Artificial Venous Valve

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Abstract

Chronic venous insufficiency - or CVI - is a very common medical condition in which veins in the legs cannot pump enough oxygen-poor blood back to the heart. It is caused by faulty valves within the leg veins, and causes blood to pool in the legs, which can lead to edemas and even open ulcers. Typically, treatment consists of anti-inflammatory drugs and diuretics, along with the use of items such as compression stockings. Now scientists have developed a method of mass-producing artificial venous valves, that could replace the malfunctioning natural ones. According to the researchers, the artificial valves could be implanted in the leg veins via a catheter inserted through the patient's skin. There is no word at this point on clinical trials or availability. End-stage deep venous insufficiency is unrelenting venous hypertension with sequelae, and no standard option is available, or all options have been tried and found wanting. In such cases, there is an opportunity for an artificial venous valve to be used as a native valve. For decades, substitute valves have been studied experimentally, raising hope of bench-to-bedside transfer. Venous valves have been made entirely of non-

autologous tissues: synthetics, xenografts, or allografts. Many have failed in early experimental evaluation, with some advancing to the clinical arena, but few remain in research and development. However, the majority of these valve studies await confirmation by other investigators over extended periods.

1. Introduction

In the circulatory system, veins (from the Latin vena) are blood vessels that carry blood toward the heart. Most veins carry deoxygenated blood from the tissues back to the heart; exceptions are the pulmonary and umbilical veins, both of which carry oxygenated blood to the heart. Veins differ from arteries in structure and function; for example, arteries are more muscular than veins, veins are often closer to the skin and contain valves to help keep blood flowing toward the heart, while arteries carry blood away from the heart. In general, veins function to return deoxygenated blood to the heart, and are essentially tubes that collapse when their lumens are not filled with blood. The thick outermost layer of a vein is made of connective tissue, called tunica adventitia or tunica externa. There is a middle layer of bands of smooth muscle called tunica media, which are, in general, thin, as veins do not function primarily in a contractile manner. The interior is lined with endothelial cells called tunica intima. The precise location of veins is much more variable from person to person than that of arteries [1]. Veins often

display a lot of anatomical variation compared with arteries within a species and between species. Most veins are equipped with valves to prevent reverse blood flow. The valves were described by Jacques Dubois, but their true function was later discovered by William Harvey [2]. The largest veins in the human body are the venae cavae. The superior vena cava caries blood from the arms and head to the right atrium of the heart. The inferior vena cava carries blood from the legs and abdominal to the heart. The inferior vena cava is retroperitoneal and runs to the right and roughly parallel to the abdominal aorta along the spine. The pulmonary veins carry relatively oxygenated blood from the lungs to the heart. The superior and inferior venae cavae carry relatively deoxygenated blood from the upper and lower systemic circulations, respectively. The portal venous system is a series of veins or venules that directly connect two capillary beds. Examples of such systems include the hepatic portal vein and hypophyseal portal system. Veins are classified in a number of ways, including superficial vs. deep, pulmonary vs. systemic, and large vs. small. Superficial veins are those whose course is close to the surface of the body, and have no corresponding arteries, whereas Deep veins are deeper in the body and have corresponding

arteries. Communicating veins (or perforator veins) are veins that directly connect superficial veins to deep veins.The pulmonary veins are a set of veins that deliver oxygenated blood from the lungs to the heart. Systemic veins drain the tissues of the body and deliver deoxygenated blood to the heart. Veins are translucent, so the color a vein appears from an organism's exterior is determined in large part by the color of venous blood, which is usually dark red as a result of its low oxygen content. Veins appear blue because the subcutaneous fat absorbs low-frequency light, permitting only the highly energetic blue wavelengths to penetrate through to the dark vein and reflect back to the viewer. A study found the color of blood vessels is determined by the following factors: the scattering and absorption characteristics of skin at different wavelengths, the oxygenation state of blood, which affects its absorption properties, the diameter and the depth of the vessels, and the visual perception process [3]. Veins return blood to the heart from all the organs of the body. The large veins parallel the large arteries and often share the same name, but the pathways of the venous system are more difficult to trace than those of the arteries. Many unnamed small veins form irregular networks and connect with the large veins. Many

veins, particularly those in the arms and legs, have one-way valves. Each valve consists of two flaps (cusps or leaflets) with edges that meet. Blood, as it moves toward the heart, pushes the cusps open like a pair of one-way swinging doors. If gravity or muscle contractions try to pull the blood backward or if blood begins to back up in a vein, the cusps are pushed closed, preventing backward flow. Thus, valves help the return of blood to the heart—by opening when the blood flows toward the heart and closing when blood might flow backward because of gravity.

The main problems that affect the veins include the following:

1. Abnormal connections of the arterial blood flow into veins called arteriovenous malformations or shunts, which are present at birth
2. Inflammation
3. Clotting
4. Defects that lead to swelling (distention) and varicose veins

The veins in the legs are particularly affected because when a person is standing, blood must flow upward from the leg veins, against gravity, to reach the heart. The body has superficial veins, located in the fatty layer under the skin, and deep veins, located in the muscles and along the bones. Short veins, called connecting veins, link the superficial and deep veins. The deep veins play a significant role in propelling blood toward the heart. The one-way valves in deep veins prevent blood from flowing backward, and the muscles surrounding the deep veins compress them, helping force the blood toward the heart, just as squeezing a toothpaste tube ejects toothpaste. The powerful calf muscles are particularly important, forcefully compressing the deep veins in the legs with every step. The deep veins carry 90% or more of the blood from the legs toward the heart.

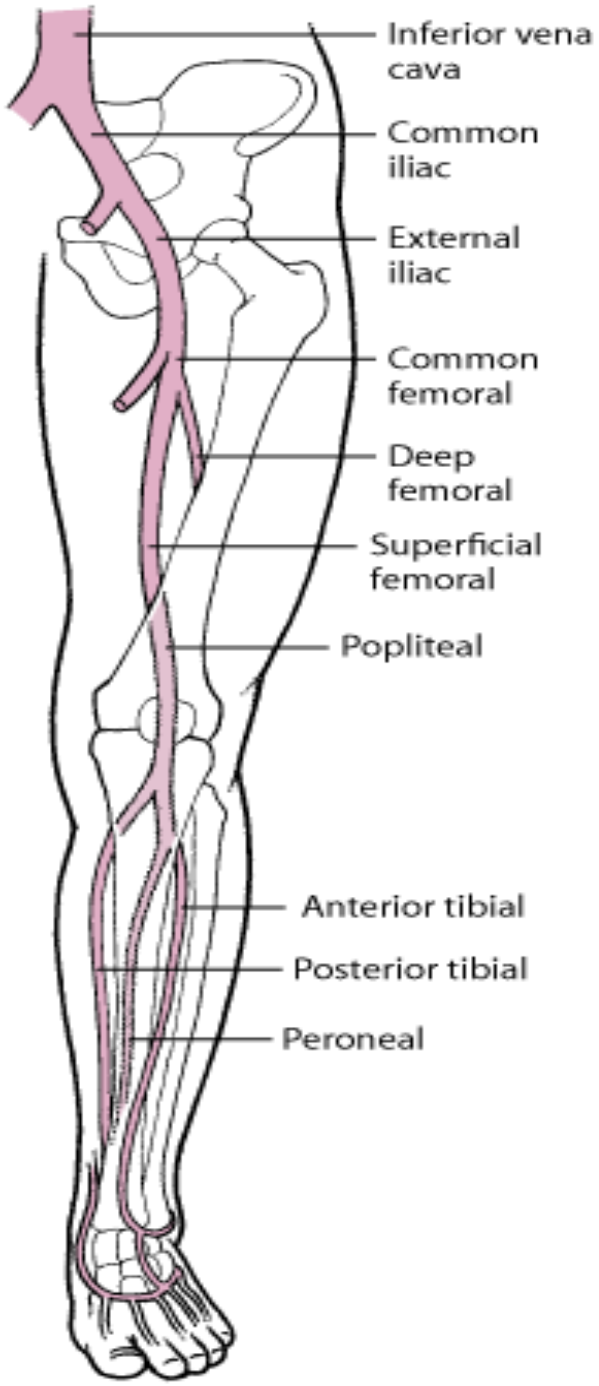

Figure 2: Deeo Veins of the Legs

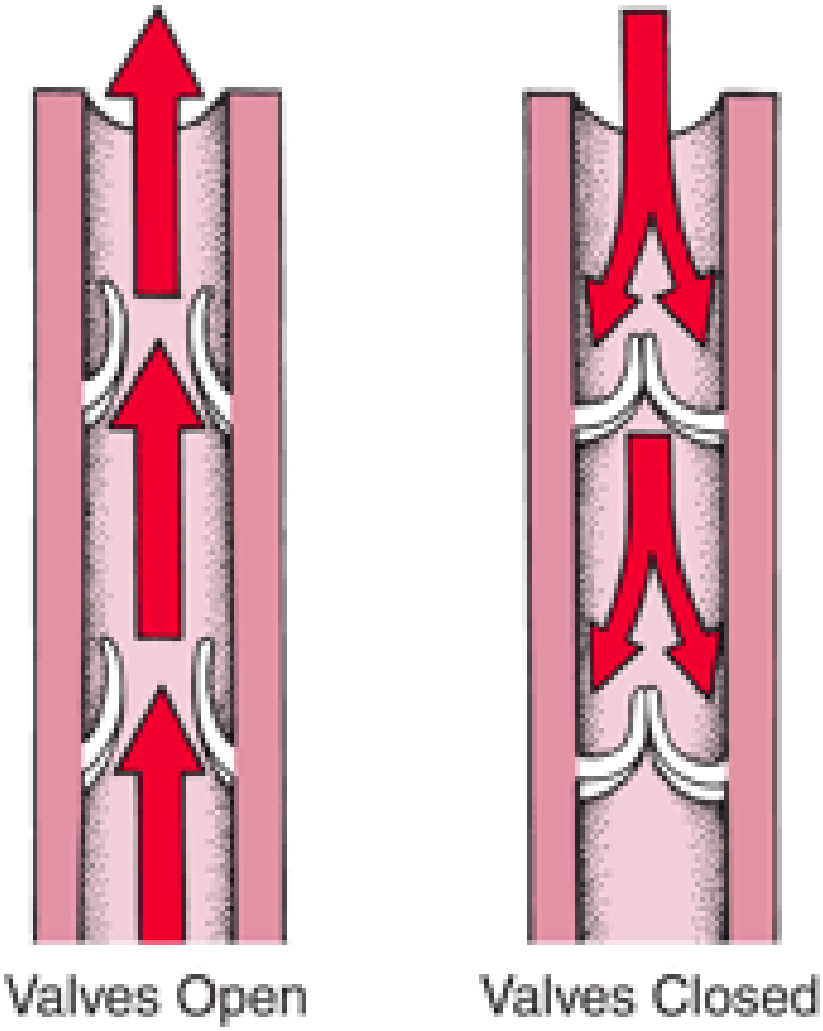

Figure 2: One-Way Valves in the Veins

One-way valves consist of two flaps (cusps or leaflets) with edges that meet. These valves help veins return blood to the heart. As blood moves toward the heart, it pushes the cusps open like a pair of one-way swinging doors (Figure 2. shown on the left). If gravity momentarily pulls the blood backward or if blood begins to back up in a vein, the cusps are immediately pushed closed, preventing backward flow (Figure 2. shown on the right).

2. Venous valves

Any of the small cusps or folds found in the tunica intima of many veins, serving to prevent backflow of blood [4]. Most of our blood volume is carried in the veins (64%). Veins can expand to hold large amounts of blood. Veins are blood vessels that carry blood from the body back to the heart. Blood return from the legs occurs mainly through the deep veins. Within the veins, especially those of the legs are valves. Venous valves are bicuspid (two) flap like structures made of elastic tissue. The valves function to keep blood moving in one direction. Once the blood has passed from the arteries through the capillaries, it is flowing at a slower rate because little pressure remains to move the blood along. Blood flow in the veins below the heart is helped back up to the heart by the muscle pump. The walls of the veins are thin and somewhat floppy. To compensate for this many veins are located in the muscles.

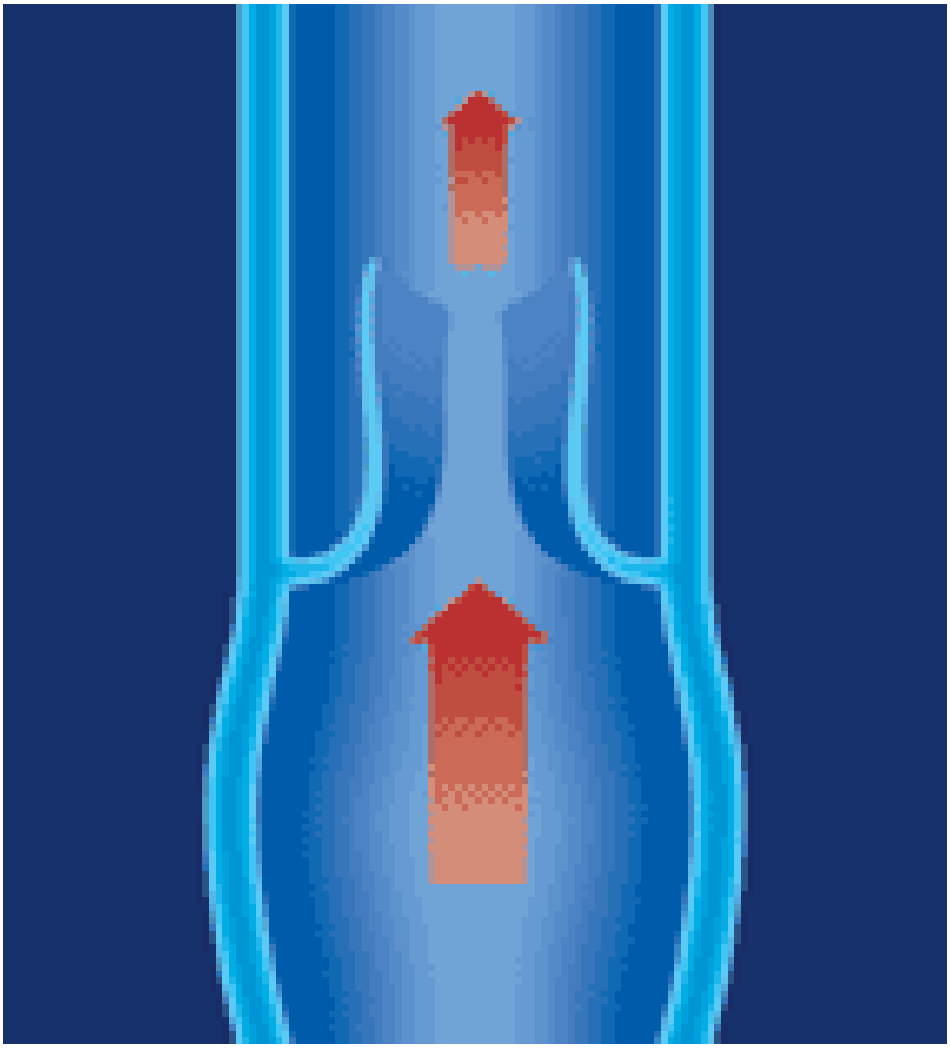

Figure 3: Valves open when muscles contract allowing blood to return to the heart

The flow of blood in the venous system is complex for several reasons: the low pressure within the veins, flow rates that vary from high (during muscle contraction) to almost no flow during quiet standing or sitting positions, the effects of gravity, the collapsible nature of the venous wall, the presence of valves, and the large volume of blood carried in the veins. Movement of the leg squeezes the veins, which pushes the blood toward the heart. When the muscles contract the blood within the veins is squeezed up the vein and the valves open.

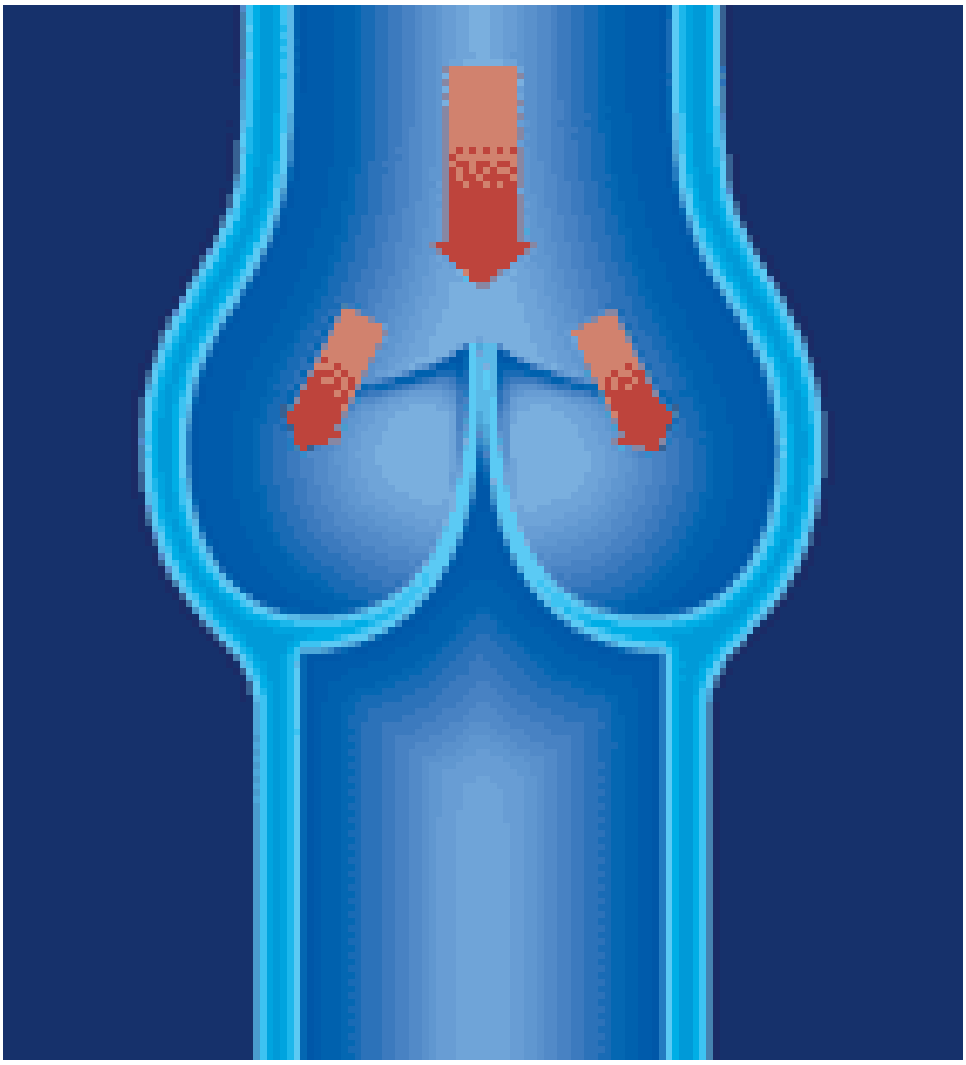

Figure 4: Valves close when muscles relax Blood can not flow backwards

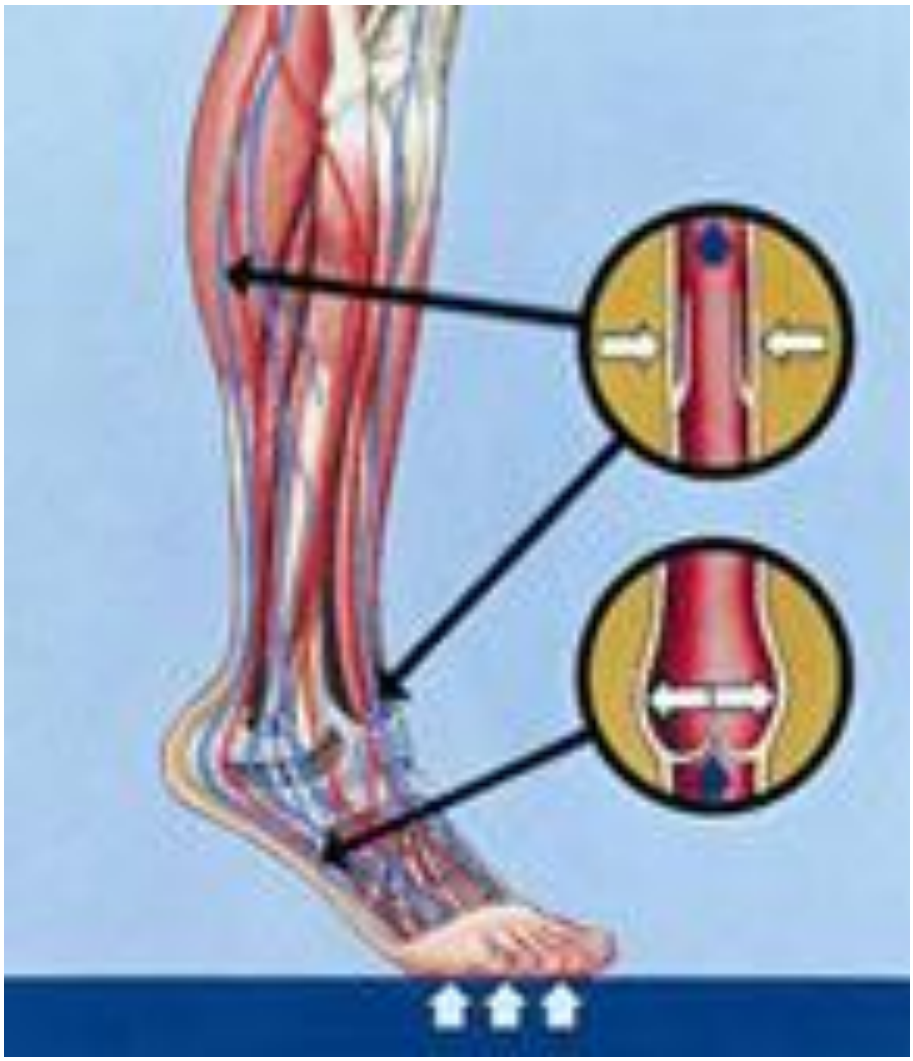

Figure 5: The veins carry oxygen depleted blood back to the heart from the rest of the body

When the muscle is at rest, the valves close helping to prevent the backward flow of blood. This is referred to as the muscle pump [5]. In the legs, the veins have to fight gravity to deliver the blood back. This is aided by the surrounding muscles when a person is walking or doing other activities. When a person stands still or sits, the pumping motion of the blood stops, and the blood tries to move backwards. The venous valves are in place to block this backwards motion, also called reflux [6].

3. Role of venous valves

Blood flow in the major veins of the lower extremity depends, in part, on the pumping action produced by leg muscle contractions. Retrograde flow is prevented by venous valves [7].

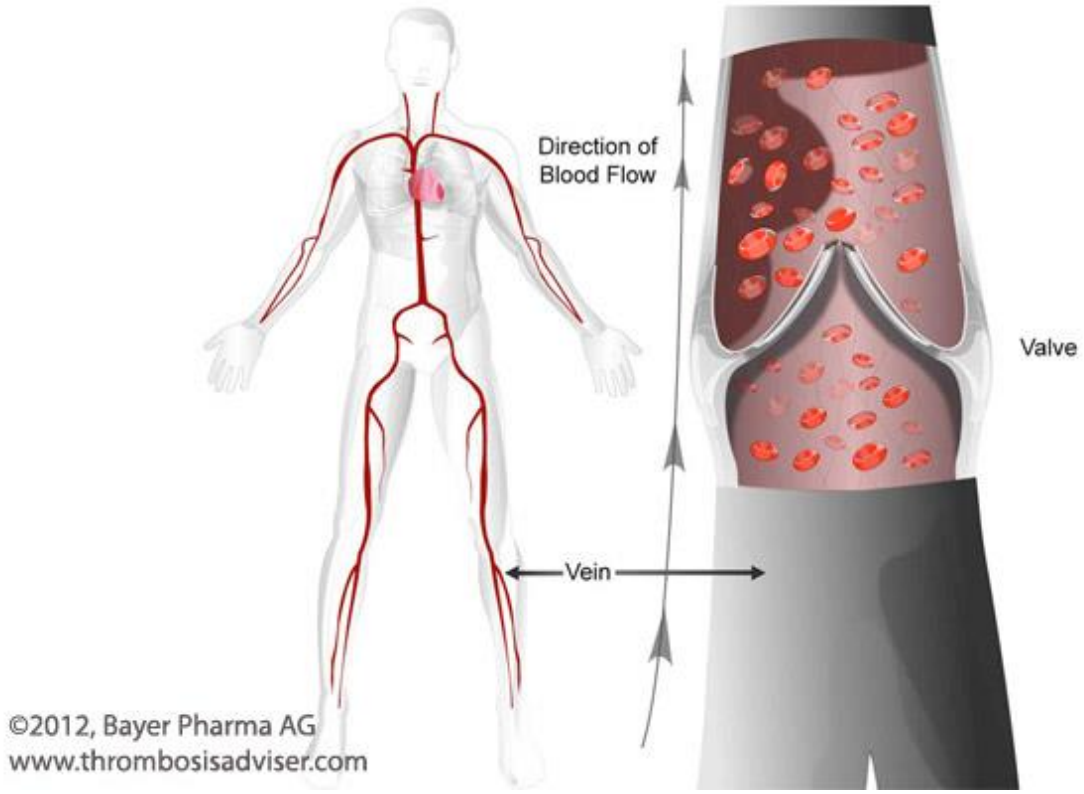

Figure 6: Role of venous valves

4. Venous problems

Spider veins are a common minor problem. These are small red or purplish dilated end vessels. While they may be unattractive they pose no harm. Other venous problems may cause leg discomfort, leg swelling, and in severe cases skin breakdown. Vein problems affect both men and women and are more likely to occur the older we age.

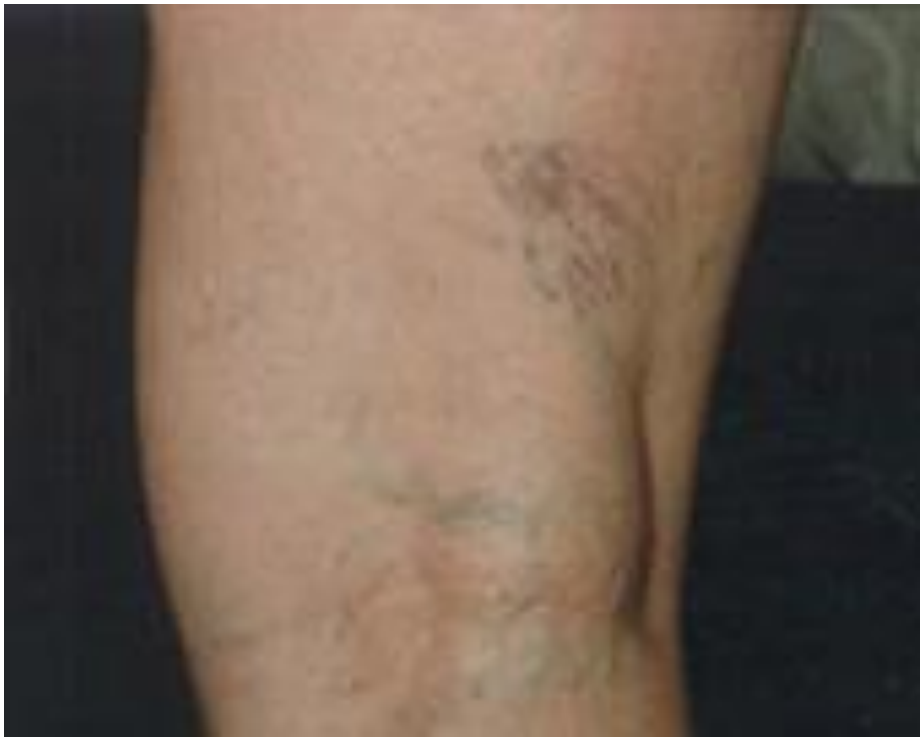

Figure 7: Spider veins

The walls of a vein may be weak and bulge and twist as with varicose veins. When veins continually over-expand the valves fail to close properly. Venous blood then falls backwards putting more pressure on the valves below. Eventually these valves may also weaken and pooling or venous congestion results while standing or sitting.

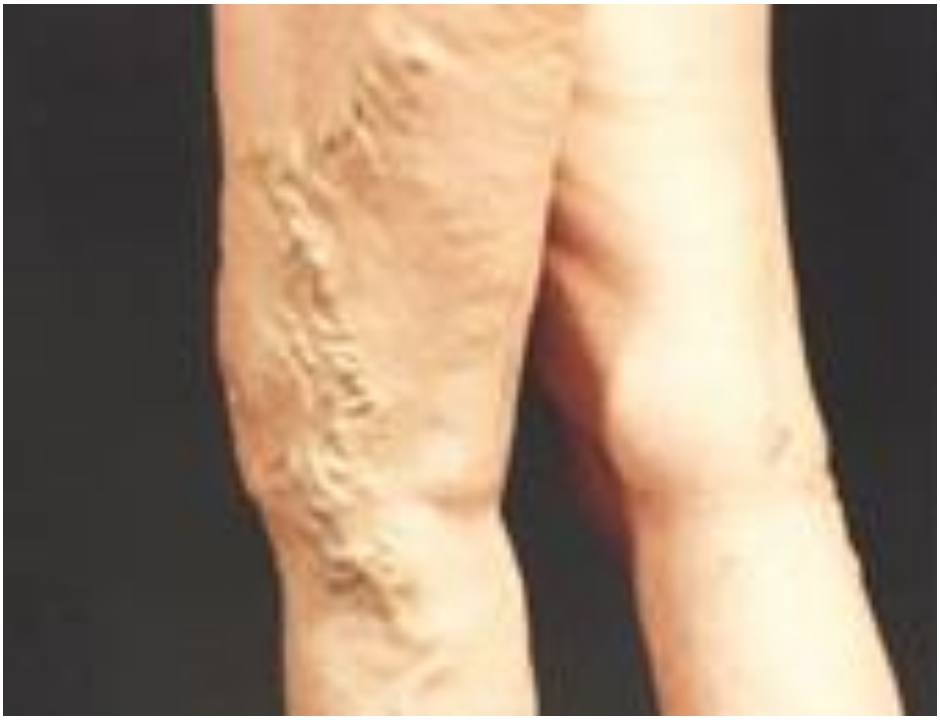

Figure 8: Varicose vein

A blood clot in a deep vein (DVT) most often occurs near a venous valve. The DVT can permanently damage the vein wall and valve. Damage, scarring or fibrosis to the vein wall and valve cause them to become incompetent resulting in reflux (backward) flow of blood and venous congestion [8].

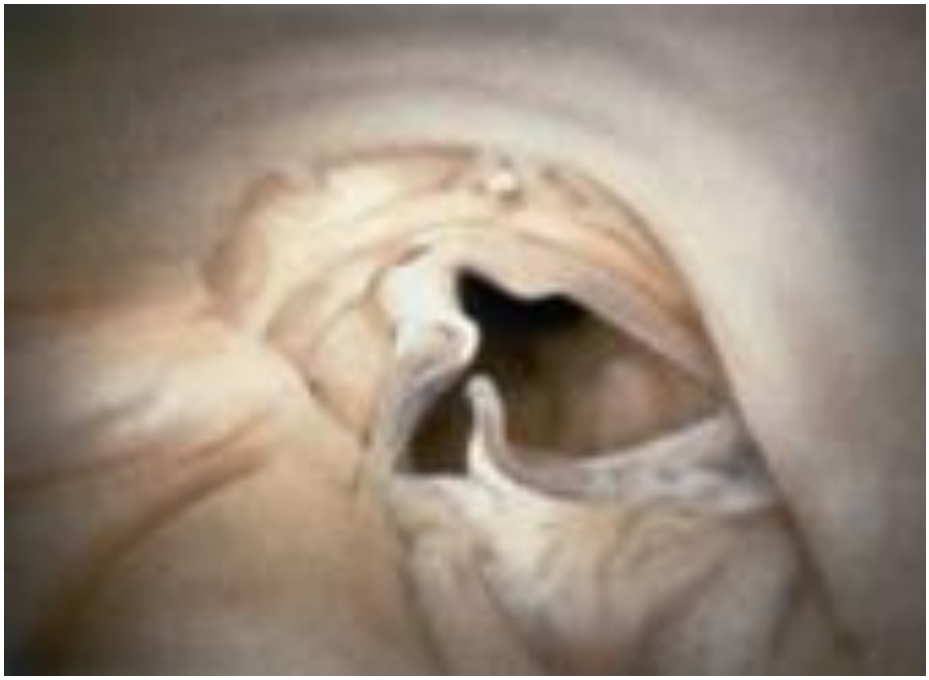

Figure 9: Damaged venous valve

5. Venous insufficiency

Venous insufficiency is a condition in which the veins have problems sending blood from the legs back to the heart.

5.1. Causes

Normally, valves in your deeper leg veins keep blood moving forward toward the heart. With chronic venous insufficiency, vein walls are weakened and valves are damaged. This causes the veins to stay filled with blood, especially when you are standing. Chronic venous insufficiency is a long-term condition. It occurs because a vein is partly blocked, or blood is leaking around the valves of the veins.

Risk factors for venous insufficiency include:

1. Age
2. Being female (related to levels of the hormone progesterone)
3. Being tall
4. Family history of this condition
5. History of deep vein thrombosis in the legs

6. Obesity
7. Pregnancy
8. Sitting or standing for a long periods

5.2. Symptoms

1. Dull aching, heaviness, or cramping in legs
2. Itching and tingling
3. Pain that gets worse when standing
4. Pain that gets better when legs are raised
5. Swelling of the legs
6. Redness of the legs and ankles
7. Skin color changes around the ankles
8. Varicose veins on the surface (superficial)
9. Thickening and hardening of the skin on the legs and ankles (lipodermatosclerosis)
10. Ulcers on the legs and ankles
11. Wound that is slow to heal on the legs or ankles

6. Exams and tests

Your doctor will do a physical exam and ask about your symptoms and medical history. Diagnosis is often made based on the appearance of leg veins when you are standing or sitting with your legs dangling.

A duplex ultrasound exam of your leg may be ordered to:

1. Check blood flow in the veins
2. Rule out other problems with the legs, such as a blood clot

7. Treatment

Your doctor may suggest that you take the following self-care steps to help manage venous insufficiency:

1. Wear compression stockings to decrease swelling.
2. Do not sit or stand for long periods. Even moving your legs slightly helps keep the blood flowing.
3. Care for wounds if you have any open sores or infections.
4. Lose weight if you are overweight.

If your condition is severe, your doctor may recommend the following treatments:

1. Sclerotherapy: Salt water (saline) or a chemical solution is injected into the vein. The vein hardens and then disappears.
2. Ablation: Heat is used to close off and destroy the vein. The vein disappears over time.
3. Vein stripping: Small surgical cuts (incisions) are made in the leg near the damaged vein. The vein is removed through one of the incisions.

4. Bypass: This is surgery to reroute blood flow around the blocked vein. A tube or blood vessel taken from your body is used to make a detour around, or bypass, the damaged vein.
5. Valve repair: A small incision is made in the leg and the damaged valve is repaired.
6. Angioplasty and stenting: This is a procedure to open a narrowed or blocked vein. Angioplasty uses a tiny medical balloon to widen the blocked vein. The balloon presses against the inside wall of the vein to open it and improve blood flow. A tiny metal mesh tube called a stent is then placed inside the vein to it from narrowing again.

Surgery (varicose vein stripping) or other treatments for varicose veins may be recommended if you have:

1. Leg pain, which may make your legs feel heavy or tired
2. Skin sores caused by poor blood flow in the veins
3. Thickening and hardening of the skin on the legs and ankles (lipodermatosclerosis)

8. What causes CVI?

Over the long-term, blood pressure that is higher than normal inside your leg veins causes CVI. This can lead to damage to the valves, which can further worsen the problem. In some instances, the valves that prevent blood from flowing "backwards," can be congenitally defective. Other causes of CVI include deep vein thrombosis (DVT) and phlebitis, both of which cause elevated pressure in your veins by obstructing the free flow of blood through the veins.

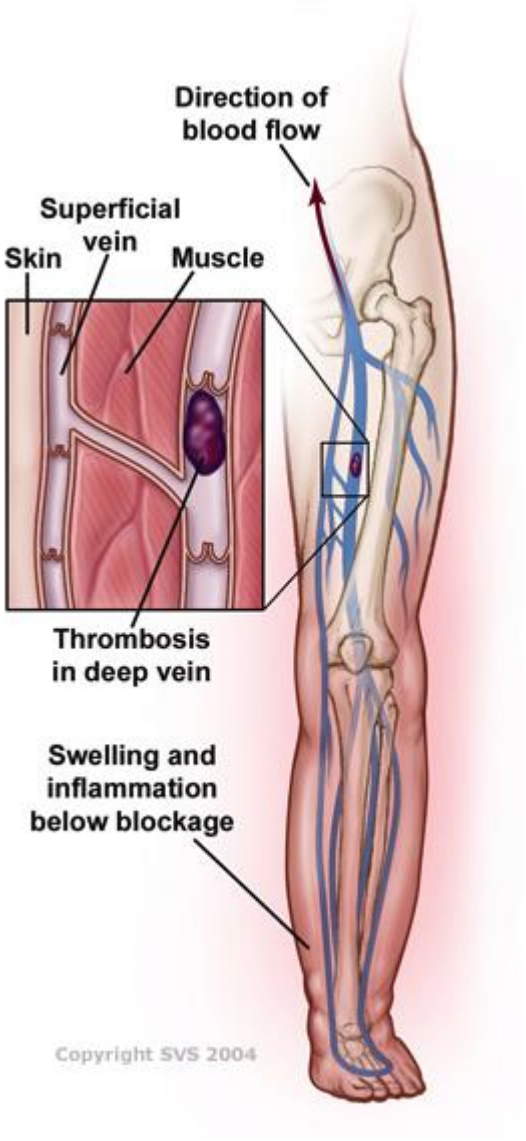

Figure 10: Thrombosis in deep vein

DVT occurs when a blood clot (properly called a thrombus) blocks blood from flowing toward the heart, out of a deep or perforating vein. The blood trying to pass through the blocked veins can increase the blood pressure in the vein, which, in turn, overloads your valves. Vein valves that do not work properly are called incompetent because they stretch and no longer work efficiently, and incompetent valves contribute to CVI. DVT is a potentially serious condition that causes leg swelling and requires immediate medical attention because sometimes the blood clots in the veins can break off and travel to the lungs. This condition is called a pulmonary embolus. Phlebitis occurs when a superficial or deep vein becomes swollen and inflamed. This inflammation causes a blood clot to form, which can also lead to DVT. Factors that can increase your risk for CVI include a family history of varicose veins, being overweight, being pregnant, not exercising enough, smoking, and standing or sitting for long periods of time. Although CVI can affect anyone, your age and sex can also be factors that may increase your tendency to develop CVI; women older than 50 most often get CVI.

9. What tests will I need?

First your physician asks you questions about your current general health, past medical history, and symptoms. In addition, your physician conducts a physical exam. Together these are known as a patient history and exam. Your physician may measure the blood pressure in your legs and will examine the varicose veins. To confirm a diagnosis of CVI, the physician may order a duplex ultrasound test or sometimes another test called a venogram. Duplex ultrasound uses painless sound waves higher than human hearing can detect. Duplex ultrasound allows your physician to measure the speed of blood flow and to see the structure of your leg veins. A venogram is an x-ray that also allows your physician to see the anatomy of your veins. During this test, your physician injects a dye, properly called contrast, which makes the blood in your veins appear on an x-ray.

10. How is CVI treated?

CVI is usually not considered a serious health risk. Your physician will focus his or her treatment on decreasing your pain and disability.

10.1. Compression stocking

For mild cases of CVI, your physician may recommend compression stockings. Compression stockings are elastic stockings that squeeze your veins and stop excess blood from flowing backward. In this way, compression stockings can often also help heal skin sores and prevent them from returning. You may need to wear compression stockings daily for the rest of your life. You can help avoid leg swelling and other symptoms by occasionally raising your legs and avoiding standing for long periods of time to decrease the pressure in the veins. When you do need to stand for a long period, you can flex your leg muscles occasionally to keep the blood flowing. You can also help lessen the symptoms of CVI by maintaining your ideal body weight or losing weight if you are overweight.

More serious cases of CVI may be treated with injections, called sclerotherapy, or with surgical procedures. Fewer than 10 percent of people with CVI require surgery to correct the problem. Surgical treatments include ablation, vein stripping, bypass surgery, valve repair, and angioplasty or stenting of a vein.

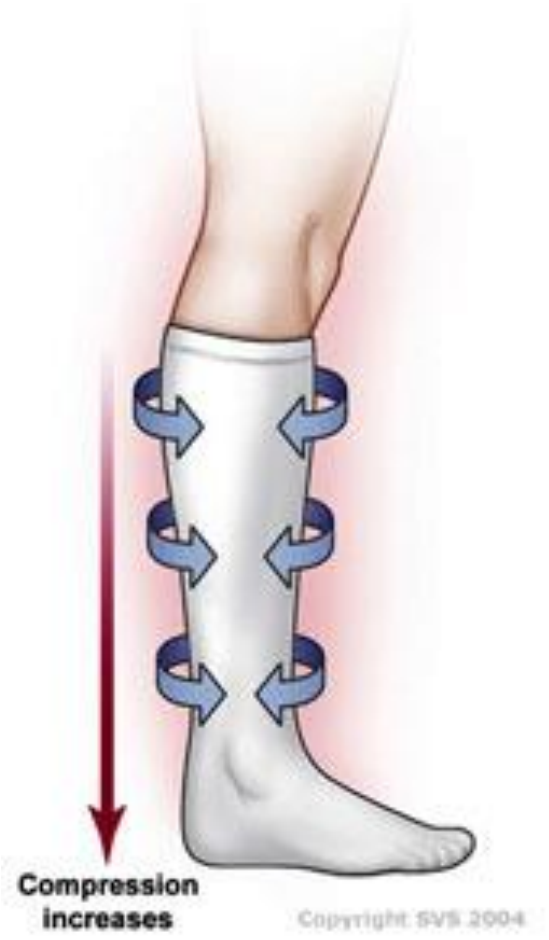

Figure 11: Compression increases direction

10.2. Sclerotherapy

In sclerotherapy, your physician injects a chemical into your affected veins. The chemical scars your veins from the inside out so your abnormal veins can then no longer fill with blood. Blood that would normally return to the heart through these veins returns to the heart through other veins. Your body will eventually absorb the veins that received the injection.

10.3. Ablation

Ablation uses a thin, flexible tube called a catheter inserted into a varicose vein. Tiny electrodes at the tip of the catheter heat the walls of your varicose vein and destroy the vein tissue. As with chemical sclerotherapy, your varicose vein is then no longer able to carry blood, and it is eventually absorbed by your body.

10.4. Vein stripping

To perform vein stripping, your physician first makes a small incision in the groin area and usually another incision in your calf below the knee. Then your physician disconnects and ties off all veins associated with the

saphenous vein, the main superficial vein in your leg. Your physician then removes this vein from your leg. A procedure called ambulatory phlebectomy, or small incision avulsion, can be done either alone or together with vein stripping. Small incision avulsion allows your physician to remove individual varicose vein clusters from the leg through tiny incisions.

10.5. Bypass

For more extensive problems, your surgeon may recommend bypass surgery to treat CVI that occurs in the upper thigh or pelvis. For example, your surgeon can connect an artificial vein, called a graft, or a transplanted vein to a vein not affected by CVI to help blood flow from your affected leg around the blocked vein. Most vein surgery can be performed through small incisions. Usually bypass surgery is safe, although there is a small risk of DVT and infection at incision points. Your physician will only recommend this procedure in the most serious instances.

10.6. Valve repair

In valve repair, your surgeon shortens the valves inside your vein to improve valve function. After making a small incision into your skin, your surgeon cuts into the affected vein. Your surgeon then folds or tucks the valve flaps. He or she may place a fabric sleeve around the outside of your affected vein to help press the walls of the vein together to maintain valve function.

10.7. Bypass Angioplasty and Stenting

In more severe cases of CVI, your surgeon may recommend angioplasty or stenting. An angioplasty is the use of a balloon to push open a narrowed or blocked portion of the vein. A stent is a metal-scaffold tube that helps to keep the narrowed areas open. In some instances, depending on where the vein blockage is, this may be used to open up the blockage. The procedure is performed through small needle punctures in the veins, either behind the knee or in the groin. Typically angioplasty and stenting are safe procedures [9].

11. Outlook (Prognosis)

Chronic venous insufficiency tends to get worse over time. By taking self-care steps, you may be able to ease discomfort and slow the condition from getting worse. It is likely that you will need medical procedures to treat the condition.

12. When to Contact a medical professional

Call for an appointment with your health care provider if:

1. You have varicose veins and they are painful
2. Your condition gets worse or does not improve with self-care, such as wearing compression stockings or avoiding standing for too long
3. You have a sudden increase in leg pain or swelling, fever, redness of the leg, or leg sores

13. Alternative names

Chronic venous insufficiency; Chronic venous stasis; Chronic venous disease [10-11]

14. Artificial venous valves

There are no commercially available artificially venous valves. This is largely due to high failure rates, and biocompatibility issues. Prosthetic venous valves are believed to be able to restore normal vein functioning as an alternative to other surgical procedures. The proposed artificial valve will be able to be implanted into the vein through a catheter. The valve is designed to mimic the natural venous valve, by allowing blood to flow naturally when it's being pumped by contraction, and stopping blood flow when there is an absence of contractions.

15. Venous valve structure

The synthetic valve is comprised of two different parts, a solid frame and flexible leaflets.

1.Solid Frame:

Comprised of a circular base that was formed from photo-activated polymer resin. The solid frame also contains a flange support structures to hold the flexible leaflets.

2. Flexible Leaflets:

a) Made of a polymer called BioSpan. After templates for the leaflets were created, they were then cut to shape by scalpel.

b) Made to mimic the flaps of a normal valve, by completely closing the passageway to block blood from moving backwards.

c) They are attached to the frame by connecting them to the flanges.

16. (2:1) Ratio trials

To test the design of the valve, a model that was two times larger than the desired valve was created. The valve was placed into set up where the valve was tested in a flow loop, with water as the fluid. During the tests, a few problems arose in the design of the valves. When closed, the leaflets had an undesirable sagging. The bases of the valves were susceptible to breaking where the flanges met the edge of the base. This was due to the bending stress caused by the fluid. The problems were corrected by adding a beveled edge and an extra shoulder like extension to the supporting flange.

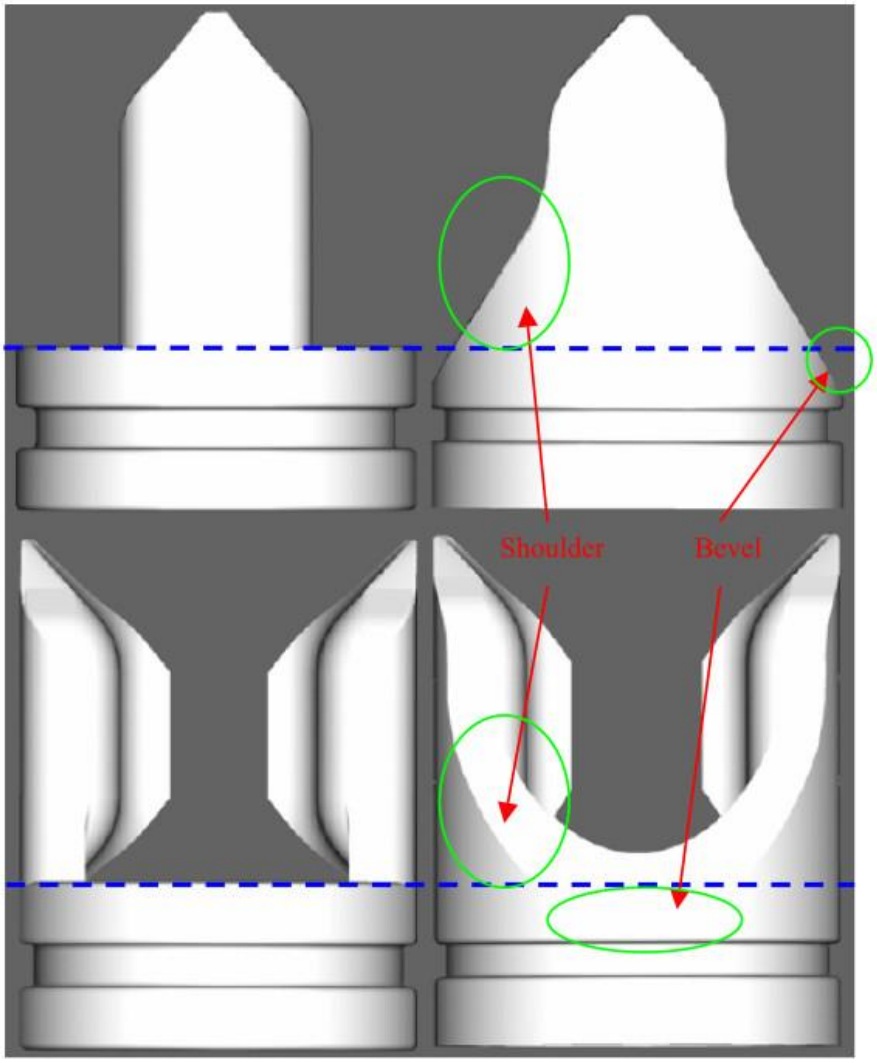

Figure 12: Ratio trials

17. Size configuration testing

After the design problems were all worked out in the 2x tests, the valves were tested at their desired size. For the tests, four valves with varying flange lengths (1.25,2.50,3.75 and 5.00mm), underwent a series of procedures in the same fashion as the 2x tests, with a blood substitute as the fluid. Also a test with no valve at all was used to simulate the conditions of CVI, in which the valve usually fails. The tests were meant to simulate four different body movements. The movements were, breathing while laying down, ankle flexion while laying down, standing breathing and standing ankle flexion. The two main parameters that were calculated for the valves were the Percent Reflux, or the amount of fluid that flows “backwards” through the valve, and Energy Retention, the amount of energy being retained by the valve in the form of potential energy. These tests showed that the valves with the 2.50 and 3.75mm flanges were superior to the 1.25 and 5mm flange valves.

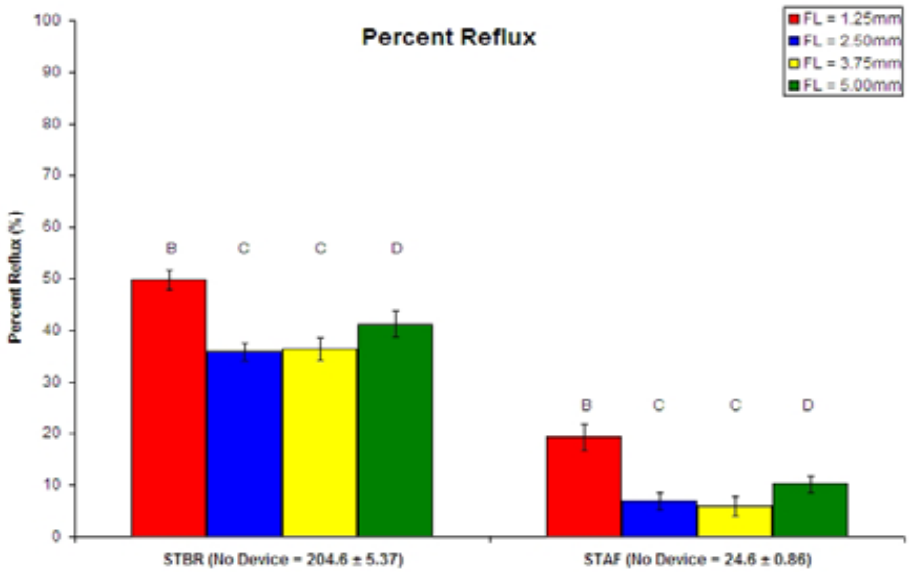

Figure 13: Percent reflux

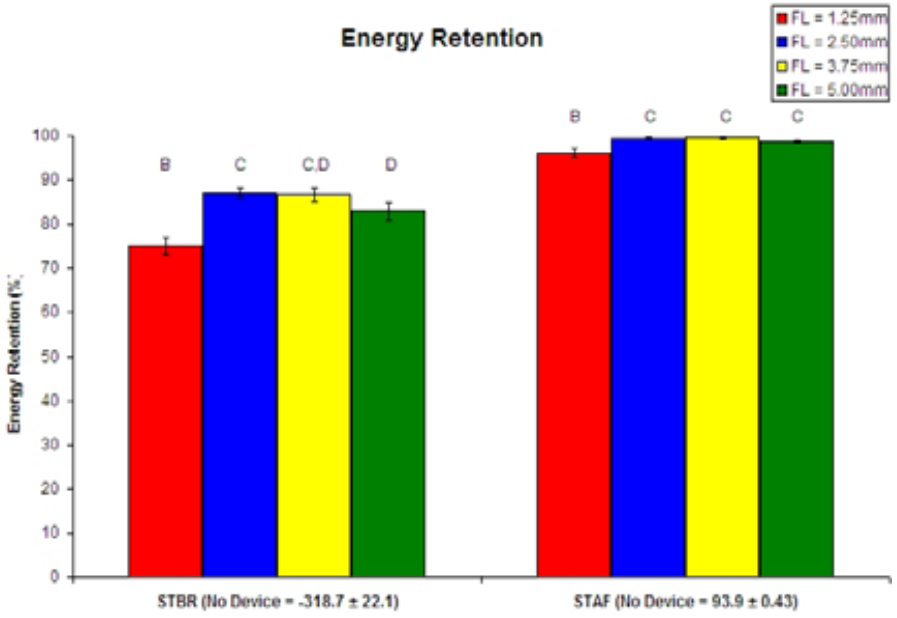

Figure 14: Energy retention

18. An ongoing quest to treat end-stage deep venous insufficiency

End-stage deep venous insufficiency is unrelenting venous hypertension with sequelae, and no standard option is available, or all options have been tried and found wanting. In such cases, there is an opportunity for an artificial venous valve to be used as a native valve. For decades, substitute valves have been studied experimentally, raising hope of bench-to-bedside transfer. This quest is reviewed with an emphasis on current clinical practice. Venous valves have been made entirely of non-autologous tissues: synthetics, xenografts, or allografts. Many have failed in early experimental evaluation, with some advancing to the clinical arena, but few remain in research and development. Valves constructed from autogenous cells, or from autogenous venous tissue, not originally “de novo” valve tissue, have proven more promising. A variety of techniques have been used clinically, and improved venous hemodynamics and valve competency have been demonstrated. However, the majority of these valve studies await

confirmation by other investigators over extended periods. It is apparent from the current literature that venous ulceration will recur even after the most aggressive treatment of superficial and perforator disease in patients with clinical class $C_{5,6}$ disease [12]. Ulcer recurrence is more common in patients with postthrombotic deep venous insufficiency (~ 70%), but is also seen in patients with primary deep venous insufficiency (~ 30%). The role of proximal iliac vein obstruction may be more prominent than once expected [13], but surgery to correct deep venous insufficiency (DVI) remains an appropriate option in selected patients. Even in the best hands, and with an architecturally preserved venous valve, about one-third of internal valvuloplasty repairs will fail within 5 years. Those requiring valve transposition or transplantation procedures fare less well, with only about 30% to 40% of valves competent at 5 years [14-15]. In the face of unrelenting symptomatic deep venous insufficiency, and the lack of a standard treatment option, there is an opportunity for the use of an artificial venous valve. The quest to address this need has been ongoing for decades, and many avenues have been explored. The standard dictionary definition of "artificial" is "not arising from natural growth." Therefore, and for this

review, an artificial venous valve is not considered as a “de novo” venous valve. In general, two categories of artificial venous valves have been studied: valves devoid of auto-genous components; and valves constructed, at least partially, from autogenous components.

19. Nonautogenous Valves

Some investigations have never advanced past the point of a promising valve studied for hemodynamic responsiveness. In a lyophilized cadaveric vein, a valve acts mechanically much like a native valve when rehydrated [16]. The cusps withstood greater than 350 mm Hg retrograde pressure without leakage, and the closure time was 0.31± 0.03 seconds. No animal implants or clinical investigations have been reported. Some valves tested in animal models fared quite poorly, and, therefore, further investigation was deemed unwarranted. Fresh allograft vein segments containing a valve were transplanted into the femoral vein of 14 dogs with only 7% patent at four weeks [17]. A human umbilical vein fitted over an aluminum mandrel, sculpt-ured into a bicuspid valve and then glutaraldehyde-fixed, was implanted as a xenograft. All ten canine transplants failed in three days. A liquid pellethane bicuspid valve was poured and fashioned using the same aluminum mandrel as that used for the umbilical vein experiment. All 10 canine implants thrombosed in 8 days. Animal studies, or occasionally even unrelated clinical studies, raised hope. Platinum or pyrite-carbon–covered, titanium, center-hinged bileaflet valves implanted in the dog femoral vein

had 100% patency and competency at three months. Unfortunately, extensive neointimal overgrowth resulted in valve failure within 2 years [18]. These results hold some promise that modifications might be able to extend valve life into a useful clinical range. Decellularization of allograft veins containing valves could provide a transplant devoid of potentially immunogenic donor cells. A cryopreserved decellularized allograft, used as an arteriovenous fistula (AVF) for dialysis access, incited little antigenic response, with good overall function. When implanted into the right ventricular outflow tract, a relatively high flow situation, pulmonary valve allografts functioned well for at least 6 months in a sheep model. Implantation of pulmonary valve allografts as an adjunct to the Ross procedure did not induce an antibody response, as determined by panel reactive antibody (PRA) testing [19]. However, decellularized vein–containing valve allografts, implanted as venous valves in recipient sheep, and unaided by supportive anticoagulation, all failed in six weeks [20].

Although this animal study was unsuccessful, clinical experience, with the same material as an AVF or cardiac valve, suggests that further study might be rewarding. There are valve substitutes free of autogenous tissue that have

advanced to clinical trial. A single allograft valve utilizing standard allogenic cross-matching, and cryo-preservation for storage, has reached this level of investigation. As a preamble to the clinical trial, dog erythrocyte antigen–matched and cryopreserved veins containing valve allografts were transplanted into recipient dogs with experimental hind limb venous insufficiency. Following ligation of a post-implant high-flow dAVF at 3 to 6 weeks, all four transplants remained patent and competent for three more weeks, at which time sacrifice demonstrated acceptable histologic findings [21]. The inner surface had an endothelial-like cell covering, and cusp sinuses were free of thrombus. A multicenter feasibility study unfortunately suggested that a low-grade rejection phenomenon was damaging the allogenic femoral vein valves, with primary patency rate of 67% and primary competency rate of only 56%. A two-year clinical study reported a disappointing 27% patency and competency rate. The cryopreserved valve allograft failed in early and midterm clinical trial, and is not considered a suitable valve substitute for treating DVI. Another clinical investigation utilized a cryopreserved allograft pulmonary valve monocusp implanted surg-ically into the common femoral vein in patients with longstanding,

active venous ulcerations (> 3 years). It was difficult to determine if the patients had an autogenous alternative, but the technique is unique. Fourteen of 40 (33%) implants were incompetent at follow-up, the length of which was not clearly stated. If the valve remained competent, the clinical results were excellent (24/27 or 89%), while recurrent reflux led to recurrent ulceration or non-healing. Mention of an immunogenic reaction, especially without blood type– specific matching, was considered a problem. No further report has been forthcoming.

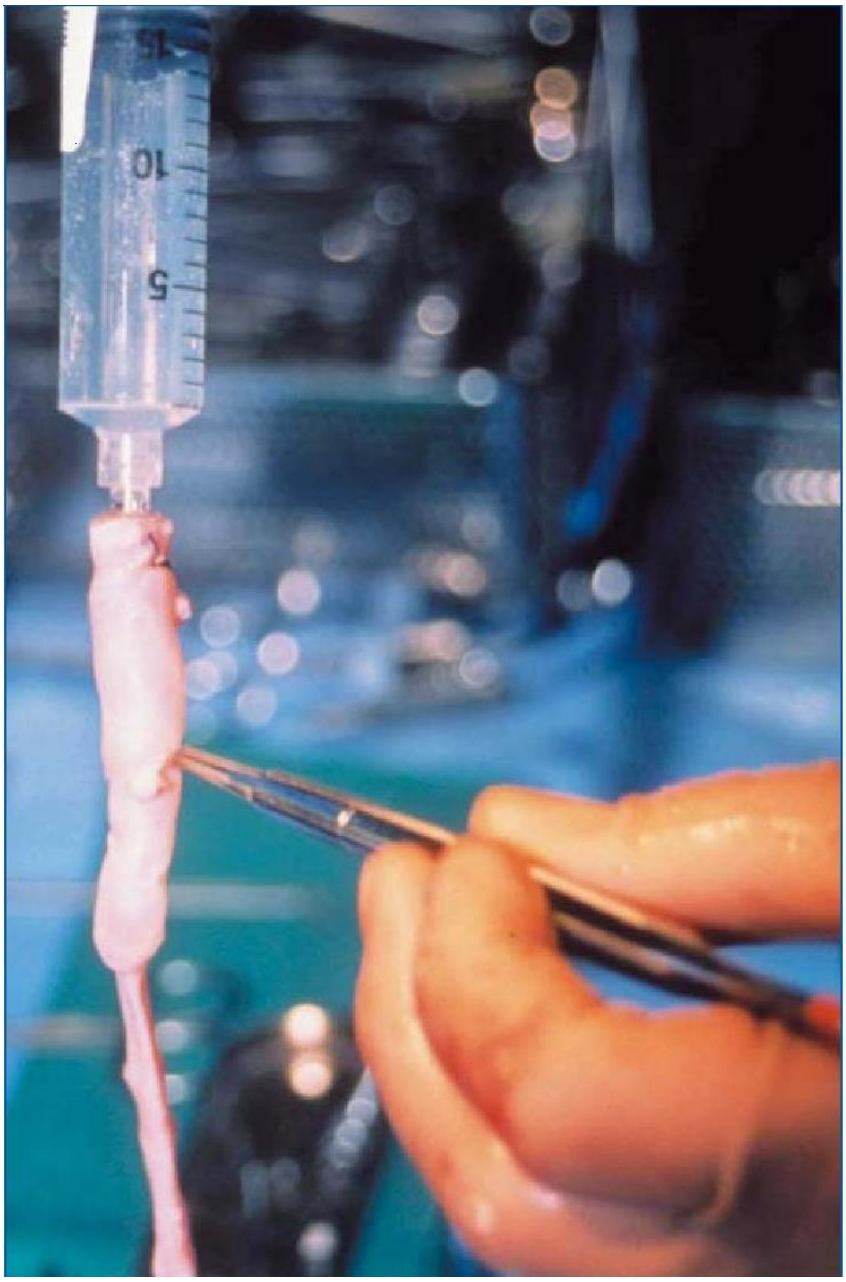

Figure 15: Photograph showing valve competence prior to implant of a cryopreserved vein-containing valve

Cryopreserved femoral valved vein (cryovalve) is available from CryoLife (CryoLife, Inc. Kennesaw, Ga). During testing, the valve remains competent to at least 125 mm Hg of retrograde pressure. Data suggest that primary valvuloplasty may be required post-thaw to ensure initial competence. As noted previously; this valve fails quickly over time, but what if one could temper the chronic rejection that seems to damage the valve over time? [22-23]. Immunosuppressive agents would have to be well tolerated and not risk systemic infection. The suggested mechanism of rejection is the cytotoxic T cell response to foreign endothelium, which could be modified with agents such as aziathioprine or cyclosporin A. No clinical trials have tested this hypothesis. Glutaraldehyde-preserved vein-containing valve allografts, with adjuvant distal AVF support, remained patent (80%), but rarely competent (25%), in a 7-week canine study. Glutaraldehyde-preserved bovine cardiac valves function well as human heart valves, and there is one report of a successful open surgical implantation of a glutaraldehyde-preserved pericardial allograft mono-cusp valve designed to treat a patient with DVI. This tissue is no longer available from the supplier, so the authors have changed their line of investigation. The technology existed to construct

glutaraldehyde-preserved bovine venous valves for clinical use, and therefore this became an area for investigation. Early hemodynamic testing of bovine jugular vein valves proved very promising, and the vein diameter was of appropriate size for human use. The possibility of valve transplantation by a percutaneous route was demonstrated experimentally and reported in the literature. Subsequently, in a swine model, a glutaraldehyde-preserved bovine vein-containing valve was implanted via a percutaneous route. In the three surviving animals, the valves were patent and competent. Further experimentation in an even larger animal study suggested that this approach was possible, but there was still some concern with valve competence, since while 5 of 5 valves at 4 weeks were patent, only 3 were competent. Additional unpublished data supported the concept that a clinical feasibility trial was appropriate. A report from the Jobst Institute confirmed that two percutaneous placements of this device were accomplished as a phase 1 trial [24]. Recruitment was difficult due to the stringent criteria to insure that only end-stage patients were being treated. At approximately 1.3 years of follow-up, both stent valves were patent, but one was found to be incompetent at 14 months. These and other early results

were somewhat discouraging, and pointed to a need to redesign. The new design likely failed to solve clinical concerns since the parent company no longer exists. The most recent venture into the use of a nonautoge-nous valve for clinical use is a bioprosthetic valve made of porcine small intestinal submucosa (SIS).

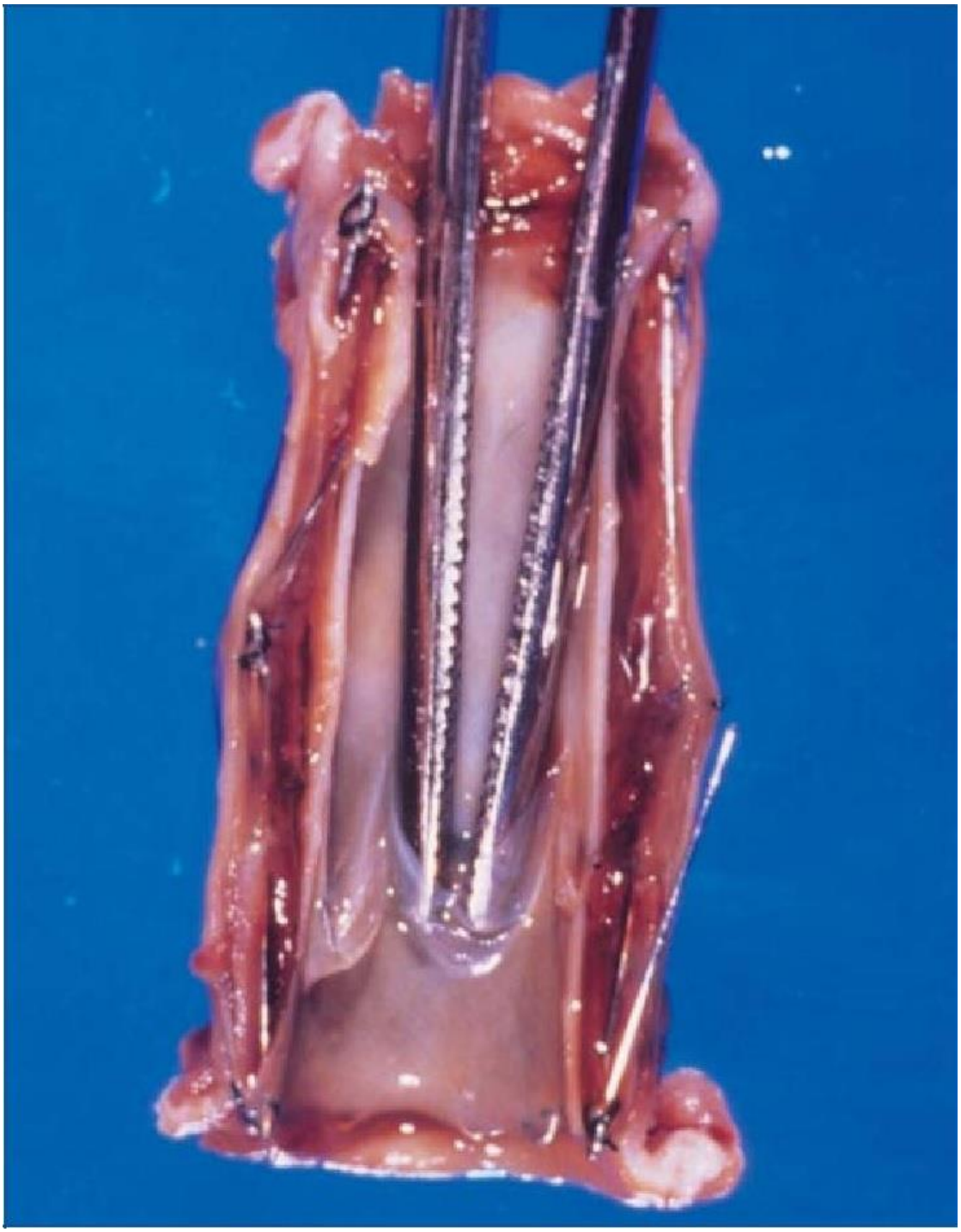

Figure 16: Photograph of a vein-containing valve that has been

attached to a Z–stent and explanted after percutaneous implanta-tion into a canine model. Note the normal appearance of the valve, highlighted by the instrument, with some narrowing at the proximal end of the stent.

A biopros-thetic, bicuspid stent-based xenograft valve was devel-oped and deployed percutaneously in the external jugular vein of a sheep model. SIS is essentially a collagen skeleton with growth factors, which was stretched over a square metal frame with a slit cut to form the valve opening. The valve was found to be resistant to thrombosis, and becomes repopulated with endothelial cells from the recipient. An 88% patency and competency rate was reported, but tilting led to valve malfunction or occlusion in 3 animals. Three patients were treated, thus demonstrating the feasibility of the approach. A design change enabled automatic centering of the valve, and 6 of 8 valves were competent at 5 weeks in an animal study [25]. The company sponsoring the project (Cook, Inc., Bloomington, Ind.) is continuing research and development, with early clinical studies performed outside the United States. A third design change is planned to improve venous valve hemodynamics and prevent cusp thickening.

20. Autogenous Valves

Repopulating a decellularized valved vein allograft with donor smooth muscle and endothelial cells would make a transplant much like an autogenous valve, but with an allograft infrastructure. This hybrid is difficult to catego-rize, but, I believe, fits the autogenous category best for the purposes of this review. In a sheep model, such a seeded allograft was transplanted into the external jugular vein of the cell donor. Devoid of long-term anticoagulation, 9 of 12 seeded allografts were patent and competent at 12 weeks. One transplant had occluded, and two valves were frozen by neointimal ingrowth. These allografts did perform much better than unseeded allografts, which universally failed, but not as well as 8 autografts, which were all patent and competent. This is promising experimental work. Intussusception of an autogenous vein forms a bicuspid valve by placing two sutures 180 degrees from each other to hold the intussusceptum in place. The tissue is autogenous, but the valve is artificially constructed. In canine studies performed without chronic anticoagula-tion, short-term patency was excellent, with valve competence demonstrated at physiologic pressures. The valve was, of course, thicker than a native valve by virtue of its method

of construction [26]. When transplanted into the femoral vein of a canine DVI model, the 90% venous refill time was modestly improved, but not the venous filling time, suggesting a less rapidly responsive valve when compared to a native valve. The British experience with this type of valve was evaluated by the Harvey strip test and descending venography, and long-term competence (1-112 days) was demonstrated in animals. All 41 valves were immediately competent by the strip test, 38 by descending venography, and 24 of 27 fully competent to a vertical pressure gradient of up to 250 cm H_2O in this animal study. A modification to allow thinner valve cusps showed that the valve opened rapidly with minimal retrograde pressure, closed at a pressure of 3 to 5 cm of water, and could withstand physiologic hydro-static pressure without reflux. In the absence of prolonged anticoagulation, a thin layer of thrombus formed along the thinned cusp walls, resulting in valve incompetence. Overall, with some modifications, this could function as a substitute valve, but animal studies have raised concerns as to optimal function and a higher-than-normal risk of thrombosis. Although an invaginated valve has been used in the saphenous system to prevent reflux, this valve design has not yet been investigated in the deep

venous system of patients. There are clinical reports of attempts to use autogenous venous tissue to fashion intraluminal venous valve cusps. It is my belief that this avenue of study initially resulted from the pressing need for a valve during surgery, when no other option was available. Raju and Hardy report a small series of de novo valve reconstruction procedures [27]. Using autogenous vein from various locations, and after trimming adventitia and part of the media, semilunar cusps were cut to shape and sutured into the recipient vein. The non-endothelial surface was directed toward the lumen to decrease the risk of thrombosis. All 7 valves were patent at 15 to 24 months of follow-up, primary healing of venous ulcers was recorded in 6 patients, with one requiring a skin graft to complete the healing process. No recurrences were noted. Plagnol et al invaginated a stump of the great saphenous vein into the femoral vein to make a bicuspid valve, and 19 of 20 clinical reconstructions were patent and competent at a mean of ten months. Reflux was noted in one case because of insufficient valve length. I have some concerns regarding invagination of an adventitial surface into the venous lumen, but these are not substantiated in this report. Maleti made bicuspid or monocusp venous valves by dissecting an inner layer from the

thickened post-phlebitic vein wall to form the cusp(s). The initial 7 cases were sufficiently successful to warrant further study. At the 2005 American Venous Forum, Lugle and Maleti reported the construction of 18 venous valves in 16 patients with recurrent or non-healing venous ulcers. Six months of chronic anticoagulation was standard. At an average of 22 months, 83% of the valves remained primarily patent, with improved duplex and air plethysmographic findings. Early thrombosis below the valve was observed in two patients, and one patient experienced a late occlusion after beginning oral contraceptives. Corcos et al report one case in which the "intimal flap" method of constructing a venous valve was successful in healing a venous ulcer, and in improving venous hemodynamics [28]. The early and midterm results are certainly promising for all the reported autogenous vein methods of new valve construction, but few methods have been substantiated by other investigators.

21. Conclusions

Valve cusps made of autogenous vein are currently the only artificial venous valves available with at least preliminary data to support their use in cases of chronic deep venous insufficiency, for which there are no standard options. Non-autogenous, off-the-shelf venous valve substitutes are in research and development, or have hitherto failed clinical evaluation. With modifications, some of the latter do hold promise for the future.

22. Future work

In the future, the scientists hope to incorporate drug delivery reservoirs within the flanges themselves. The reservoirs would administer their drugs through channels made of rate controlling materials. Multiple reservoirs per flange would also make it possible to contain more than one drug at a time, being able to cure multiple symptoms at once.

Finding a biocompatible material for the frame would also lessen the rejection rate of the synthetic valves. Creating a leaflet molding process, and finding a new way to attach the leaflets to the frames would shrink the valve to valve design variability. Making the frame out of a expandable material would also allow the synthetic valves to be deployed into the affected veins via a catheter [29].

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