Pressure trap created by vein valve closure and its role in graft stenosis

Saphenous vein graft stenosis has become the leading cause of reoperation in coronary bypass operations. We investigated the role of vein valves in vein graft stenosis by studying 14 human saphenous veins placed in a simulator of the left side of the heart in parallel with the arterial system. The vein had a variable resistance and a capacitance simulating the distal vascular bed. The pressures at the proximal and distal ends of the vein and the venous flow were measured while the following were changed: venous flow 200 to 0 ml/min, aortic pressure 150/120 to 80/60 mm Hg, cardiac output 3 to 5 L/min, and compliance of distal vascular bed 0 to 1 ml of air. The pressures at both ends of the vein were the same when venous flow rate was greater than 60 ml/min and the vein valve remained open. As the venous flow decreased the valve began to open and close in each cardiac cycle. The flow rate at which the valve began to close ranged from 30 to 10 ml/min. When the valve closed, it trapped the pressure in the segment distal to the valve. Because the segmental hypertension is expected to accelerate atherosclerotic changes, the pressure trap created by closure of the vein valve could be an important cause of vein graft stenosis. (*J THORAC CARDIOVASC SURG* 1994;107:707-16)

Mano J. Thubrikar, PhD, Francis Robicsek, MD, and Brett L. Fowler, BS, *Charlotte, N.C.*

Atherosclerotic occlusion of autogenous saphenous vein grafts is a common complication of arterial bypass operations. Unlike the artery, the saphenous vein is a valved conduit that permits only unidirectional flow. It is therefore necessary to reverse the vein when it is used as an arterial graft. Though most vein grafts provide good long-term patency, a significant share of them have atherosclerotic occlusive changes. The purpose of this study was to investigate the heretofore undescribed phenomenon that a pressure trap may develop between the vein valve and the runoff and the possibility that this may indeed be an important factor in the development of vein graft atherosclerosis.

Several investigators have demonstrated that the autologous vein grafts commonly used to bypass coronary and

other occluded arteries are susceptible to atherosclerosis.¹⁻¹¹ Why atherosclerotic occlusions develop in some vein grafts and not in others is not understood. Kalan and Robert¹¹ reported that late atherosclerotic changes are usually diffuse in grafts used for more than 1 year. Others implicated the valve sites in the occurrence of stenotic lesions.¹²⁻¹⁴ Phillips, Okies, and Starr¹⁵ reported that in vein grafts used for coronary artery bypass the valves remained competent at the end of the first year. Bond and associates¹⁶ observed in the canine model that 6 of 14 valves remained intact in femoral vein implanted in the arterial position for 6 months. In the experiments of Bosher and colleagues,¹⁷ 17 of 25 valves remained intact in jugular vein implanted in the carotid artery position in dogs for a period of 1 week to 6 months.

Overall patency of vein graft has been described by several investigators.^{5, 8, 10, 18, 19} For graft patency the flow through the graft is thought to be an important parameter. An initial flow rate of greater than 45 ml/min is thought to be important to keep the graft patent, whereas an initial flow rate of less than 20 ml/min is thought to lead to graft occlusion.¹⁸ Singh¹⁴ has suggested that the presence of the vein valve may cause sluggish velocity of blood flow and thereby lead to graft stenosis, whereas several others have claimed that the presence of the vein valve may in fact augment the forward flow to the

From Heineman Medical Research Laboratory at the Carolinas Medical Center and the Sanger Clinic, Charlotte, N.C.

Presented at the American Heart Association Scientific Sessions, New Orleans, La., November 1992.

Received for publication June 14, 1993.

Accepted for publication Sept. 14, 1993.

Address for reprints: Francis Robicsek, MD, The Sanger Clinic, PA, 1001 Blythe Blvd., Suite 300, Charlotte, NC 28232.

Copyright © 1994 by Mosby-Year Book, Inc.

0022-5223/94 \$3.00 + 0 12/1/51772

Fig. 1. Experimental setup to study flow through vein grafts. Superpump system is designed to simulate left side of heart. P_1 and P_2 represent proximal and distal pressures with respect to vein valve. Resistance and capacitance of distal venous bed are also indicated.

myocardium and thereby offer an advantage over the vein graft without the valve^{15, 20-22}. The focus of the majority of studies in the past has been blood flow through the vein valve,^{6, 15, 18, 20-25} and in this regard the present study offers new information on the function of the vein valve. We explored the role in vein graft stenosis of the pressure trap created by the presence of the vein valve.

Methods

The 14 valved human saphenous vein segments studied were obtained freshly from the operating room, when the harvested vein for some clinical reason was not used in the course of coronary operations (for example, unsuitable length or diameter, left over segments). The vein segments, approximately 3 to 4 inches long, were cannulated and placed in a pulse duplicator built to simulate the human circulation (VSI, Vivitro Systems, Inc., Victoria, British Columbia, Canada). The pulse duplicator produced physiologic pressures and pulsatile flows and allowed alterations in the systemic pressure and in the cardiac output while maintaining the physiologic waveforms of pressure

and flow. The systemic pressure was regulated by adjusting resistance and compliance on the VSI pump. Cardiac output was regulated by manipulating pump stroke volume and rate. Fig. 1 shows, schematically, the simulator of the left side of the heart and the placement of the vein in parallel to the arterial circuit. To simulate the distal vascular bed supplied by the vein graft, we added adjustable resistance and capacitance to the venous outflow. The resistance was created by using a fine metering valve with a Vernier adjustment scale (NuPro Co., Willoughby, Ohio).

In vivo, compliance of the distal vascular bed and of the vein graft may change under different conditions. For example, different lengths and different elastic properties of the vein will add different compliances. The compliance of the vein will be different at different systemic pressures. Also, the compliance of the distal vascular bed may change with the systemic pressure and with the amount of dilation of the vascular bed. So that the effect of compliance on the dynamics of the vein valve could be studied, a compliance chamber that contained either 1 ml or 0 ml of air was added to the distal end of the vein graft (Fig. 1). When there was no air in the chamber the only compliance present was that of the vein segment distal to the valve. When

Fig. 2. Schematic drawing of pressures and flows in vein graft. Proximal and distal pressures are same when mean flow rate through vein graft is high (that is, 100 ml/min) and vein valve remains open all the time. When mean flow rate decreases (that is, 50 to 25 to 0 ml/min) valve begins to open and close and pressure is trapped in distal segment. Consequently, diastolic pressure begins to rise in distal segment.

1 ml air was added to the chamber, the volume of the air changed by approximately 0.04 ml when the pressure changed from 80 mm Hg to 120 mm Hg.

The system was filled with normal saline solution. In the vein, pressures were measured on both sides of the vein valve with Sorenson Transpac disposable transducers (North Chicago, Ill.). Flow through the vein was measured with an electromagnetic flow probe (4 mm diameter, Cliniflow II, model FM 701D flowmeter, Carolina Medical Electronics Inc., King, N.C.).

In the course of the experiments the cardiac output and the systemic pressure were maintained constant while the flow through the vein was gradually decreased by increasing the resistance of the distal vascular bed. For the higher mean flow rates (>60 ml/min) the vein valve did not close and the pressure at the proximal and the distal ends were the same (but out of phase). When the vein valve closed, the pressure at the distal end was higher than the pressure at the proximal end. The maximum mean flow at which the vein valve first began to close was read from the flowmeter at the time when the diastolic pressure at the distal end was 2 to 5 mm Hg greater than that at the proximal end. To visualize the position of the valve (open or closed) we used intravascular ultrasound (CVIS, Cardiovascular Imaging Systems Inc., Sunnyvale, Calif.). A 4.3F ultrasound

intravascular catheter was introduced into the vein and the motion of the valve leaflets during pulsatile flow was visualized and recorded on a videotape. The difference in the diastolic pressures at the proximal and distal ends of the vein was measured while the venous flow was further decreased.

These measurements were repeated for the following conditions: (1) venous flow rate ranging from 200 to 0 ml/min; (2) systemic pressures of 80/60, 120/80, and 150/120 mm Hg while the cardiac output was held at 3 L/min; (3) cardiac outputs of 3, 4, and 5 L/min while the systemic pressure was kept at 120/80 mm Hg; and (4) varying the compliance of the distal vascular bed from 0 to 1 ml air.

The pump pulse rate was 72, 80, and 100 beats/min, respectively, for the cardiac (pump) outputs of 3, 4, and 5 L/min. Most of the experiments were done at a systemic pressure of 120/80 mm Hg, a cardiac output of 3 L/min, and a pulse rate of 72 beats/min.

Results

High flows through the vein graft. In all conditions, that is, various systemic pressures and cardiac outputs, the venous valve offered no significant resistance to flow,

Fig. 3. Cross-sectional images of three vein grafts (A, B, and C) in region of valve obtained with intravascular ultrasound technique. Valve can be seen in closed (A1, B1, C4) and open (A2, B2, C3) positions. C1, C2, and C3 show images at various levels of valve as ultrasound catheter is pulled through valve. C1 is just before valve, C2 is just into valve, and C3 is near free margin of leaflet.

and the pressures at both ends of the vein were the same but out of phase when the mean venous flow rate was greater than 60 ml/min. The vein valve remained open during the entire cardiac cycle and the pulsatile flow through the vein was similar to that expected in any non-valved cylindrical tube such as an artery. Typical flows and pressures under such conditions are shown in Fig. 2 at a mean flow rate of 100 ml/min.

Vein valve closure and the pressure trap. As the resistance of the distal bed was increased the venous flow decreased and the vein valve began to open and close in each cardiac cycle.

This dynamic motion of the vein valve was visualized with the intravascular ultrasound technique and, perhaps for the first time, the valve of the venous conduit was seen and videotaped in a situation simulating the arterial position. The valve opened and closed rapidly in each cardiac cycle much like the semilunar cardiac valves.²⁶ The orifice of the open venous valve was almost always nearly elliptical, and never circular, unlike that of the aortic valve. Fig. 3 shows the open and closed valve, as well as the configurations of the valve leaflets at various depths through the valve.

The mean flow rate at which the valve began to close ranged from 32 ml/min to 12 ml/min. When the valve closed, it "trapped" the pressure in the segment distal to the valve. With the proximal pressure 120/80 mm Hg, systolic pressure in the distal segment was unaltered, but the diastolic pressure rose from 80 mm Hg to as high as

118 mm Hg as the venous flow decreased further. Fig. 2 shows the proximal and distal pressures as they related to the decrease of the venous flow and demonstrates the pressure trap in the distal segment as an increase in the diastolic pressure. Fig. 4 also shows the pressure trap in the segment distal to the vein valve, and Fig. 5 is a continuous recording of the pressure and flow, which also demonstrates this pressure trap.

The phenomenon of vein valve closure in bypass grafts is entirely a function of the relative resistances in the systemic vascular bed and distal (e.g., coronary) vascular bed supplied by the graft. Whenever the systemic vascular resistance is lower than the resistance of the distal vascular bed, the diastolic pressure in the proximal segment of the vein graft will fall below that in the distal segment and thereby produce a tendency for retrograde flow to occur through the graft. The retrograde flow will be stopped abruptly by closure of the vein valve and the diastolic pressure will be trapped in the distal segment. Thus the pressure trap occurs because the vein valve closes, and the vein valve closes because there is a tendency for the fluid to drain more rapidly through the proximal than through the distal vascular bed. The functioning valve, therefore, divides the vein graft into two segments: (1) a normotensive proximal segment and (2) a hypertensive distal segment (Fig. 4).

The effect of compliance, systemic pressure, and cardiac output on the vein valve closure. The maximum mean flow at which the vein valve starts to close was

Fig. 4. Schematic drawing of pressures proximal (P_1) and distal (P_2) to vein valve in conditions of poor drainage when valve begins to open and close. Elevated diastolic pressure in distal segment makes that segment hypertensive.

Fig. 5. Actual traces of pressures and flow in vein graft showing pressure trap when flow is reduced and disappearance of pressure trap when flow is restored.

determined for various compliances, systemic pressures, and cardiac outputs (Figs. 6 and 7). The compliance of 1 ml air was used in the system. One milliliter air changes the volume by only 0.04 ml for a pressure change of 80 to 120 mm Hg. If one notes that in each pulse the artery may dilate 2.5% circumferentially and about 3% longitudinally^{27, 28} and that the vein may behave similarly, then the compliance of 6 to 10 cm long vein will be equivalent to that produced by 1 ml of air.

The vein valve closed at higher mean flow rates for a higher compliance (1 ml air) than for a lower compliance (no air). For example, at the systemic pressure of 120/80 mm Hg the valve began to close at a mean flow rate of 20 ml/min for 1 ml air compliance and at 15 ml/min for

0 ml air compliance. The effect of compliance was the same at other systemic pressures and cardiac outputs (Figs. 6 and 7).

The effect of systemic pressure is shown in Fig. 6. Both at a high pressure (150/120 mm Hg) and at a low pressure (85/60 mm Hg), the mean flow at valve closure was lower than that at the normal pressure (120/80 mm Hg). It should be noted that the pulse pressure was different at these three systemic pressures. The pulse pressure was 30 and 25 mm Hg at the systemic pressures of 150/120 and 85/60 mm Hg, respectively, whereas the pulse pressure was 40 mm Hg at the systemic pressure of 120/80 mm Hg. Therefore the mean flow at closure appears to correlate better with the pulse pressure rather than with the

Fig. 6. Flow at which vein valve begins to close versus systemic pressure at cardiac output of 3 L/min. Notations 0 c.c. and 1 c.c. refer to amount of air used in compliance chamber. At all three systemic pressures increase in compliance caused valve to close at higher mean flow rates. Mean flow did not correlate directly with systemic pressure but did correlate with pulse pressure (shown in parentheses). Flow increased as pulse pressure increased.

systemic pressure. For example, the mean flow rates at closure were 20, 12, and 10 ml/min, respectively, at pulse pressures of 40, 30, and 25 mm Hg (Fig. 6), that is, the mean flow rate at valve closure decreased as the pulse pressure decreased.

The effect of cardiac output is shown in Fig. 7. The mean flow rates at valve closure increased as the cardiac output increased. For example, at 0 ml air compliance, the mean flow rate at closure increased from 15 to 16.5 to 20 ml/min as the cardiac output increased from 3 to 4 to 5 L/min, respectively. When the flow was decreased further, beyond that at which the valve first began to close, then the valve continued to open and close.

Pressure gradient versus venous flow. Because flow through the valve occurs in systole, the systolic pressures were the same on both sides of the valve. When the vein valve started to close, the pressure in the distal segment

Fig. 7. Flow at valve closure versus cardiac output at systemic pressure of 120/80 mm Hg. In general, mean flow increased with cardiac output, and at any given cardiac output mean flow increased with compliance. Notations 0 c.c. and 1 c.c. refer to amount of air used in compliance chamber.

was trapped and the diastolic pressure there became higher than that in the proximal segment (Fig. 2). A further decrease in the flow continued to trap more and more pressure distally. We have plotted the diastolic pressure gradient, that is, the difference between the diastolic pressures in the distal and the proximal segments, versus the venous flow in Figs. 8 and 9. There are three important observations to be made from these figures. First, as the venous flow decreased the diastolic pressure gradient increased with the distal diastolic pressure becoming higher all the time. The maximum gradient attainable in these experiments equaled the pulse pressure, that is, when there is no distal drainage, the distal segment will have the systolic pressure throughout the cardiac cycle whereas the proximal segment will have the normal systolic-diastolic pressure fluctuations. Second, with increasing compliance, the diastolic pressure gradient will increase proportionally at any given venous flow rate (compare Figs. 8 and 9). Third, different veins have dif-

Fig. 8. Difference ($\Delta P [P_2 - P_1]$) in diastolic pressures proximal (P_1) and distal (P_2) to valve versus venous mean flow. Diastolic pressure gradient increased as venous flow decreased. CO, Cardiac output.

ferent flows at the start of the valve closure and different diastolic gradients for a given venous flow. These differences could be due to their various geometry (length, diameter, thickness) and individual elastic properties that result in different compliances. In the present study the length of the vein segment distal to the valve was variable and was not measured. This by itself produced different compliances in the system.

Discussion

In the past, the phenomenon of pressure trap caused by the presence of the vein valve has gone unnoticed. The present study has brought this important phenomenon into focus by establishing that competent valves in saphenous vein bypass grafts cause hypertension in the portion of the graft distal to the valve whenever flow in the graft falls below some critical level, at which point there is a reversal of the normal forward pressure gradient and consequent closure of the valve.

Fluid dynamics and pressure trap in saphenous vein grafts. In conditions of high mean flow rates (>60 ml/min) the saphenous vein graft with a valve behaves like a cylindrical tube (e.g., artery). When the venous flow rate begins to decrease, the venous valve begins to open and close and the leaflet movement appears similar to that reported for the aortic valve.²⁶ The orifice of the open venous valve, however, is elliptical, whereas that of the aortic valve is circular.²⁶ This difference may relate to the

Fig. 9. Diastolic pressure gradient ($\Delta P [P_2 - P_1]$) versus venous flow. Gradient increased as flow decreased. Vein grafts 1, 2, 3, and 4 are same as those shown in Fig. 8. Note that greater compliance shown in Fig. 8 meant greater starting flows. Both figures also show that different veins have different starting flows. Relationship between flow and gradient appears almost linear. CO, Cardiac output.

number of leaflets in the valve; that is, the aortic valve has three leaflets whereas the venous valve has only two leaflets.

The closure of the venous valve is related to the tendency of reverse flow to occur through the vein graft. Once the valve is closed the pressure distal to the valve remains trapped and the decay of the pressure is controlled solely by the drainage through the distal bed. As the resistance of the distal bed increases, the flow through the vein graft decreases and the decay of the distal pressure slows down, which leads to a greater amount of pressure being trapped. Thus the less the flow through the vein, the greater the difference in the diastolic pressures between the distal and the proximal segments (Figs. 8 and 9). Many investigators have observed that the presence of the vein valve results in augmentation of forward flow.^{15, 20-22} Phillips, Okies, and Starr¹⁵ reported that in patients the forward coronary flow may be augmented by as much as 29% to 31% if the valve is present in the vein graft compared with flows when the valve is absent. Baba and associates²⁰ reported that in dogs when the vein graft was placed in a left anterior descending coronary artery position there was an 11% increase in the forward flow with the valve present compared with the flow without a valve. These investigators also suggested that the augmentation occurs because of the increase in forward flow and prevention of reverse flow.^{15, 20-22} It is obvious that the reported augmentation of flow occurs because of the

pressure trap, that is, with the valve closed there is greater pressure in the distal vein segment to drive the flow through the distal vascular bed and hence to augment the forward flow. These investigators did have the pressure trap occurring in their experiments, but it went unnoticed.

The flow rates at which the vein valve begins to close (that is, 25 to 35 ml/min) are in the range of flow rates seen in the vein graft in vivo in both the coronary artery bypass position and femoropopliteal bypass position. Graft flow rates have been reported ranging from 14 to 180 ml/min in the coronary^{15, 18, 23} and 13 to 190 ml/min^{6, 24} in the femoropopliteal positions. When low flow rates occur in patients, then not only will the vein valve close but it will also trap pressure and create a diastolic pressure gradient across the valve of 15 to 30 mm Hg (Figs. 8 and 9).

In our observations, flow at valve closure correlated well with the pulse pressure rather than with the mean pressure (Fig. 6). Also, the flow at closure increased as the cardiac output increased (Fig. 7). However, it should be noted that the pulse rates were higher at higher cardiac outputs and that the pulse rate by itself could influence the flow at closure.

We have observed that different veins have different flows at the start of valve closure and that these differences may be attributed to their different diameters, total lengths, length of the segment distal to the valve, valve geometry, and compliance. Such differences are expected to be present also in vivo. It may also be noted that removal of the valve abolishes the pressure trap and that the phenomenon of the pressure trap occurs even with blood as a fluid in this system, as observed in our subsequent experiments.

The possible role of the pressure trap in vein graft atherosclerosis. Vein grafts undergo adaptive intimal hyperplasia as a result of their exposure to arterial pressure and flow. We postulate that in a manner similar to that in *car* in vitro studies, the vein valve also opens and closes in vivo and creates a pressure trap, which makes the segment of the vein distal to the valve hypertensive. Furthermore, in vivo, forces such as myocardial contraction or compression by the leg muscle may indeed produce reverse flow through the graft, in which case the trapped pressure in the graft may far exceed the systolic pressure. Because the vein is already undergoing adaptive hypertrophic changes, the hypertension in the distal segment may exacerbate these changes. Even if some of the vein valves were to start to disappear at the end of 1 to 2 years, they will leave the valve remnants behind. The valve

remnants could become the sites of endothelial damage, microthrombus formation, and platelet aggregation. The enhanced proliferative changes in the distal segment of the graft could add to the changes at the valve remnant site or to the changes in the functioning valve, which could then lead to stenosis at the valve site. This mechanism of graft stenosis could be responsible for the reported 20% graft failure rate in the first year of implantation^{8, 10, 18} and for the graft stenosis in subsequent years.

Schwartz and colleagues²⁹ reported that in rabbits myointimal thickening in the vein graft was due mainly to intraluminal pressure or wall tension and was independent of blood flow or shear stress. Kohler, Kirkman, and Clowes³⁰ observed that smooth muscle cell mass and matrix deposition in vein grafts in rabbits were reduced when the wall stress was reduced. Our previous studies have emphasized that the wall stress caused by luminal pressure is a major contributing factor to atherosclerosis in both the rabbit model^{27, 31-35} and in human beings^{36-37a} and that the reduction of wall stress reduces both endothelial injury^{38, 39} and atherosclerosis.^{32, 33} In the studies of Bercell and associates,⁴⁰ uptake of low-density lipoproteins was two to three times greater in the vein grafts subjected to arterial pressure and flow than in controls grafts, and Finck and colleagues⁴¹ reported a similar increase in the albumin permeability in vein grafts. Born⁴² has also emphasized the role of wall stress in atherosclerosis. These observations support the hypothesis that the pressure trap in the vein graft could have deleterious effects on graft patency.

We thank Shekhar Patil for his technical assistance in some of these experiments.

REFERENCES

1. Ejrup B, Hierton T, Moberg A. Atheromatous changes in autogenous venous grafts: functional and anatomical aspects [case report]. *Acta Chir Scand* 1961;121:211-8.
2. Beebe HG, Clark WF, DeWeese JA. Atherosclerotic change occurring in an autogenous venous arterial graft. *Arch Surg* 1970;101:85-8.
3. Grondin CM, Meere C, Castonguay Y, Lepage G, Grondin P. Progressive and late obstruction of an aorto-coronary venous bypass graft. *Circulation* 1971;43:698-702.
4. Lawrie GM, Morris GC Jr, Chapman DW, Winters WL, Lie JT. Patterns of patency of 596 vein grafts up to seven years after aorta-coronary bypass. *J THORAC CARDIOVASC SURG* 1977;73:443-8.
5. Lawrie GM, Lie JT, Morris GC Jr, Beazley HL. Vein graft patency and intimal proliferation after aortocoronary

- bypass: early and long-term angiopathologic correlations. *Am J Cardiol* 1976;38:856-62.
6. Mundth ED, Darling RC, Moran JM, Buckley MJ, Linton RR, Austen WG. Quantitative correlation of distal arterial outflow and patency of femoropopliteal reversed saphenous vein grafts with intraoperative flow and pressure measurements. *Surgery* 1969;65:197-206.
7. Szilagyi DE, Elliott JP, Hageman JH, Smith RF, Dall'Olmo CA. Biologic fate of autogenous vein implants as arterial substitutes: clinical, angiographic and histopathologic observations in femoral-popliteal operations for atherosclerosis. *Ann Surg* 1973;178:232-46.
8. Grondin CM, Lespérance J, Bourassa MG, Pasternac A, Campeau L, Grondin P. Serial angiographic evaluation in 60 consecutive patients with aorto-coronary artery vein grafts 2 weeks, 1 year, and 3 years after operation. *J THORAC CARDIOVASC SURG* 1975;67:1-6.
9. DeWeese JA, Terry R, Barner HB, Rob CG. Autogenous venous femoropopliteal bypass grafts. *Surgery* 1966;59:28-39.
10. Bourassa MG, Lespérance J, Campeau L, Simard P. Factors influencing patency of aortocoronary vein grafts. *Circulation* 1972;45 and 46(Suppl):179-85.
11. Kalan JM, Robert WC. Morphologic findings in saphenous veins used as coronary arterial bypass conduits for longer than 1 year: necropsy analysis of 53 patients, 123 saphenous veins, and 1865 five-millimeter segments of veins. *Am Heart J* 1990;119:1164-84.
12. Whitney DG, Kahn EM, Estes JW. Valvular occlusion of the arterialized saphenous vein. *Ann Surg* 1976;42:879-87.
13. Mills NL, Ochsner JL. Valvulotomy of valves in the saphenous vein graft before coronary artery bypass. *J THORAC CARDIOVASC SURG* 1976;71:878-9.
14. Singh RN. Flow disturbance due to venous valves: a cause of graft failure. *Cathet Cardiovasc Diagn* 1986;12:35-8.
15. Phillips SJ, Okies JE, Starr A. Improvement in forward coronary blood flow by using a reversed saphenous vein with a competent valve. *Ann Thorac Surg* 1976;21:12-5.
16. Bond MG, Hostetler JR, Karayannacos PE, Geer JC, Vasko JS. Intimal changes in arteriovenous bypass grafts: effects of varying the angle of implantation at the proximal anastomosis and of producing stenosis in the distal runoff artery. *J THORAC CARDIOVASC SURG* 1976;71:907-16.
17. Boshier LP, Deck JD, Thubrikar MJ, Nolan SP. Role of the venous valve in late segmental occlusion of vein grafts. *J Surg Res* 1979;26:437-46.
18. Urschel HC, Razzuk MA, Wood RE, Paulson DL. Factors influencing patency of aortocoronary artery saphenous vein grafts. *Surgery* 1972;72:1048-63.
19. Mills NL. Saphenous vein graft valves: "the bad guys." *Ann Thorac Surg* 1989;48:613-4.
20. Baba H, Djordjevic M, Kiso I, et al. Hemodynamic effects of venous valves in aorto-coronary bypass grafts. *J THORAC CARDIOVASC SURG* 1976;71:774-8.
21. Weissenhofer W, Schueller EF, Schenk GW Jr. The fate of venous valves in the arterial tree. *J Surg Res* 1974;17:200-3.
22. Phillips SJ. The augmentation of peripheral forward blood flow by prevention of flow reversal with a vein valve. *J THORAC CARDIOVASC SURG* 1971;61:746-51.
23. Stinson EB, Olinger GN, Glancy DL. Anatomical and physiological determinants of blood flow through aortocoronary vein bypass grafts. *Surgery* 1973;74:390-400.
24. Barner H, Judd DR, Kaiser GC, Willman VS, Hanlon CR. Blood flow in femoropopliteal bypass vein grafts. *Arch Surg* 1968;96:619-27.
25. Kakos GS, Oldham HN Jr, Dixon SH Jr, Davis W, Hagen PO, Sabiston DC Jr. Coronary artery hemodynamics after aorto-coronary artery vein bypass: an experimental evaluation. *J THORAC CARDIOVASC SURG* 1972;63:849-53.
26. Thubrikar MJ. Dynamics of the aortic valve. In: *The aortic valve*. Boca Raton, Fla.: CRC Press, 1990:39-49.
27. Thubrikar MJ, Roskelley SK, Eppink RT. Study of stress concentration in the walls of the bovine coronary arterial branch. *J Biomech* 1990;23:15-26.
28. McDonald DA. The elastic properties of the arterial wall. In: *Blood flow in arteries*. Baltimore: Williams & Wilkins, 1974:238-282.
29. Schwartz LB, O'Donohoe MK, Purut CM, Mikat EM, Hagen PO, McCann RL. Myointimal thickening in experimental vein grafts is dependent on wall tension. In: *Proceedings of the Thirty-ninth Scientific meeting of The International Society for Cardiovascular Surgery, Scientific Sessions*. International Society for Cardiovascular Surgery, 1991:40-1.
30. Kohler TR, Kirkman TR, Clowes AW. The role of wall stress in vein graft thickening. In: *Program Book of the International Society for Cardiovascular Surgery*. [Abstract]. 1988:40.
31. Thubrikar MJ, Manuel L, Eppink RT. Intramural stress at arterial bifurcation in vivo. In: *Proceedings of the Fortieth Annual Conference on Engineering in Medicine and Biology*. Niagara Falls, 1987;29:208.
32. Thubrikar MJ, Nolan SP. Prevention of atherosclerosis by reduction of arterial intramural stress in rabbits [Abstract]. *Fed Proc* 1987;46:720.
33. Thubrikar MJ, Baker JW, Nolan SP. Inhibition of atherosclerosis associated with reduction of arterial intramural stress in rabbits. *Arteriosclerosis* 1988;8:410-20.
34. Thubrikar MJ, Baker JW, Nolan SP. Effect of reduced arterial intramural stress on atherosclerosis and endothelial morphology [Abstract]. *Medical and Biological Engineering and Computing*. *J Int Fed Med Biol Eng* 1991;20(2 Pt 2):267.
35. Thubrikar MJ, Eppink RT, Nolan SP. Wall stress as a major contributor to atherosclerosis. [Abstract]. *Physics in Medicine and Biology*. *J Int Org Med Phys* 1988;33(Suppl):1252.
36. Thubrikar MJ, Salzar RS, Eppink RT. Correlation between intramural stress and atherosclerotic lesions in

- human carotid artery bifurcation [Abstract]. *Arteriosclerosis* 1990;10:821a.
37. Robicsek R, Thubrikar MJ. Freedom from atherosclerosis of intramyocardial coronary arteries and its relation to mural stress [Abstract]. *Circulation* 1992;86(Suppl):I180.
  - 37a. Robicsek R, Thubrikar MJ. The freedom from atherosclerosis of intramyocardial coronary arteries: reduction of mural stress—a key factor. *Eur J Cardiothorac Surg* [In press].
  38. Baker JW, Thubrikar MJ, Parekh JS, Forbes MS, Nolan SP. Change in endothelial cell morphology at arterial branch sites caused by a reduction of intramural stress. *Atherosclerosis* 1991;89:209-21.
  39. Thubrikar MJ, Baker JW, Parekh JS, Forbes MS, Nolan SP. Effect of arterial wall stress on endothelial cell morphology [Abstract]. *FASEB J* 1989;3:A1216.
  40. Bercell SA, Sheppeck R, Moosa HH, et al. Mechanisms of vein graft atherosclerosis: LDL metabolism and endothelial cytoskeletal reorganization [Abstract]. In: *Proceedings of the SVS/ISCVS Joint Annual Meeting*. 1990:50.
  41. Finck SJ, Mashburn JP, Kottke BA, Orszulak TA. Evaluation of arterialized vein graft permeability with Evans blue dye and iodine 125—labeled albumin. *Ann Thorac Surg* 1989;48:646-50.
  42. Born GVR. The carotid plaque in extracranial cerebrovascular disease. In: Robicsek F, ed. *Extracranial cerebrovascular disease: diagnosis and treatment*. New York: Macmillan Publishing, 1986:36-46.

Bound volumes available to subscribers

Bound volumes of *THE JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY* are available to subscribers (only) for the 1994 issues from the Publisher, at a cost of \$82.50 for domestic, \$106.28 for Canadian, and \$100.50 for international subscribers for Vol. 107 (January-June) and Vol. 108 (July-December). Shipping charges are included. Each bound volume contains a subject and author index and all advertising is removed. Copies are shipped within 60 days after publication of the last issue of the volume. The binding is durable buckram with the JOURNAL name, volume number, and year stamped in gold on the spine. *Payment must accompany all orders*. Contact Mosby-Year Book, Inc., Subscription Services, 11830 Westline Industrial Drive, St. Louis, Missouri 63146-3318, USA; phone 1 (800) 453-4351 or (314) 453-4351.

Subscriptions must be in force to qualify. Bound volumes are not available in place of a regular JOURNAL subscription.