Vascular Access Surveillance: Case Study of a False Paradigm

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ABSTRACT

The hemodialysis vascular access surveillance controversy provides a case study of how enthusiasm for a new test or treatment can lead to adoption of a false paradigm. Paradigms are the beliefs and assumptions shared by those in a field of knowledge, and are commonly included in clinical practice guidelines. The guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommend that arteriovenous vascular accesses undergo routine surveillance for detection and correction of stenosis. This recommendation is based on the paradigm that surveillance of access blood flow or dialysis venous pressure combined with correction of stenosis improves access outcomes. However, the quality of evidence that supports this paradigm has been widely criticized. We tested the validity of the surveillance paradigm by applying World Health Organization (WHO) criteria for evaluating screening tests to a literature review of published vascular access studies. These criteria include four components: undesired condition, screening test, intervention, and desired outcome. The WHO criteria show that surveillance as currently practiced fails all four components and provides little or no significant benefit, suggesting that surveillance is a false paradigm.

Once a paradigm is established, however, challenges to its validity are usually resisted even as new evidence indicates the paradigm is not valid. Thus, it is paramount to apply rigorous criteria when developing guidelines. Regulators may help promote needed changes in paradigms when cost and safety considerations coincide.

Paradigms and the Dysfunction Hypothesis

The guideline era has formalized the establishment of paradigms in the practice of medicine. Paradigms are the beliefs and assumptions shared by those in a field of knowledge (1). Once a paradigm is established, challenges to its validity are usually resisted even as new evidence accumulates indicating that the paradigm is not valid. Data that contradict or refute the established paradigm are often rejected or ignored, and the paradigm may influence interpretation of new data and even influence what is publishable. Consequently, publication bias may persist until enough evidence and pressure are applied that the old paradigm is finally replaced by the new.

Paradigms are often incorporated into clinical practice guidelines and may even become government mandates. Or, conversely, new guidelines may become the new paradigms. Thus, it is paramount to apply rigorous criteria when developing guidelines. Otherwise, the guidelines may not improve patient outcomes and could even be harmful.

The hemodialysis vascular access surveillance controversy provides a useful case study of how acceptance of less rigorous criteria can lead to establishment of costly and ineffective guidelines – a false paradigm (2). However, the controversy also illustrates how to implement a more rigorous and successful approach.

The vascular access surveillance controversy begins with the premise that stenosis-induced thrombosis is the most important cause of vascular access failure (3). The synthetic graft usually develops stenosis at the venous anastomosis or downstream vein. The native arteriovenous fistula also develops stenosis, but to a lesser degree, usually at the arteriovenous anastomosis or downstream vein (4).

Access surveillance is based on the “dysfunction hypothesis” (3), which states that stenosis causes measurable access dysfunction, and this dysfunction reliably precedes and accurately predicts thrombosis. More specifically, the hypothesis indicates that stenosis can be accurately diagnosed before thrombosis by screening for reduced access blood flow (Qa) or increased dialysis venous pressure (VP).
Qa is measured by several methods, such as ultrasound dilution (the gold standard), ionic conductance, and duplex ultrasound (4). VP is measured by a transducer in the venous portion of the dialysis circuit that returns dialyzed blood to the patient (4). As stenosis progresses, intra-access pressure increases upstream to the stenosis, and this “venous pressure” is transmitted through the dialysis needle to the transducer. Static VP measurements, which are measured with the dialysis blood pump turned off, are the preferred method of detecting increased intra-access pressure. Methods that estimate static VP from VP measured with the blood pump running (derived static VP) are also acceptable. VP is adjusted for mean arterial pressure (VP/MAP) because an increase in MAP causes VP to increase.

Thus, Qa and VP/MAP are surrogates for stenosis. It is implicit in the dysfunction hypothesis that there is enough lead time to allow for intervention referral and correction of stenosis before thrombosis, and that intervention successfully treats stenosis. Upon referral, an angiogram is usually performed to confirm the presence of significant stenosis (generally >50%), which is usually corrected by balloon angioplasty. Prevention of thrombosis is beneficial as it avoids unscheduled intervention procedures that may be accompanied by central venous dialysis catheters, hospitalizations, and increased costs of care. It has also been widely assumed that preemptive correction increases access survival.

Access Surveillance Guidelines

Years ago, two paradigm-changing nonrandomized studies (5,6) reported success in preventing access thrombosis and failure. They reported that VP measurements, when combined with preemptive angioplasty, yield large reductions in thrombosis rates and replacement of accesses. Further nonrandomized studies of VP and Qa surveillance supported these findings (4,7).

These reports led the vascular access guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) (4,7) to recommend that grafts and fistulae undergo routine surveillance for detection and correction of stenosis. In Qa surveillance, the guidelines recommend intervention referral when graft Qa is <600 ml/minute, or Qa has decreased by >25% and falls below 1,000 ml/minute; fistula referral is recommended when Qa is <400–500 ml/minute. Grafts and fistulae are also referred if static VP/MAP has increased to >0.50 or derived static VP/MAP >0.55. The guidelines emphasize that trend analysis, rather than single measurements, should guide referral decisions.

NKF-KDOQI (4,7) applied an evidence-based approach to developing the guidelines. In retrospect, however, the supporting studies lacked evidence that meets established quality standards, and this has led to a prolonged debate concerning the soundness of the guidelines (2). As indicated by the dashed arrow in Fig. 1, the need for randomized controlled trials (RCTs) was not considered essential, and studies that used historical or nonconcurrent control groups were considered acceptable evidence.

A comparison of the results of nonrandomized studies versus RCTs shows why RCTs are needed to limit bias and confounding. Allon reviewed six nonrandomized studies of graft thrombosis that evaluated clinical monitoring (e.g. physical exam) or surveillance by various methods (8). These studies evaluated a historical control period followed by a period in which grafts were referred for preemptive angioplasty if monitoring or surveillance measurements met referral criteria. All six studies reported substantial reductions in thrombosis rates. In contrast, five RCTs found no reduction in thrombosis.

Nonrandomized studies are generally not suitable for establishing guidelines for a number of reasons, especially their bias toward finding a treatment benefit (9–11). For example, historical control groups may not be comparable to current treatment groups that may benefit from recent improvements in care. Also, more attention may be given to treatment groups when researchers are aware that they are studying new or potentially better treatments.

WHO Criteria

The World Health Organization (12) has recommended rigorous criteria for evaluating screening tests that can be applied to test validity of the surveillance paradigm. The WHO approach considers four basic components (Fig. 2): undesired condition, screening test, intervention, and desired outcomes. Analysis of these components helps to explain why surveillance has not been as successful as anticipated (2).

The Undesired Condition

The undesired condition is stenosis-induced access thrombosis. WHO criteria require that the epidemiology and natural history of the condition, from latent to overt disease (i.e. stenosis leading to thrombosis), are
understood. There should be a disease marker that accurately predicts thrombosis, and a latent or early symptomatic stage (e.g. reduced Qa) that allows time for an intervention to be applied that improves outcomes (reduced thrombosis). However, it appears that we do not have a sound understanding of disease progression from latent to overt disease or a reliable early symptomatic stage. For example, all thrombosis is not caused by stenosis, and all stenosis does not cause thrombosis (3).

This is illustrated by mathematical models, which have improved understanding of the influence of stenosis on access hemodynamics (13–15). The models show that the relation between Qa and stenosis is sigmoidal: as stenosis progresses, Qa initially remains unchanged, but then rapidly decreases as critical stenosis is reached (Fig. 3). The inflow artery is usually narrower than the outflow vein, and the narrower the artery, the greater the delay in the Qa decrease. VP/MAP behaves similarly in that the increase is delayed (14,15). Then, assuming that stenosis progresses at a constant rate, Qa or VP/MAP may change so rapidly at critical stenosis that standard monthly Qa or twice monthly VP measurements may not detect the change before thrombosis. Moreover, the influence of arterial diameter yields the surprising result that the VP/MAP referral threshold of >0.50 does not indicate any particular level of stenosis (15). Rather, the threshold is reached at stenoses ranging from 38 to 73%.

Another issue affecting surveillance is the large hemodynamic variation that occurs during dialysis when measurements are taken (16). Qa is determined by MAP, central venous pressure, and vascular resistance of the access circuit (13). All three variables rapidly change during dialysis and vary from session to session, making Qa an unreliable predictor of stenosis.
These factors highlight our lack of knowledge of the undesired condition (stenosis-induced thrombosis) and impair our ability to predict its occurrence during the latent or early symptomatic stage.

The Screening Test

The screening test must be simple, unbiased, and validated with adequate reproducibility in detecting the marker (stenosis) that causes the undesired condition (thrombosis). There should be suitable well-defined thresholds for intervention referral that confirm the presence of significant stenosis.

The above discussion of access hemodynamics, however, predicts that Qa and VP/MAP should lack accuracy in predicting thrombosis. This has been confirmed by analysis of predictive accuracy with receiver operating characteristic (ROC) curves (17–21). For example, Qa and decrease in Qa (ΔQa) had a sensitivity of 80% at false-positive rates of 50–60% (21). Moreover, in the majority of thromboses, no ΔQa measurement was available because thrombosis occurred before the second measurement could be taken.

The Intervention

Preemptive intervention, usually angioplasty with or without stenting, should yield better outcomes than late or no treatment.

The goal of surveillance is to identify and correct stenosis-induced access dysfunction while avoiding harm. However, as indicated above, a high sensitivity in predicting thrombosis is accompanied by a high false-positive rate that probably yields many unnecessary intervention procedures (21). Furthermore, it is now recognized that angioplasty of a relatively stable stenosis may be harmful. Angioplasty causes an increase in cellular proliferation that is associated with neointimal hyperplasia (22). Consequently, angioplasty has been used as a tool to induce neointimal hyperplasia in studies of stenosis pathophysiology (23). Thus, angioplasty provides a temporary benefit that may accelerate progression of neointimal hyperplasia. We speculate that surveillance has not prolonged access survival in RCTs because false-positive referrals have yielded unnecessary and harmful intervention procedures that impair access survival.

The Desired Outcome

There should be evidence from RCTs that surveillance is effective in reducing morbidity and in yielding desired outcomes (reduced thrombosis and prolonged access survival).

A systematic review and meta-analysis of RCTs evaluated the ability of surveillance to prevent thrombosis (24). Qa surveillance of fistulae was associated with reduced risk of thrombosis, but no significant improvement in fistula survival. The reduction in thrombosis awaits confirmation because it is based upon only four studies of 360 subjects. Moreover, there was no evidence that graft surveillance by Qa or duplex ultrasound reduced thrombosis or improved graft survival.

Some have argued that the RCTs had inadequate power, and would have shown a benefit if they had included more patients (25). However, given the failure of surveillance to meet the first three WHO criteria (12) (Fig. 2), it seems unlikely that larger studies would have yielded better outcomes. Importantly, the paradigm-changing surveillance studies (5,6) were also underpowered, but nevertheless found large improvements in outcomes. In retrospect, this suggests that these studies were biased.

In summary, surveillance fails all four basic components of the WHO criteria (Fig. 2) (12). There is little evidence that surveillance as currently widely practiced (monthly Qa measurements or twice monthly VP/MAP measurements) provides a significant benefit. Surveillance might improve outcomes if measurements were taken more frequently. More frequent measurements would make it easier to detect a trend among highly variable Qa or VP/MAP measurements, and make it easier to detect rapid stenosis-induced changes before thrombosis. However, Qa measurements take significant time; thus, it is unlikely that measurements can be more frequent than the standard monthly protocol. In contrast, online methods are available that allow recording of derived static VP measurements at every dialysis session (26).

Impact of False Paradigms

The medical community has a long history of enthusiastically adopting new tests and treatments without adequate supporting evidence. This reflects the optimistic “can do” philosophy of care providers, who often assume that intervention in a disease process is better than observation, even when there is little or no evidence to support such an activist approach. The surveillance controversy provides a good case study of this philosophy, which has led the nephrology community to adopt a false paradigm that continues to be widely supported both in practice and in guidelines despite accumulating evidence to the contrary.

We should recall that much of clinical practice is not based upon “settled science”, but rather is subject to change depending on results of ongoing research. Application of highly specific guidelines, such as testing and treatment with specific threshold targets, requires recognition that they are, indeed, merely guidelines, and are subject to change as new evidence develops. However, this caution is frequently forgotten, and guidelines are often elevated to a level of dogma that is inappropriate to the original aims or quality of data used to derive the guidelines (27). Also, in this era of increased government regulation, highly specific guidelines may become government mandates that are particularly slow to change (28,29). Moreover, government regulators are tempted to introduce new mandates with targets that have not been validated by RCTs (30).

For example, the Centers for Medicare and Medicaid Services (the U.S. Government sponsored insurance
payor for dialysis) now requires vascular access surveillance (31). This mandate has been criticized for impairing quality improvement, which is the opposite of what is intended (22,29). Unfortunately, the mandate has made it impossible to do the RCTs that are needed to determine the proper role of surveillance. Dialysis units are unwilling to participate in clinical trials if patients are randomized into a control group that excludes surveillance measurements (25).

It follows that adaptability in responding to new evidence is paramount. Regulators may help promote needed changes in paradigms when cost and safety considerations coincide. A recent example is the reduction in the target hemoglobin level in treating anemia in dialysis patients. A target of at least 11.0 g/dl was once considered optimal (32), and it was widely accepted that ability to meet the target was an indicator of adequate care. However, more recent evidence indicates that adverse outcomes are increased when levels are somewhere above 11.5 g/dl, although the threshold where risk begins to increase is not known (33,34). Thus, a target that was once considered optimal may be associated with unacceptable risks. In the USA, Medicare has recently bundled payment for erythropoiesis-stimulating agent (ESA) treatment of anemia with other dialysis services (35). Dialysis units previously received higher payments if they prescribed higher ESA doses; in contrast, the bundled payment is the same regardless of the dose. Bundling of payments has therefore provided a strong economic incentive for dialysis units to limit ESA dose, and recent data confirm a trend of reduced dose of ESAs accompanied by a reduction in the percentage of patients with hemoglobin levels > 12 g/dl (36).

The prolonged access surveillance controversy illustrates how adaptability may be the exception rather than the rule when there are no such incentives. Surveillance programs promote an increase in referrals to interventionists, who benefit from Medicare’s current fee for service payment for procedures. Thus, unlike ESA treatment of anemia, Medicare’s method of paying for intervention procedures does not help promote the needed abandonment of the surveillance paradigm. Moreover, one wonders whether continued application of the surveillance paradigm actually promotes neointimal hyperplasia by encouraging unnecessary angioplasty procedures, and thereby does more harm than good.

Conclusion

The goal of access surveillance is to accurately identify accesses that are likely to benefit from preemptive intervention, while avoiding intervention in accesses that are unlikely to benefit. However, this goal remains elusive after more than 20 years of publications in this field. Until successful methods of surveillance are demonstrated, the best approach for guidelines may be to recommend an access maintenance program without specifically recommending surveillance measurements with preemptive intervention.

References