the sensitivity and specificity of a diagnostic test into account when a test is selected. A sensitive test ... should be chosen when there is an important penalty for missing a disease ... Highly specific tests are particularly needed when false-positive results can harm the patient physically, emotionally, or financially."***
>
> Quote from Hulley SB, Cummings SR: [2] Designing Clinical Research. Philadelphia: Williams & Wilkins, 1988]:
> ***"The value of diagnostic test depends not only its sensitivity and specificity but also on the prevalence of disease…."***

We applied the scientific criteria for graft thrombosis events, considering prevalence of disease and cost benefit analyses (Bayes theorem). We then analyzed the available data and Dr. Paulson's results and concluded that the actual value 77/23 percent, were well above the scientific criteria for grafts. **Our conclusion was that Dr. Paulson's paper actually proved flow as a good predictor of graft thrombosis.**

After this data was published, Dr. Paulson didn't dispute the claim or justify his 80/20 criteria, but announced: **"In reviewing our data, we have discovered that the sensitivity we reported was actually the specificity (I - FPR), and the true sensitivity was 59%" [Semin Dial. 2001 Nov-Dec;14(6):459-60,]**

So the sensitivity for this one set of data was no longer 77 percent as originally reported, but now changed to 59 percent. In my letter to the editor [Semin Dial. 2001 Nov-Dec;14(6):460-61] I wrote that my statisticians could not support this new value of 59 percent based on the original data presented in the article because a change in one set of data points would affect many other data points and invalidate the tables. Even with that, other data reported in Table 2: Accuracy of Qa or ΔQa in Predicting Thrombosis Within One Month, still accurately predicted thrombosis. For example, Paulson listed a delta QA drop of more than 10 percent as providing a sensitivity of 76 percent and an FPR of 25 percent!

After this, Dr. Paulson continued to publish more negative reviews based on his original article but which never addressed the changes in data and tables. I would ask the authors of these 20+ review/meta-analysis publications to review the study concerns identified here and the statistical analysis methods chosen for the 80/20 percent criteria.

Ok, so that's two papers – you said earlier that there was one more RCT?

The third study that claims surveillance failure is, **"A randomized controlled trial of blood flow and stenosis surveillance of hemodialysis grafts"** by Dr. S.J. Ram, Dr. Work and again, Dr. Paulson. The study was a small RCT of 101 subjects: 34 in a control group, 32 in flow monitoring group and 35 in a "stenosis" group. The authors said that the rationale behind flow measurement in dialysis access depends on two assumptions: one that monthly flow measurements accurately predict thrombosis and the other that timely intervention reduces thrombosis and prolongs graft life. As to the first assumption, the KDOQI guidelines call for measurements below a certain value or a drop over 25 percent over four months to a value below 1 L/min. During the study, KDOQI guidelines were not followed and patients were only screened for low flows!

The authors also stated:
"Qa is an inaccurate predictor of thrombosis mainly because wide hemodynamic variation is present throughout dialysis, and this impairs the reproducibility of Qa measurement."

And, they again pointed back to their own studies. However, a study by Dr. M. Agharazii back in 2000: **"Variation of intra-access flow early and late into hemodialysis"** found: "We conclude that variation in Qac during HD is relatively small, especially when values are corrected for MAP. Therefore, according to our results, Qac measures by using the ultrasound dilution method made at any time during HD should be reliable for most patients."

Their second assumption was, "timely intervention reduces thrombosis and prolongs graft life." Yes, but where is the data on intervention? Where is the value of delta flow? Is this again a situation with a failed intervention? Flow surveillance with ultrasound dilution is intended to identify patients with hemodynamically significant stenosis, which it again did in this case. Prolonging access life however, depends on a successful intervention, as was clearly found in the study by Murray BM *et al*. **"Access flow after angioplasty predicts subsequent arteriovenous graft survival"** [J Vasc Interv Radiol. 2006 Feb;17(2 Pt 1):303-8.] Again, in the discussion, no limitations of the study were discussed, but only the problems with access flow.

Did you communicate with either of the authors about this?

Certainly I did, both in person and when I couldn't get an answer, in a comment to the journal [Am J Kidney Dis. 2001]. Their response was to not answer any of my actual questions on the science, but to say (Dr. Paulson) that, because I worked with Transonic, my criticisms were 'not balanced' which I don't accept. As a scientist, I applied the same unbiased scientific concepts to my work as to others.

At the end of the day, Transonic surveillance is simply a tool that has been developed at the request of clinicians who wanted hard measurement data to support their subjective clinical assessments and to guide patient care. Transonic collaborated with Dr. Thomas Depner and Dr. Jeffry Sands, leading dialysis care innovators, in developing the technology. Supported by NIH grants, its accuracy was extensively and independently validated, including against MRI in humans. The reproducibility of access flow during a single session and from day to day was also clinically confirmed in multiple studies.

So what's your takeaway here for those in the dialysis community that are looking at the KDOQI guidelines?

I think it's important to look at the original surveillance studies in great detail and in the context of its intended use. I'm concerned that people rely on meta-analysis to inform themselves rather than the original studies on Transonic surveillance. I'm also concerned that Transonic access surveillance, the gold standard, gets grouped with other less accurate methods of surveillance such as venous pressure. Also, a real risk in our USA cost sensitive for-profit dialysis system is that dialysis clinics may not provide the nephrologist with the key diagnostic tools needed if it impacts their bottom line. De-escalating surveillance leaves patients at risk – the option then becomes a subjective manual exam, which depends on the training of the staff, and which is not a quantitative mLs per minute measurement. This is the 21st century. Would you want a clinician identifying septic shock by putting their hand on your head to take your temperature? A 2017 Boston Children's Hospital report **"Arteriovenous Access Monitoring with Ultrasound Dilution in a Pediatric Hemodialysis Unit"** showed a 3.9 times decrease in the rate of thrombosis after initiating Transonic surveillance for their pediatric patients! The 2017 Spanish RCT with 207 patients by Dr. Inés Aragoncillo: **"Adding access blood flow surveillance reduces thrombosis and improves arteriovenous fistula patency"** also supports the efficacy and cost savings of implementing Transonic surveillance! If you kill the requirement to perform surveillance, what is left for these kids and all other patients? I think all ESRD patients deserve the best care informed by the most factual and accurate data possible.

Nikolai Krivitski holds a Ph.D. in biomedical engineering, and Doctorate of Science in Biology, He has authored 52 publications in peer review journals, many of which are most referenced in the field; holds over 30 patents and was the PI in 16 NIH SBIR grants. He has developed new technologies in the fields of microsurgery, hemodialysis, critical care and interventional radiology that are used in tens of thousands of patients annually around the world. A frequent presenter, Dr. Krivitski has been an invited speaker at 46 conferences in 20 countries.

KDOQI Guidelines Review

What You Need to Know About Vascular Access Surveillance

Read the Studies

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