Mathematical Model Demonstrates Influence of Luminal Diameters on Venous Pressure Surveillance

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Background: The reliability of dialysis venous pressure (VP) in detecting stenosis is controversial. A mathematical model may help to resolve the controversy by providing insight into the factors that influence static VP.

Design, setting, participants, and measurements: This study used inflow artery and outflow vein luminal diameters from duplex ultrasonound studies of 94 patients. These diameters were applied to a mathematical model, and how they affect the relation among VP, mean arterial pressure (MAP), blood flow, and stenosis was determined. Whether VP/MAP is a valid adjustment for the influence of MAP on VP, and whether the standard VP/MAP referral threshold of 0.50 is valid, were also determined.

Results: It was found that there is an approximate one-to-one relation between MAP and VP, so VP/MAP is a valid adjustment. Also, the 0.50 threshold successfully identifies most grafts with stenosis of 65% or more. However, the ratio of artery/vein diameters varied widely between patients, and the ratio independently influences VP/MAP. When the inflow artery is relatively narrow, the VP/MAP increase is delayed followed by a more rapid increase as critical stenosis is reached.

Conclusions: VP/MAP is a valid adjustment for the influence of MAP on VP, and the standard VP/MAP threshold of 0.50 warns of the transition to critical stenosis. However, relatively narrow arteries cause a delay followed by a rapid increase in VP/MAP that may not be detected before thrombosis unless measurements are very frequent. Clinical trials that emphasize trend analysis with frequent measurements are needed to evaluate the efficacy of VP surveillance.


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recommendation is similar to proposals that Q be adjusted for MAP (Q/MAP) or systolic blood pressure (15-17). However, we recently used the model to show that Q increases by only 50% when MAP is doubled, so Q/MAP is an overcorrection (18). Therefore, it is important to determine whether the VP/MAP adjustment is valid.

The effectiveness of VP surveillance is part of the ongoing controversy. The K/DOQI guidelines (11) recommend referral when static VP/MAP is >0.50 or derived static VP/MAP is >0.55. The guidelines emphasize that trends are more important than a single measurement. However, some have found that VP surveillance predicts stenosis or thrombosis (19,20), and some have not (21). Also, a recent study (22) found no correlation between Q and VP/MAP. It suggested that artery and vein diameters may vary between patients and thereby affect VP by altering resistances in the graft circuit. To our knowledge, however, no one has systematically analyzed the relation among VP, diameters, and stenosis.

In this study, we addressed the surveillance controversy by using the model to analyze the relation among static VP, MAP, luminal diameters, Q, and stenosis. We determined whether VP/MAP is an accurate adjustment for changes in MAP and whether a single VP/MAP threshold can warn of critical stenosis or low Q. The model improves understanding of the limitations of VP surveillance and indicates how to apply the method optimally.

Materials and Methods

Model of Graft Circuit

We previously described the assumptions of the mathematical model, the in vitro apparatus, and the clinical data used to validate the model (12,13). The model includes the inflow artery, arterial and venous anastomoses, graft, stenosis, and outflow vein (Figure 1). It resembles a loop graft anastomosed end to side to the radial or brachial artery and cephalic vein. Nevertheless, the principles developed herein also apply to a straight graft (13). The model uses sophisticated pressure-flow equations from the engineering literature to describe each segment of the circuit (12,13). The in vitro study showed that upstream segments can disturb flow in downstream segments. By making minor adjustments to some of the equations, however, we were able to obtain a valid description of the circuit (12,13):

$$\Delta P_{\text{TOTAL}} = MAP - CVP = \Delta P_{\text{ARTERY}} + \Delta P_{\text{AA}} + \Delta P_{\text{GRAFT}} + \Delta P_{\text{VA}} + \Delta P_{\text{STENOSIS}} + \Delta P_{\text{VEIN}}$$

where CVP denotes central VP, AA denotes arterial anastomosis, and VA denotes venous anastomosis. The $\Delta P_{\text{TOTAL}}$ equation determines relations between the variables that characterize the circuit: Q, circuit pressures, luminal diameters, viscosity, and other variables and constants. We related blood viscosity ($\mu$, g/cm per s) to hematocrit (Hct, %) with the following equation: $\mu = 0.01 + (5.6 \times 10^{-4})$Hct (23). The lengths of the artery, graft, vein, and stenosis were set equal to 40, 34, 40, and 1 cm, respectively. We defined stenosis as percentage reduction in luminal diameter. Q and VP should be only mildly sensitive to stenosis length because frictional energy losses are greater at the exit than within a stenosis (24). We assumed a uniform graft diameter of 0.60 cm and selected artery and vein diameters that were representative of our patients (see Measurements in Patients). Conditions were as follows: MAP = 93 mmHg, CVP = 5 mmHg, and Hct = 36% except when indicated otherwise.

The $\Delta P$ equations for the artery, graft, and vein depend on whether flow is laminar or turbulent. A minimum "entrance length" is required for laminar flow to develop fully. For most large arteries, the entrance length approaches the length of the artery, so laminar flow is usually not fully developed. Therefore, we used Shah’s laminar entry-flow equation to model such flow (25,26). We used a modified Blasius equation to model turbulent flow (12,27). The in vitro study (12) showed that the graft and vein exhibit turbulent flow, whereas the artery may exhibit laminar entry-flow or turbulent flow, depending on the Reynolds number: $Re = \rho Q / 15 \pi D \mu$ ($\rho$ is blood density in g/cm³, Q is in ml/min, and D is diameter in cm) (24). We used Shah’s equation when Re <1500 (25,26) and used the modified Blasius equation when Re ≥1500 (12,27). We modeled the stenosis with a modified Young’s equation (12,28). Anastomoses were modeled by adding two equations together: A T-junction equation that defines $\Delta P$ across the junction of two tubes (29), plus $\Delta P$ caused by increases (30) or decreases (31) in luminal diameter (Bernoulli’s Law [24]).

Relation between VP/MAP and Resistance

The effect of luminal diameters on VP/MAP is understood by deriving the relation between VP/MAP and vascular resistance (22). Q is determined by the following equation: $Q = (MAP - CVP) / (R_{\text{IN}} + R_{\text{OUT}})$. $R_{\text{IN}}$ and $R_{\text{OUT}}$ are vascular resistances upstream (inflow) and downstream (outflow) to the venous dialysis needle, respectively. Thus, $R_{\text{IN}} + R_{\text{OUT}}$ is the total circuit resistance from ascending aorta to right atrium. Q can also be defined by the pressure drop downstream to the venous needle: $Q = (VP - CVP) / R_{\text{OUT}}$ (Figure 1). These two equations can be rearranged to give the following equations:

$$VP = Q(R_{\text{IN}} + R_{\text{OUT}}) + CVP$$
$$MAP = Q(R_{\text{IN}} + R_{\text{OUT}}) + CVP$$

Taking the ratio of the two equations yields equation 1:

$$\frac{VP}{MAP} = \frac{Q(R_{\text{IN}} + R_{\text{OUT}}) + CVP}{Q(R_{\text{IN}} + R_{\text{OUT}}) + CVP}$$

$$\text{Relation between VP/MAP and Resistance}$$
Because CVP is small, this equation can be approximated by equation 2:

\[
\frac{VP}{MAP} \approx \frac{R_{OUT}}{R_{IN} + R_{OUT}}
\]  

(2)

Measurements in Patients
To ensure that we used representative artery and vein diameters, we used duplex ultrasound studies of 94 patients with grafts from a previous clinical trial (2,13). A single ultrasound technologist performed studies with a Siemens Sonoline Versa scanner and a 7.5- or 5.0-MHz linear transducer (Siemens Medical Systems, Issaquah, WA). Luminal diameters were measured where they were most representative of the artery and vein within a few centimeters of anastomoses. These locations had the smallest diameters of arteries and veins in the circuit and therefore largely controlled inflow and outflow resistances.

Analysis
The \( \Delta P_{TOTAL} \) equation was used to compute relations between pressures, \( Q \), diameters, and stenosis. After fully defining the equation (Figure 1), we used Microsoft Excel Solver (the Generalized Reduced Gradient nonlinear optimization code; Microsoft, Redmond, WA) to determine these relations. The pressure just upstream of the venous anastomosis was taken to be static VP.

Results
In analyzing the graft circuit, it is important to select representative diameters of the inflow artery and outflow vein. We obtained such diameters from measurements in 94 patients (2,13) (Table 1). Diameters varied widely, but the artery was generally narrower than the vein. We used the ratio of artery/vein diameters to assess the influence of diameters on VP. We considered low, median, and high ratios (Table 2). The low and high ratios of 0.40 and 1.28 encompassed 95% of patients (13).

Validity of VP/MAP Adjustment
Because MAP affects VP, the VP/MAP ratio is used to adjust for changes in MAP during surveillance (11). However, this adjustment is valid only if a change in MAP causes a proportionally equal change in VP. Therefore, we used the model to determine the relation between VP and MAP (Figure 2). The model predicts that there is a nearly one-to-one relation between VP and MAP so that doubling of MAP causes VP to approximately double. Doubling MAP when stenosis is 0% increases VP by 86%, whereas at stenosis of 50% or more, VP almost exactly doubles. Therefore, VP/MAP is a valid adjustment for the influence of MAP.

Relation between VP and Artery/Vein Ratio
Figure 3 shows how differences in relative diameters of the artery and vein affect pressures in the circuit at 50% stenosis. A relatively narrow artery (low artery/vein ratio) increases vascular resistance and yields a large drop in pressure across the artery. Consequently, the pressure drop across the rest of the circuit (including the stenosis) is small. A relatively wide artery (high ratio) provides minimal resistance, so pressure does not significantly fall until the arterial anastomosis is crossed, and the largest pressure drop is across the stenosis. Figure 3 shows that VP varies widely depending on the artery/vein ratio.

Figure 4 shows that the artery/vein ratio controls the relation between VP/MAP and stenosis. At a high ratio, the standard VP/MAP referral threshold of 0.50 is reached when stenosis is only 39%, whereas at a low ratio, the threshold is not reached until stenosis is 72%. Although a single threshold does not accurately predict stenosis, Figure 4 shows that each graft has a specific relation between VP/MAP and stenosis.

Figure 5 further illustrates the relation among VP/MAP, artery/vein ratio, and stenosis. The data in Figure 5 were computed with the artery and vein diameters of the 94 patients in Table 1. As the artery/vein ratio increases, VP/MAP increases until the four curves approach the limiting value of 1.0. The threshold of 0.50 successfully identifies most grafts with stenosis of 65 and 75%. It is a key confirmation of the model that at 50% stenosis, the average VP/MAP of 0.49 agrees with the referral threshold of 0.50 (Figure 6). However, individual values vary widely from 0.17 to 0.98.

Relation between VP/MAP and Q
Finally, we used the model to predict the relation between VP/MAP and Q. Figure 7 shows that the artery/vein ratio controls the relation between VP/MAP and Q: For a given VP/MAP, a higher ratio yields a higher Q. The referral threshold of 0.50 occurs at Qs that range from 808 to 2141 ml/min. Figure 7 also indicates that each graft has a specific relation between VP/MAP and Q. Figure 8 shows the relation between VP/MAP and Q at the luminal diameters of the 94 patients. The data are widely scattered, but it is clear that as Q decreases, the mean of the VP/MAP values increases.

Discussion
This study used a mathematical model of the graft vascular circuit to determine relations among static VP, MAP, artery and vein luminal diameters, stenosis, and Q. Representative diameters were obtained from duplex ultrasound studies of 94 pa-

Table 1. Duplex ultrasound measurements of luminal diameters in 94 patients

<table>
<thead>
<tr>
<th>Luminal Diameters</th>
<th>Mean ± SEM</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflow artery (cm)</td>
<td>0.592 ± 0.013</td>
<td>0.575</td>
<td>0.34 to 1.15</td>
</tr>
<tr>
<td>Outflow vein (cm)</td>
<td>0.803 ± 0.026</td>
<td>0.745</td>
<td>0.28 to 1.67</td>
</tr>
<tr>
<td>Ratio of artery/vein</td>
<td>0.793 ± 0.028</td>
<td>0.769</td>
<td>0.32 to 2.29</td>
</tr>
</tbody>
</table>

*Artery versus vein: \( P < 0.001 \) by paired \( t \) test.
Two important results provide broad validation of surveillance concepts (11). First, there is an approximate one-to-one relation between VP and MAP, so VP/MAP is a valid adjustment for the influence of MAP on VP. Second, the standard referral threshold of 0.50 is a valid indicator of the transition to critical stenosis.

The validity of the VP/MAP adjustment supports its application during surveillance. Therefore, our result is consistent with the report (19) that VP/MAP has greater accuracy in predicting graft outcomes than VP. The effect of MAP on Q differs in that doubling MAP only increases Q by 50% (13). The different effects that MAP has on Q and VP are not intuitive but rather follow from the equations in the model. These are complex nonlinear equations that include Q raised to various powers, plus a number of variables and constants. Our calculations with equation 1 in the Materials and Methods section show that an increase in MAP causes increases in Q and circuit resistances that yield a nearly constant VP/MAP.

A key prediction of the model is that the ratio of artery/vein diameters controls the relation between VP and stenosis or Q. The influence of diameters on VP/MAP is explained by showing how relative upstream and downstream resistances affect VP/MAP (22). VP/MAP can be approximated by equation 2 in the Materials and Methods section:

\[
\frac{VP}{MAP} \approx \frac{R_{OUT}}{R_{IN} + R_{OUT}}
\]  

\(R_{IN}\) and \(R_{OUT}\) are vascular resistance upstream (inflow) and downstream (outflow) to the venous dialysis needle, respectively. VP/MAP approximates the fraction of total circuit resistance that is downstream to the venous needle. If the inflow artery is narrow relative to the vein, then \(R_{IN} \gg R_{OUT}\) and VP/MAP will be close to 0. This result makes sense because the high upstream resistance causes a large pressure drop, so the pressure is low by the time the needle is reached. It follows that stenosis will not have a significant effect on VP/MAP until it is far advanced (Figures 3 and 4). In contrast, if the artery is wide relative to the vein, then \(R_{IN} \ll R_{OUT}\) VP/MAP may therefore be >0.50 even if stenosis is <50%. This result makes sense because when the artery is wide, there will be little pressure drop until the arterial anastomosis is crossed. Thus, the pressure may still be high when the needle is reached.

The foregoing indicates that a single threshold, such as the standard VP/MAP = 0.50 for static VP (11), does not accurately identify 50% stenosis. This is illustrated in Figure 6, which shows that at 50% stenosis, predicted VP/MAP values vary from 0.17 to 0.98. Nevertheless, most stenoses of 65 and 75% are above the 0.50 threshold (Figure 5). Sullivan et al. (32) showed that cumulative probability of thrombosis rapidly increases from 33% at 50% stenosis to 90% at 75% stenosis. Therefore, 0.50 represents a key threshold that warns of the transition to critical stenosis. Moreover, a specific relation between VP/MAP and stenosis is established when diameters and other key characteristics of a graft circuit are specified (Figure 4). Such a specific relation validates the concept that observing for an increase in VP/MAP can identify an increase in stenosis.

In evaluating the relation between Q and progressive stenosis, we previously found that Q initially remains unchanged but then rapidly decreases (13). The inflow artery is generally narrower than the outflow vein, and a narrower artery promotes a longer delay followed by a more rapid reduction in Q. Assuming that stenosis progresses at a constant rate, this delay would make it difficult for standard monthly surveillance to detect a decrease in Q before thrombosis occurs. Figure 4 shows a similar phenomenon for VP/MAP. As the artery/vein ratio decreases, the VP/MAP increase is delayed followed by a more rapid increase when critical stenosis is reached. Thus, the ratio’s influence on VP/MAP could impair the effectiveness of surveillance. However, VP measurements are easier to obtain at every dialysis session so that there is minimal delay in detecting the rapid rise in VP/MAP.

Besarab et al. (20,33) found that a high VP/MAP is associated with low Q, whereas Spergel et al. (22) found no correlation between VP/MAP and Q (Figure 9). Thus, we used the model to examine the relation between these variables. Figure 7 confirms that there is a negative correlation between VP/MAP and Q that is controlled by the artery/vein ratio. Figure 8 shows

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**Table 2. Hypothetical luminal diameters and luminal diameter ratios that were used in mathematical model**

<table>
<thead>
<tr>
<th>Type of Artery/Vein Ratio</th>
<th>Inflow Artery Diameter (cm)</th>
<th>Outflow Vein Diameter (cm)</th>
<th>Value of Artery/Vein Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ratio</td>
<td>0.400</td>
<td>1.000</td>
<td>0.40</td>
</tr>
<tr>
<td>Median ratio from Table 1</td>
<td>0.575</td>
<td>0.745</td>
<td>0.77</td>
</tr>
<tr>
<td>High ratio</td>
<td>0.950</td>
<td>0.745</td>
<td>1.28</td>
</tr>
</tbody>
</table>

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**Figure 2. Predicted relation between VP and MAP over a range of stenoses. Conditions: Ratio of artery/vein diameters had median value of 0.77 (Table 2), CVP = 5 mmHg, hematocrit (Hct) = 36%**.
that the data from the model are widely scattered when the ratios of the 94 patients are considered together. However, the data clearly show that as Q decreases, the mean of the VP/MAP values increases. The data are scattered because artery and vein luminal diameters vary widely between patients, and these diameters dominate Q (13) and VP/MAP until stenosis is far advanced.

It is important to confirm the model with clinical data. The model predicts that at 50% stenosis, the mean VP/MAP is 0.49 (Figure 6). This result closely agrees with the observation that 0.50 is the optimum threshold for detecting 50% stenosis in patients with grafts (33).

As further confirmation, we can compare the model with clinical data on the relation between VP/MAP and Q (Figure 9) (22). The scatter in Figure 9 is wider than that in Figure 8, but this difference is easily explained. Measurement errors always increase the scatter of clinical data. For example, in practice, the arm opposite the graft supplies the MAP that is used to compute VP/MAP, and this often differs significantly from MAP in the graft arm (16). Also, Figure 9 includes VP/MAP values that are >1.0, which is physiologically impossible. In contrast, values that are generated by a model are restricted to patterns that are determined by the model’s access anatomy and equations and by selected values of key variables (Figure 7). For example, unlike Figure 9, Figures 7 and 8 lack VP/MAP and Q values that are both low. This combination is caused by inflow stenosis, which we did not include in the model. Asif et al. (34) recently found that 29% of grafts have an inflow stenosis. It follows that Figure 8 is consistent with Figure 9.

Finally, angioplasty treatment of outflow stenosis causes an increase in Q combined with a decrease in VP (35). This important observation also suggests that VP measurements during angioplasty procedures may help to confirm successful treatment of hemodynamically significant stenosis.
Conclusion

The model provides insights that may help to resolve the surveillance controversy. The artery/vein ratio controls the relation between VP/MAP and stenosis, and this ratio varies widely between patients. The standard referral threshold of 0.50 does not accurately identify 50% stenosis per se but does warn of the transition to critical stenosis. In addition, each graft has a specific VP/MAP versus stenosis relation, so an increase in VP/MAP indicates an increase in stenosis. However, the rate at which VP/MAP increases with stenosis may influence surveillance outcomes. Relatively narrow inflow arteries are predicted to delay the stenosis-induced increase until critical stenosis is reached. Assuming that stenosis progresses at a constant rate, the delay and then rapid increase in VP/MAP helps to explain why surveillance often fails to warn of thrombosis. Therefore, it is likely that the monthly or even twice-monthly measurement schedule of most programs is not adequate. Online data collection that is available in many dialysis units allows easy analysis of measurements from every session. Such a frequency may be needed to ensure that there is no delay in discovering that VP/MAP has increased. Randomized, controlled trials that emphasize trend analysis with frequent measurements are needed to evaluate the efficacy of VP surveillance.

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Disclosures

None.

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