Elasticity and fistula maturation

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Influence of arterial elasticity and vessel dilatation on arteriovenous fistula maturation: a prospective cohort study

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Abstract
Background. Arteriovenous fistula maturation requires dilatation of the anastomosed artery and vein. The factors that affect dilatation and the mechanisms by which dilatation promotes maturation are not understood. This pilot study tested two hypotheses: that low arterial elasticity is associated with maturation failure, and that vessel dilatation is required for adequate fistula blood flow during dialysis.

Methods. Thirty-two patients underwent preoperative measurement of small artery elasticity index, and pre-anastomosis measurement of artery and vein luminal diameters during fistula surgery. Fistulas were considered mature if they were used successfully in three consecutive treatments within 6 months. A mathematical model was used to determine whether vessel dilatation is needed for adequate fistula flow.

Results. Six fistulas were excluded from analysis of maturation because dialysis did not begin within 6 months. Twenty-one of the remaining 26 fistulas were located in the upper arm. Six of 26 failed to mature, and all 6 developed stenosis. The average small artery elasticity index was lower in failed than in matured fistulas (2.25 versus 3.71 ml/mmHg x 100, P = 0.02). Artery and vein diameters of the 32 patients ranged from 2.5 to 5.0 and 3.5 to 7.0 mm, respectively. When the diameters were applied to the mathematical model, predicted fistula flows ranged from 412 to 1380 ml/min.

Conclusions. Low arterial elasticity is associated with stenosis and fistula maturation failure. However, vessel dilatation is not needed for adequate blood flow except at the smaller diameters in this study. We speculate that low elasticity promotes development of stenosis. Larger studies are needed to confirm these promising results and to determine whether therapies directed at improving elasticity can improve maturation.

Keywords: arteriovenous fistula; haemodialysis; hemodynamics; stenosis; vascular access

Introduction

The native arteriovenous fistula is the preferred haemodialysis access because mature fistulas survive longer and are associated with lower morbidity and mortality than synthetic grafts. However, 20–60% of fistulas fail to mature sufficiently to support dialysis [1–3]. Thus, the high rate of maturation failure is a major unsolved problem.

Dilatation of the anastomosed artery and vein are key steps in fistula maturation. However, the vessels of dialysis patients have properties that may impair dilatation. Arteries may develop increased intimal and medial thickening, medial calcification and increased stiffness with decreased flow-mediated dilatation [4–6]. Veins may develop intimal

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and medial thickening [7]. Since the artery is generally narrower than the vein, the artery is the chief source of vascular resistance in a new fistula. Thus, arterial dilatation may be a key step in maturation.

These observations have led to suggestions that vascular compliance should be assessed preoperatively by ultrasound techniques [8]. In support of this concept, measurement of venous distensibility [9] and arterial dilatation in response to fist clenching [10] have predicted maturation outcome. However, others [11] did not confirm that the response to fist clenching is predictive. Thus, the benefit and optimum criteria for evaluating vascular compliance are currently unknown. Also, ultrasound techniques require significant time, expense and skill, whereas an ideal test would be rapid, inexpensive and require little training.

Another issue is that we do not understand the mechanisms by which vessel dilatation promotes maturation [1,2]. For example, it is widely assumed that without dilatation, blood flow will be inadequate for dialysis. However, to our knowledge, the influence of luminal diameters on flow has not been systematically studied. Evaluation of this influence requires an analysis of relations among flow, luminal diameters, circuit pressures and other variables in the fistula circuit. This has not been done in clinical studies because such relations are complex and not easily discerned from clinical data. Alternatively, a mathematical model is a powerful tool for determining such relations because it allows one to control circuit conditions while changing the values of selected variables at will [12–15].

These considerations led us to test two hypotheses: first, that low arterial elasticity is associated with maturation failure, and second, that vessel dilatation is required for adequate fistula blood flow. We measured elasticity with a tonometer technique that is easy to apply, and used a well-established mathematical model to determine the relationship between vessel diameters, blood flow and circuit pressures [12–15].

**Subjects and methods**

We enrolled 32 adult patients with end-stage kidney disease who were scheduled to undergo fistula surgery from September 2006 through May 2007. The study received institutional review board approval and all patients gave written informed consent. On the day of surgery, patients underwent preoperative measurement of arterial blood pressure, and small and large artery elasticity indexes, with the HDI/PulseWave CR-2000 System (Hypertension Diagnostics, Inc., Eagan, MN, USA). This instrument uses a noninvasive tonometer to perform pulse contour analysis of radial artery waveforms [16,17]. Average measurements of blood pressure and elasticity were obtained over 16 cardiac cycles. Measurements were taken in the radial artery of the arm in which the fistula was created. After the patient rested in the supine position for 5 min, a blood pressure cuff was placed on the arm, and a padded wrist stabilizer was placed on the wrist in order to limit movement. The stabilizer prevented artery occlusion during waveform measurement and assured adequate venous return from the hand. The tonometer was positioned on the skin above the artery and was secured with a loop strap. We used the average of three measurements taken ∼1 min apart.

Blood testing was done within 1 month of surgery. Serum calcium and phosphorus levels were measured by the Synchron LX autoanalyzer (Beckman Coulter, Fullerton, CA, USA), plasma ionized calcium by the Bayer RapidLab 855 Analyzer (Bayer Diagnostics, Tarrytown, NY, USA), intact serum parathyroid hormone by the Immulite 1000 Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA) and plasma haemoglobin by the Beckman Coulter LH 750 (Beckman Coulter).

The same vascular surgeon created all fistulas and took all diameter measurements. Pre-anastomosis artery and vein diameters were measured with intraluminal probes during surgery. Dialysis staff and physicians who managed the fistulas and made cannulation decisions were blinded to elasticity measurements. The primary outcome of the study was fistula maturation. When the study was planned, there was little consensus on how maturation should be defined [1]. We defined maturation as successful and (in the nephrologist’s judgment) adequate dialysis during three consecutive treatments within 6 months of surgery.

**Mathematical model**

We used a well-established mathematical model to estimate blood flow in an upper extremity fistula [12–15]. The model was originally applied to synthetic grafts, but was easily adapted to fistulas by eliminating one of the two anastomoses. Anastomosis of the artery to the vein yields a high flow circuit with a large dissipation of energy and pressure before flow crosses the anastomosis. Brachial artery fistulas, arterial blood flow is antegrade from the axilla to the hand (Figure 1A). However, radiocephalic fistulas develop unusual flow distributions in forearm vessels because the ulnar artery is connected to the radial artery through the palmar arch. Pressure in the radial artery at the anastomosis may be higher than, equal to, or less than pressure in the distal radial artery (Figure 1A–C). Lower pressure is most common, and this induces retrograde flow from the ulnar artery through the distal radial artery to the anastomosis [18].

We assumed no flow in the brachial or radial artery distal to the anastomosis. The following considerations show that this assumption should not impair accuracy of flow predictions. In the normal vascular circuit, brachial artery flow is only ∼50 ml/min and radial artery flow is typically < 25 ml/min [1]. Also, digital artery pressure is reduced in brachial...

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**Fig. 1.** Flow distribution in upper extremity vessels with vein anastomosed end-to-side to artery. Brachial artery fistulas have antegrade flow in brachial artery distal to anastomosis (A). In radiocephalic fistulas, flow in radial artery distal to anastomosis ranges from antegrade, to no significant flow, to retrograde (A–C) [18].
Elasticity and fistula maturation

Table 1. Characteristics of matured and failed fistula groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Matured (N = 20)</th>
<th>Failed (N = 6)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
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<tr>
<td>Patient age (years)</td>
<td>50.8 ± 3.5</td>
<td>46.2 ± 6.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Female (%)</td>
<td>35</td>
<td>33</td>
<td>1.0</td>
</tr>
<tr>
<td>African American (%)</td>
<td>85</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>45</td>
<td>67</td>
<td>0.6</td>
</tr>
<tr>
<td>Body mass index (BMI, kg/m²)</td>
<td>26.4</td>
<td>34.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>25</td>
<td>17</td>
<td>1.0</td>
</tr>
<tr>
<td>Blood measurements</td>
<td></td>
<td></td>
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<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.03 ± 0.16</td>
<td>8.87 ± 0.13</td>
<td>0.6</td>
</tr>
<tr>
<td>Plasma ionized calcium (mg/dl)</td>
<td>4.07 ± 0.07</td>
<td>4.13 ± 0.15</td>
<td>0.6</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>4.91 ± 0.29</td>
<td>5.62 ± 0.63</td>
<td>0.4</td>
</tr>
<tr>
<td>Serum parathyroid hormone (ng/l)</td>
<td>446.4 ± 97.0</td>
<td>470.7 ± 58.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Plasma haemoglobin (g/dl)</td>
<td>11.97 ± 0.27</td>
<td>11.80 ± 0.64</td>
<td>0.7</td>
</tr>
<tr>
<td>Vascular measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>152.3 ± 5.1</td>
<td>179.3 ± 10.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86.6 ± 2.5</td>
<td>101.3 ± 6.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>65.7 ± 4.4</td>
<td>78.0 ± 4.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Large artery elasticity index (ml/mmHg × 10)</td>
<td>8.55 ± 0.68</td>
<td>7.45 ± 1.08</td>
<td>0.5</td>
</tr>
<tr>
<td>Small artery elasticity index (ml/mmHg × 100)</td>
<td>3.71 ± 0.29</td>
<td>2.25 ± 0.33</td>
<td>0.02</td>
</tr>
<tr>
<td>Fistula characteristics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Artery luminal diameter (mm)</td>
<td>3.73 ± 0.17</td>
<td>3.33 ± 0.25</td>
<td>0.3</td>
</tr>
<tr>
<td>Range of artery luminal diameters (mm)</td>
<td>2.5–5.0</td>
<td>2.5–5.0</td>
<td>–</td>
</tr>
<tr>
<td>Vein luminal diameter (mm)</td>
<td>4.60 ± 0.19</td>
<td>4.42 ± 0.53</td>
<td>0.3</td>
</tr>
<tr>
<td>Range of vein luminal diameters (mm)</td>
<td>3.5–7.0</td>
<td>3.5–7.0</td>
<td>–</td>
</tr>
<tr>
<td>Upper arm fistula (%)</td>
<td>80</td>
<td>83</td>
<td>1.0</td>
</tr>
<tr>
<td>Weeks for fistula to mature</td>
<td>14.4 ± 1.0</td>
<td>–</td>
<td>–</td>
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</table>

*Data are percentage or mean ± SE.

artery fistulas, indicating distal artery flow is less after fistula creation [19]. Thus, in brachial artery fistulas and in radiocephalic fistulas with antegrade arterial flow, antegrade flow distal to the anastomosis should be much less than fistula flow unless fistula flow is very low. On the other hand, in radiocephalic fistulas with retrograde radial artery flow, fistula flow could potentially be higher than predicted because retrograde flow will augment proximal antegrade flow into the fistula. This effect is probably minimal, however, because retrograde flow will raise arterial pressure at the anastomosis, thereby decreasing the pressure drop from the heart to the anastomosis. The smaller pressure drop will decrease flow in the proximal radial artery above the anastomosis, thereby offsetting the contribution of retrograde flow. Also, any underestimation of fistula flow would support the conclusion in Results that dilatation is unnecessary for adequate flow.

The model is defined by a pressure drop equation (ΔP.getTotal) that is the sum of pressure drops across the segments of the fistula circuit. The MAP (mean arterial pressure) and CVP (central venous pressure) were set equal to 93 mmHg (equivalent to 120/80 mmHg) and 5 mmHg, respectively:

ΔP.getTotal = MAP − CVP = ΔP.artery + ΔP.anastomosis + ΔP.vein

(1)

The pressure drop equation establishes relationships between the variables and constants that define the circuit [12]. The lengths of the artery and vein were set equal to 40 and 42 cm, respectively, and haematocrit = 36%. We used the pre-anastomosis luminal diameters that were measured in the 32 patients.

The pressure drop equations depend upon whether flow is laminar or turbulent. A minimum entrance length is required for laminar flow to fully develop. For most large arteries, the entrance length approaches the length of the artery, so that laminar flow is usually not fully developed. We used Shah’s laminar entry-flow equation to model such flow [20,21]. We used a modified Blasius equation to model turbulent flow [12,22]. Our in vitro study [12] showed that in a synthetic graft, the graft and vein exhibit turbulent flow, whereas the artery may exhibit laminar entry-flow or turbulent flow, depending on the Reynolds number: Re = ρQ/Dµ (ρ is blood density, Q is flow, D is diameter, µ is blood viscosity) [23]. We used Shah’s equation in the artery when Re was <1500 [20,21] and used the modified Blasius equation when Re was ≥1500 [12,22]. The anastomosis was modelled by adding two equations together: a T-junction equation that defines the pressure drop across the junction of two tubes [24] plus the pressure drop caused by an increase [25] or decrease [26] in luminal diameter (Bernoulli’s Law [23]). We used the modified Blasius equation in the vein [12,22].

The total pressure drop equation was used to compute relationships between pressures, fistula flow and diameters. We used Microsoft Excel Solver (the generalized reduced gradient nonlinear optimization code) to determine these relations. Solver (Frontline Systems, Inc., Incline Village, NV, USA) is an add-in to Microsoft Excel that uses iterative methods to optimize solutions to nonlinear equations. Given that the model is nonpulsatile, calculations of flow and pressure should be considered time averaged.

Analysis

Differences between matured and failed groups were tested with the Wilcoxon rank sum test for continuous variables, and with Fisher’s exact test for categorical variables. Correlations were tested with least-squares regression analysis. Logistic regression analysis was used to determine variables that predicted fistula outcome. Because this was a prospective follow-up study, the logistic regression functions yielded probability of failure. We used both backward elimination and forward stepwise procedures to test for significance of independent variables in a multivariable model. Both procedures yielded the same final model. Likelihood ratio tests were used to test for significance (P < 0.05).

Results

Characteristics of matured and failed groups

Fistulas were considered mature if they were used successfully in three consecutive treatments within 6 months of surgery. Six of the 32 patients were excluded from analysis of maturation because they did not begin dialysis within 6 months. Of the remaining 26 fistulas, 6 (23%) failed to mature.

Table 1 shows the characteristics of the matured and failed groups. Both groups had predominantly upper arm fistulas. There were no significant differences in type of
Fig. 2. Fistulas that matured generally had a higher small artery elasticity index than fistulas that failed, but there was no association between the large artery elasticity index and maturation. Solid symbols indicate mean ± SE.

Fig. 3. Higher small artery elasticity index was associated with lower systolic blood pressure and pulse pressure.

vein (cephalic versus basilic) or artery (brachial versus radial) in the two groups. Failed fistulas did not have significantly smaller luminal diameters, but diameters in this study were generally well above the widely recommended minimum artery and vein diameters of 2.0 and 2.5 mm, respectively [27]. There were no demographic differences; however, the failed group had a trend of higher body mass index (BMI). There were no significant differences in blood levels of calcium, phosphorus, haemoglobin or parathyroid hormone levels.

Neither group had surgical complications or thrombosis in the immediate post-operative period. Thus, all failures were due to unsuccessful maturation. Five of 20 fistulas in the matured group thrombosed or had delayed maturation. All had stenosis that was treated with balloon angioplasty followed by successful maturation within 6 months of surgery. The failed group had poor dilatation, difficult cannulation and thrombosis. All had significant stenosis; treatment with angioplasty was unsuccessful and none were ever used for dialysis. All stenoses in both groups were at the anastomosis or venous outflow tract.

Relationship between elasticity and maturation

The average small artery elasticity index in the matured group was higher (i.e. there was less stiffness) than in the failed group [3.71 ± 0.29 (±SE) versus 2.25 ± 0.33 ml/mmHg x 100, \( P = 0.02 \)], but the large artery elasticity index was not significantly different (Figure 2). The failed group had higher systolic blood pressures and pulse pressures (Table 1). Both arterial elasticity indexes correlated with these pressures (Figures 3 and 4).

We used multivariable logistic regression analysis to analyse risk of maturation failure. We considered variables in Table 1 that showed significant differences between groups or had strong trends: small artery elasticity index, systolic blood pressure, pulse pressure, BMI and parathyroid hormone. We found that only the small artery elasticity index and BMI were independent predictors. A lower small artery elasticity index (\( P = 0.008 \)) a higher BMI (\( P = 0.02 \)) predicted a higher probability of maturation failure (Figure 5). A higher BMI was associated with larger vein diameter (\( R^2 = 0.158, P = 0.04 \)), and had no relation with arterial diameter.

Predicting fistula flow

We used the mathematical model to test whether vessel dilatation is needed for adequate fistula blood flow. We used the pre-anastomosis artery and vein luminal diameters of the 32 fistulas to compute flows. Figure 6 shows pressure drops across the fistula circuit at the average diameters
and at the diameters of fistulas that had the highest and lowest flow resistances. At the average diameters, arterial pressure is predicted to drop \(~\sim 60\%\) before entering the anastomosis, and predicted flow is 789 ml/min. Fistula flow is predicted to range from 412 to 1380 ml/min, so that flow is adequate for dialysis without dilatation except at the smaller diameters. The model predicts flow of only 155 ml/min at the recommended minimum artery and vein diameters of 2.0 and 2.5 mm, respectively [27].

Discussion

Six of 26 fistulas in this pilot study (23%) failed to mature within 6 months of surgery, and all had significant stenosis at the anastomosis or venous outflow tract. Our results agree with other studies that stenosis is the most common anatomic abnormality in fistulas that fail to mature [28,29]. A lower small artery elasticity index and higher BMI were the only variables that were independently associated with maturation failure in the logistic model, and elasticity had the stronger relationship. However, we were unable to identify factors that might explain why BMI independently predicted failure. Higher systolic blood pressure and pulse pressure were associated with failure in the univariable but not the multivariable model. The association of systolic and pulse pressures with failure is not surprising since low arterial elasticity promotes higher pressures by increasing pulse wave velocity [30].

It seems likely that low elasticity promotes maturation failure by impairing arterial dilatation. An important issue is whether dilatation is necessary for adequate fistula blood flow during dialysis. We addressed this issue with a mathematical model that applied the pre-anastomosis luminal diameters of the 32 patients. Artery and vein diameters ranged from 2.5 to 5.0 and 3.5 to 7.0 mm, respectively, and flow was predicted to range from 412 to 1380 ml/min. In order to avoid recirculation, access flow must be greater
than dialysis blood pump speed. If pump speed is 400 to 500 ml/min, then dilatation is not required for adequate flow except at the smaller diameters.

In contrast, the widely recommended minimum artery and vein luminal diameters of 2.0 and 2.5 mm [27], respectively, are a true dilatation challenge. The model predicts that fistula flow is only 155 ml/min at these diameters, so that failure to dilate will cause maturation failure. The failure rate of 23% in this study is lower than generally reported in the USA [1–3], and this study’s relatively large diameters help explain this result. We found no correlation between diameters and failure probably because diameters in both groups were generally well above the recommended minimum values, thereby reducing the risk of failure.

If fistula flow is often adequate without dilatation, then why is poor dilatation associated with maturation failure? Dilatation and remodelling of the vein are required so that a fistula can be cannulated with dialysis needles, but this does not explain the stenosis that commonly causes failure. We speculate that low elasticity with poor dilatation promotes failure by inducing the low shear stress and turbulence that stimulate development of stenosis [1,2]. However, additional factors may contribute to stenosis. For example, mobilization of the swing segment of the vein during surgery may disrupt the vasa vasorum, leading to ischaemic changes that promote stenosis [31].

It is notable that both study groups had low elasticity when compared with published control groups. For example, the average small artery elasticity index in the matured and failed groups was 3.71 and 2.25 ml/mmHg × 100, respectively. In contrast, one of the present authors previously obtained an average value of 7.0 ml/mmHg × 100 in a normal control group [16]. Thus, even patients whose fistulas matured had low small artery elasticity, but patients whose fistulas failed generally had the lowest values. Similarly, the average large artery elasticity index in matured and failed groups was 8.55 and 7.45 ml/mmHg × 10, respectively, whereas the previous control group had an average value of 16.1 ml/mmHg × 10 [16].

The present study did not compare flow predictions from the mathematical model with clinical measurements of fistula flow. However, we believe that the validity of the model is well established [12–15]. The model has been refined with data from an in vitro apparatus, and closely agrees with published clinical data. For example, predicted pressures in the synthetic graft circuit closely agree with pressures measured in patients [13,32]. Also, the model predicts that in grafts with 50% stenosis at the venous anastomosis, the average value of the dialysis venous pressure divided by mean arterial pressure (VP/MAP) is 0.49, and this closely agrees with the clinical observation that 0.50 is the optimum threshold for detecting 50% stenosis [14,33]. Finally, Won et al. [34] studied 50 radiocephalic fistulas with an average vein diameter of 2.7 mm and obtained an average blood flow of 175 ml/min (no arterial diameters were given). Their result closely agrees with our prediction that flow should be 155 ml/min when artery and vein diameters are 2.0 and 2.5 mm, respectively.

The tonometer that we used to measure elasticity requires little training and is easy to apply. The instrument measures arterial waveforms and uses a modified Wind-kessel model to analyse the pressure pulse contour [16,17]. The method is based on analysis of peripheral wave reflections superimposed on the diastolic decay of the basic pressure waveform. The large artery elasticity index reflects changes in the structure and compliance of large arteries, such as the aorta. The small artery elasticity index reflects changes in elasticity of arterioles and the smallest arteries, and includes reflections from branch points in the circulation. Small artery elasticity is a more sensitive measure of vascular disease than large artery elasticity [35], and may detect vascular changes before they become irreversible, whereas large artery elasticity reflects changes that may already be irreversible. The higher sensitivity of small artery elasticity in detecting vascular disease may explain why it was a better predictor of maturation.

The role of the modified Windkessel model in assessing vascular health is controversial. Some have supported the model [16,36–38], whereas others have argued that the model has significant shortcomings [39–42]. Some have criticized the model as being overly influenced by local vessel characteristics in a limb, suggesting that it may not be a true assessment of overall vascular health [42]. However, evaluation of vessels for fistula creation is primarily a local assessment, so that this property should be an advantage. In any case, in this study, the method correlated with clinical markers of arterial stiffness (systolic blood pressure and pulse pressure), and most important of all, it correlated with fistula outcome.

In conclusion, this small pilot study supports the concept that low arterial elasticity is an important factor in fistula maturation failure. The mathematical model indicates that dilatation of vessels is generally not needed for adequate fistula blood flow during dialysis unless vessel diameters are small. Thus, we speculate that low elasticity with poor dilatation promotes failure by inducing haemodynamic conditions that favour development of stenosis. This study also suggests that small artery elasticity may be useful in assessing suitability of vessels for fistula creation. We should emphasize, however, that no test can substitute for surgical skill, careful patient selection, and preoperative evaluation of vascular anatomy. Also, small vessel diameters are a dilatation challenge and should be avoided in patients who have conditions associated with poor maturation, such as peripheral vascular disease. Larger studies are needed to confirm these promising results and to determine whether therapies directed at improving elasticity can improve maturation.

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