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Tissue-Engineered Heart Valves: An Alternative Solution for Pediatric Patients

By Stefan Jockenhoevel, MD and Thomas C. Flanagan, PhD

Introduction

Despite heart valve repair being the preferred initial treatment method to address severe heart valve disease, valve repair is not feasible in a large number of pediatric patients with congenital malformations, and replacement of the valve with a biological or mechanical prosthesis is necessary. However, conventional prosthetic heart valves carry with them a number of limitations, including thromboembolism, life-threatening hemorrhagic complications, limited durability, rejection and transmission of infection. Currently available prosthetic heart valves also lack the capacity to grow and remodel, which presents a particular disadvantage in pediatric patients leading to multiple re-operations. Bioprosthetic valves in pediatric patients are also prone to tissue calcification. To overcome these limitations in the pediatric population, the focus of prosthetic valve research has shifted to the development of living tissue-engineered valves capable of growth and remodelling; many animal studies demonstrate the feasibility of the tissue engineering approach (for detailed reviews, see [1,2]).

While a number of different strategies for pediatric heart valve tissue engineering are being pursued, most studies have addressed the construction of a tricuspid/trileaflet valved conduit, designed specifically for the most frequently transplanted aortic valve, and the pulmonary valve. Design strategies are typically based on the seeding of "scaffold" materials (biological, synthetic, or a composite of both) with a suitable source of valve interstitial-like cells (VICs) and endothelial cells (ECs) in an appropriate three-dimensional configuration, followed by physical conditioning of the valve construct in a bioreactor system to develop a living, functional implant. Each of the three essential components of the technique have important, specific functions: the cells, or viable component of the valve, will ultimately construct the new tissue and endow the valve with remodelling capabilities for growth with the infant, and should also form a thrombo-resistant coating on the valve surface. The scaffold is designed to maintain the cells in a suitable anatomic configuration at the implantation site, and bioreactor conditioning guides optimal cellular and physical properties via controlled gene expression, tissue development and remodelling.

Cells

The search for a reliable cell source for a tissue-engineered heart valve has generated intense research over the last decade. Both in vitro and ex vivo studies of valve cell phenotype and behavior can provide useful information to aid the selection of suitable cell

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sources for tissue-engineered valves [3,4]. A variety of sources for both VICs and ECs has been identified thus far, and include those from: vascular tissue, skin, bone marrow, umbilical cord, placenta, and even valve tissue itself [4-11]. The most attractive sources for clinical applications of a tissue-engineered heart valve are autologous cells harvested from patients themselves using minimally-invasive surgery, therefore presenting no risk for immune rejection following re-implantation. Arterial or venous sources may also be isolated using minimally-invasive techniques, but patients with pathological vascular disease may not have suitable cells for cultivation. While these and other autologous sources may not be suitable for the geriatric population due to reduced proliferative capacities, promising cell sources for the pediatric population have been highlighted in recent reports, and include bone marrow mesenchymal stem cells (isolated by routine bone marrow puncture), umbilical cord-derived cells or chorionic villi-derived cells [7-10]. Despite such advances, there is no evidence to date, that these cell populations, or indeed, any other stem cell populations, will adapt and behave as required in vivo. Sutherland et al [9] reported the presence of differentiated ECs lining the surface of implanted tissue-engineered pulmonary valves after 4 months in vivo, following the seeding of synthetic biodegradable constructs with bone marrow-derived mesenchymal stem cells. However, as the seeded cells were not labelled prior to implantation, the origin of the endothelium remains uncertain, as it is known that structures implanted in the ovine vasculature rapidly become endothelialized by host cells [12]. Therefore, a clearer understanding of the factors involved in the differentiation of these stem cells, as well as preservation of gene expression and phenotypic function in vivo, will be critical in maintenance of normal structure and function in a tissue-engineered valve replacement.

Scaffolds

The ideal scaffold material for development of a successful pediatric tissue-engineered heart valve continues to be a matter of intense debate. Exogenous, biodegradable scaffolds are designed to immobilize the appropriate cell populations at the implantation site of a tissue-engineered structure, and also to provide appropriate mechanical stability until new tissue has been synthesized, organized and cross-linked into a stable structure. Traditionally, two principal scaffold types have been applied in the field of pediatric heart valve tissue engineering: natural, biological scaffold materials and synthetic scaffold materials. Biological scaffolds have included: decellularized native tissue (homograft or xenograft valve tissue, small intestinal submucosa, gall bladder tissue), collagen, glycosaminoglycans (GAGs) and fibrin scaffolds [13-21]. Proponents of the use of biological scaffolds argue that the natural structure of these protein materials provides a more suitable template for cell growth owing to the presence of cell ligands, in contrast to synthetic scaffolds, and that biological scaffolds are therefore more suitable for the regulation of gene expression, cell organization and tissue development.

Arguably, the most utilized biological structures to date have been decellularized valve tissue scaffolds, designed to be devoid of

antigenic foreign cell material and to be either re-seeded with appropriate autologous cells in vitro, or to attract endogenous cells from the blood or surrounding host tissue after implantation. The methods of removing the resident foreign cells from such scaffolds (homograft or xenograft) generally entail detergent treatment or enzymatic decellularization, resulting in a ready-made natural matrix scaffold for repopulation with cells from the child in question. The concept has been applied and developed by a number of groups worldwide, particularly in Europe, but to date has proven to be relatively unsuccessful. The first clinical application of these valves in the pediatric population was disastrous, with one study reporting the deaths of three out of four children receiving implants due to severe inflammation, degeneration, rupture and stenosis [22].

A second, and more technical, approach using biological scaffolds involves the in vitro reconstitution of biological proteins and cells into valvular structures. These proteins, including collagen, elastin and fibrin, as well as GAGs (mucopolysaccharides), have been formulated into sponge, film, mesh and hydrogel structures that allow excellent cell attachment and proliferation, and support the synthesis of ECM proteins by seeded cells [17-21]. Cell-mediated contraction of hydrogel scaffolds can result in tissue-like matrix densities within these structures, while aligned extracellular matrices can also be achieved by constraining the mechanical forces produced by the cells. This phenomenon has been cleverly manipulated by the groups of Tranquillo and Vesely to develop a desirable, highly-aligned ECM for the construction of tissue-engineered vascular grafts and mitral valve chordae respectively [23,24].

Fibrin, a major structural protein involved in the wound healing process, represents a potentially ideal cell delivery vehicle for the rapid synthesis of completely autologous cell-seeded structures due to its routine isolation from patients' blood. Fibrin gel scaffolds have been developed in our group as a matrix for the construction of autologous vascular grafts and heart valves [20, 21, 25, 26]. The concept is relatively straightforward: fibrin, the major structural protein of a blood clot, is formed by the enzymatic polymerization of fibrinogen monomers by thrombin in the presence of calcium ions, and when this process is performed in vitro, a gel structure consisting of fibrin mesh and trapped water is formed (Figure 1). If cells are added to the mixture during the gelation process, a high cell seeding efficiency and uniform cell distribution is achieved – ideal parameters for the formation of tissue-engineered structures. Further advantages of a fibrin scaffold include biodegradation that can be controlled by aprotinin supplementation [25], as well as the accommodation of increased ECM synthesis by seeded cells compared to other reconstituted proteins, such as Type I collagen [27,28]. We have demonstrated the formation of autologous fibrin-based tissue-engineered heart valves using an injection moulding technique (Figure 2), with the resultant valves showing excellent tissue remodelling by seeded vascular-derived cells [20,21]. A limitation of using hydrogel scaffolds for heart valve tissue engineering is the potential for valve insufficiency caused by cell-mediated shrinkage of the tissue structure; despite this, a multi-factorial approach is being pursued effectively to eliminate potential insufficiency, using both biomechanical and biochemical conditioning techniques [21,29]. Fibrin-based valves have reached the pre-clinical stage of implantation in a sheep model (Figure 3), and preliminary results are encouraging, with excellent tissue remodelling and mechanical stability demonstrable after six months in vivo [Flanagan and Jockenhoevel, unpublished results]. The concept demonstrates real potential for the creation of truly "autologous" tissue-engineered heart valves for the pediatric population.

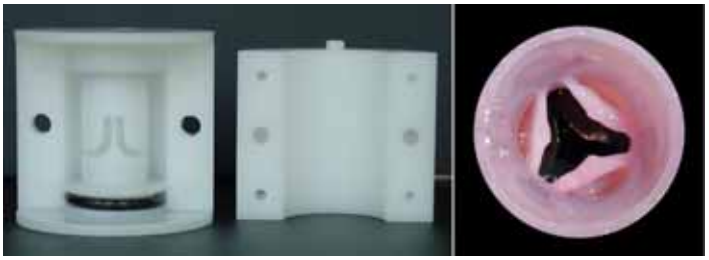

Figure 2. Customised mould (left) developed by the Jockenhoevel group for injection moulding of fibrin-based tissue engineered heart valves (right, view from outflow aspect).

A number of synthetic biodegradable polymer materials have also been used as templates for pediatric heart valve regeneration, and are favored by the leaders in this area due to their potential

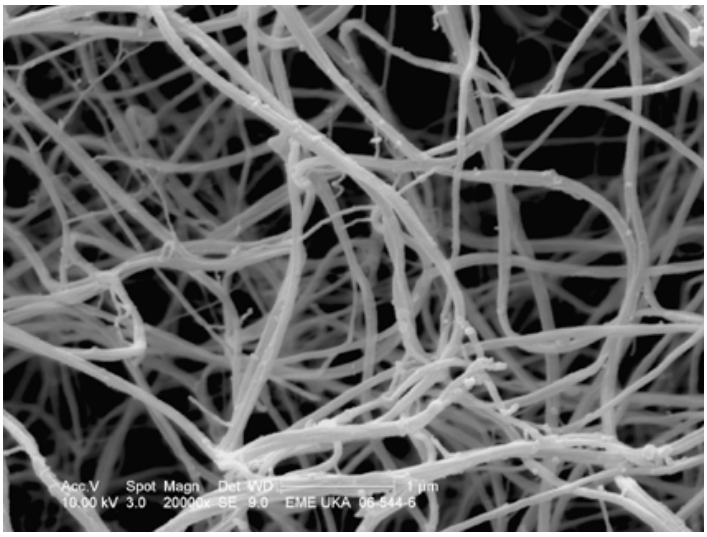

Figure 1. Mesh-like internal structure of a fibrin gel scaffold (SEM).

Figure 3. First surgical implantation of a completely autologous fibrin-based tissue-engineered heart valve in an animal model.

Figure 4. "Bioreactor" system developed by the Jockenhoevel group for mechanical conditioning of autologous heart valves prior to implantation.

for modification, reproducibility and bulk synthesis. Initial attempts by the Boston-based Mayer Group at heart valve regeneration based on synthetic biodegradable scaffolds involved the FDA-approved materials, polyglycolic acid (PGA), polylactic acid (PLA), and co-polymers thereof [5, 6]. These scaffold materials initially proved to be too stiff for suitable valve leaflet function in earlier studies, but with subsequent modifications, the group eventually demonstrated functional valves in a juvenile sheep model for up to four months using mesenchymal stem cells seeded on a co-polymer PGA/PLLA scaffold [9]. The mechanical properties of these scaffold materials were further altered by dip-coating the valve scaffolds in polyhydroxyalkanoates (e.g. poly-4-hydroxybutyrate; P4HB), which apparently renders a more flexible structure for improved valve leaflet function [30]. These valves, seeded with autologous carotid artery-derived cells, have been shown to function in a juvenile sheep model for up to five months in vivo, and demonstrated histological and mechanical similarities to native valve tissue following explanation [30]. However, the gradual production of toxic degradation products from synthetic, biodegradable materials can have potentially adverse effects on the surrounding host tissue [31, 32], and it is too early to suggest that such constructs are ready for the clinical setting.

Bioreactor Signalling

The final component of the triad for a pediatric tissue-engineered heart valve is the signalling method used to enhance or control tissue development and phenotypic properties of scaffold-seeded cells. Each heart valve is subjected to a myriad of flow, pressure and strain conditions throughout the cardiac cycle in vivo, including shear stress, cyclic loading and dynamic flexure. The heart valve "bioreactor" (Figure 4) aims to closely mimic these conditions in order to stimulate tissue development and remodelling within the structures, rendering them suitable for implantation (for bioreactor reviews, see [33,34]). Bioreactor conditioning in vitro has been shown to enhance cell proliferation within tissue-engineered heart valves, and to improve ECM synthesis and organization. Several bioreactors have been developed for routine testing and to subject pre-implantation valves to numerous mechanical conditions, including tension, compression, flexure, shear stress and pulsatile flow of cell culture medium [35-38]. This results in strengthening of the tissue and confers suitable mechanical properties for in vivo animal trials in the low pressure pulmonary system. Whether or not these conditioning techniques can be extended adequately to the variable, high pressure environment of the high pressure mitral and aortic positions remains to be elucidated.

Challenges

In a recent controversial review article published in *Circulation Research* [2], Ivan Vesely delivers an honest appraisal of the current state of the heart valve tissue engineering field: unfortunately, while many researchers in the field seem to promise much, the reality is that we remain far from being able to credibly apply tissue-engineered heart valves in a clinical setting. The challenges that need to be overcome in this field are numerous. In order to improve mechanical properties for an implantable tissue-engineered heart valve, a greater knowledge of the relationship between normal valve mechanics and intrinsic valve structure and remodelling will prove extremely beneficial. Advances in the understanding of heart valve embryology and development will aid in the design of suitable bioreactors and signalling tools to improve in vitro engineered heart valves. The design and validation of reliable markers of tissue development and remodelling, both in vitro and in vivo, will also allow significant advances in the field. Ultimately, however, successful pre-clinical studies remain of paramount importance prior to a responsible transition into the clinical setting. To date, tissue-engineered valves have not been implanted in the high pressure systemic circulation in pre-clinical studies, and only sparse evidence exists that these valves can function adequately in the low pressure pulmonary circulation. Strict validation methods will need to be developed and implemented, in order to avoid a repetition of such results as those of the Synergraft™ trial [22]. Despite the challenges ahead, significant advances have been made in this exciting and promising area of research. The approaches described, in combination with the creativity of researchers in the field, hold great potential for the development of heart valve prostheses with the ability to grow, remodel and repair their structure following implantation in the pediatric patient.

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Medical News, Products and Information

Medtronic Announces First US Clinical Trial Data on Transcatheter Valve for Congenital Heart Disease

The first U.S. clinical trial data on the Melody transcatheter pulmonary valve was presented at the *Annual Scientific Sessions of the American Heart Association* in New Orleans in November. These findings also represent the first US data on transcatheter valves in a population with congenital heart disease and the first reported US data on the use of a transcatheter valve in the pulmonary position. The Melody valve is currently investigational in the U.S.

Data was presented on 66 patients enrolled at centers in Boston, Seattle, New York, Columbus, and Miami. Encouraging from a safety perspective, was a highly acute procedural success rate of 98%. At six-month follow-up, maintenance of excellent valve competence was demonstrated as was a corresponding, clinically-significant, reduction of more than 18% in right ventricular volume. Valve competence was assessed by median pulmonary regurgitation fraction, which was down to 0% from a baseline of 30%.

Presenter of the data, Dr. Doff McElhinney, pediatric interventional cardiologist at Children's Hospital Boston, commented, "These data are very encouraging. Young patients with the types of congenital heart disease included in this study frequently require multiple open heart surgeries during the course of a lifetime. The Melody transcatheter valve is designed as a non-surgical alternative that will, at the very least, allow deferment of the next surgical intervention while protecting the heart from the strain of extra work. These multi-center data demonstrate that the Melody valve can be safely implanted with a high rate of procedural success. We have been encouraged by the excellent early function of the Melody valve and by the six-month clinical outcomes, which demonstrate clear improvements in heart size and valve function."

Of the U.S. congenital heart disease patients who require treatment each year for pulmonary valve dysfunction, approximately 1,500 are candidates for valve replacement with the Melody device. John Liddicoat, MD, General Manager of the CardioVascular Structural Heart Disease business at Medtronic, commented, "The success of the Melody valve results directly from the collaborative approach Medtronic has taken with physicians and scientists to develop technology. This successful approach has also built the foundation for a much larger program to develop transcatheter valves for all valve positions." Dr. Liddicoat concluded, "Medtronic is well positioned to be the world leader in heart valve replacement and repair. The benefits for patients are immense as we continue to develop innovative technology that is safe, reliable and easy for doctors to deploy with repeatable and confident accuracy."

The Melody valve was designed for patients with congenital heart defects who have a surgically-placed conduit between the right ventricle and pulmonary artery. When the valves in these conduits fail, the Melody valve provides a non-surgical means to restore valve function and prolong the life of a conduit, reducing the number of open heart surgeries these patients require. Using the Ensemble® system, a physician navigates the Melody valve to the heart by threading it through the body's blood vessels, eliminating the need to open the chest, minimizing trauma and offering a quicker recovery than open heart surgery.

Melody, the world's first commercially available transcatheter valve, is available in 60 centers outside the U.S. following Canadian and European approval. Medtronic B.V., a wholly owned subsidiary of Medtronic, Inc., received CE Mark on the Melody Valve and Ensemble System in 2006.

For more information visit: www.medtronic.com.

Advice About Heart Tests Before ADHD Treatment

Newswise - Stimulant medications like those often prescribed for children with Attention Deficit Hyperactivity Disorder (ADHD) raise blood pressure and heart rate, and some drugs carry warning labels for patients with heart problems. Two professional organizations are at odds over whether routine electrocardiogram (ECG) testing is necessary before a child starts taking a medication for ADHD, reports the October 2008 issue of the *Harvard Mental Health Letter.*

The controversy is about whether routine electrocardiogram (ECG) testing is necessary before a child starts taking ADHD medication. In April 2008, the American Heart Association (AHA) released a statement recommending that it was reasonable, although not mandatory, for clinicians to consider ordering an ECG in children diagnosed with ADHD before beginning treatments with stimulants or other medications.

In August, however, the American Academy of Pediatrics (AAP) published a statement recommending against routine ECGs, supporting earlier recommendations made by the American Academy of Child and Adolescent Psychiatry, citing data that sudden cardiac deaths, while tragic, are rare. Such deaths occur in about two children for every million taking ADHD medications-fewer than the eight to sixty-two sudden deaths per million that occur in the general pediatric population.

The discussion about the relationship between heart risk and ADHD medication is likely to continue. For now, Dr. Michael Miller, Editor-in-Chief of the *Harvard Mental Health Letter,* says the best advice is for doctors to assess heart disease risk by doing a physical exam and taking a careful medical history, and to rely on a mental health professional to evaluate for ADHD.

The Effect of Avalvulia on Venous Haemodynamics: a Numerical Investigation

By Constantinos Zervides, BEng, MSc, PhD; Andrew J. Narracott, MPhys, PhD; Vanessa Díaz-Zuccarini, MEng, PhD; Gaetano Burriesci, MEng, PhD; Patricia V. Lawford, BSc, PhD CIBiol; D. Rodney Hose, BSc, PhD

Introduction

Venous valves are multi-cuspal (generally bicuspid) structures which prevent retrograde flow of venous blood in the limbs. In the case of valves in the lower limb, the valves remain open when blood flows from the feet to the heart and close whenever the transvalvular pressure difference becomes negative, due to sudden changes in body position, contraction of muscle pumps (e.g. during walking or running) or breathing [1, 2]. When valvular dysfunction occurs, blood can flow distally through the veins (ie in the 'wrong' direction) and pool in the lower leg.

A rare cause of pathology is congenital venous valve aplasia (avalvulia). This condition, which is due to the failure of valves to develop, has been observed in a number of vessels including the femoral vein. Reports from Lodin et al. [3] and Plate at al. [4], studying different generations of one family, indicate that avalvulia is an inherited condition that affects both sexes in equal proportions. Typical clinical symptoms include severe orthostatic leg swelling and subsequent development of varicose veins and sometimes leg ulcers [5-7]. Since vein valve transplantation or transposition is not possible in the majority of cases due to severe vessel damage, palliative therapy is commonly adopted [8]. Congenital absence of the venous valves of the lower extremities is almost certainly under-diagnosed, but the vascular laboratory can accurately and easily differentiate between lymphoedema and venous valvular incompetence. Such differentiation may have therapeutic implications [6].

A better understanding of the changes in venous valve physiology during activities such as running or walking is essential in order to understand the effect of valvular aplasia and identify the most suitable and effective therapies. Moreover, an accurate and detailed description of pressures and blood flow in the systemic circulation would help improve understanding of a wide range of common clinical problems, such as the change in venous return associated with heart failure or the contribution of venous valves in deep vein thrombosis.

This study represents a first attempt to analyse, by means of a mathematical model, the role of venous valves in shielding the veins from the transient pressures associated with an instantaneous application of gravity (as occurs, for example, when rising from a sitting position [9]) and the effect of venous avalvulia on the venous system.

Simulation has become a third pillar of scientific research, in addition to observation and experimentation. Development of *in silico* experiments, allows hypotheses to be tested, suggesting new scenarios and facilitating comparison of results with limited clinical or experimental data. Modelling and simulation have the potential to provide insight into the behaviour of a physiological system and improve understanding of cause-effect relationships. Ultimately, they may play a role in the development of therapeutic solutions.

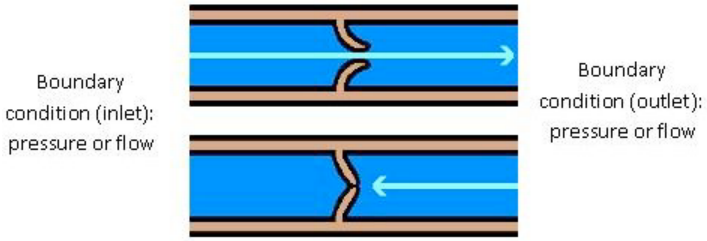

Figure 1. Schematic view of a vein and its boundary conditions. Upper panel: forward (proximal) flow, valve open (Pressure at inlet > Pressure at outlet). Lower panel: reverse (distal) flow, valve closed (Pressure at the inlet < Pressure at the outlet)

Methods

A numerical model was created and analyzed to capture the spatial and temporal pressure distributions in a collapsible tube containing valves. As the focus of this study was to capture the characteristic effects of venous valves, for simplicity, the vein was modeled as straight collapsible tube. This configuration is a simplified representation of a vein from the lower extremities. The venous valve was modeled to allow a small amount of reverse flow. This is assumed to be equal to the swept volume of the valve leaflets during the closing phase and is represented in the model by allowing a small finite volume of blood to pass back through the valve immediately prior to closure.

The system is described by means of differential equations. Differential equations arise in many areas of science and technology whenever a deterministic relationship involving continuously changing quantities and their rates of change is known or postulated. A widely-used example of differential equations dependent on time is the Michaelis-Menten kinetics describing the interaction of an enzyme with its substrate [10].

The differential equations used for this work, are based on the physical principles of conservation of momentum and mass in the system. Since the vein wall is compliant and collapsible, a mathematical law able to describe these characteristics was used [11]. In practice, the law produces a stiffening response for high negative or positive transvalvular pressures, whilst also capturing the flexibility of the vein when collapse or expansion is initiated. Figure 2 is a graphical representation of this mathematical law.

The boundaries of the system (walls, inlets and outlets) are delimited by boundary conditions. Typically, boundary conditions are applied to the boundaries of the system in the form of pressure or flow. The boundary conditions applied at the proximal and distal ends of the vein influence significantly the results.

For this study, a constant atmospheric pressure is applied at the proximal end and a constant flow rate is applied at the distal end. The choice of these conditions represents a simplification of the physiological pressures and flows in the vein segment. The proximal pressure boundary condition is chosen because it allows unimpeded reverse flow in the vein segment when gravity is ap-

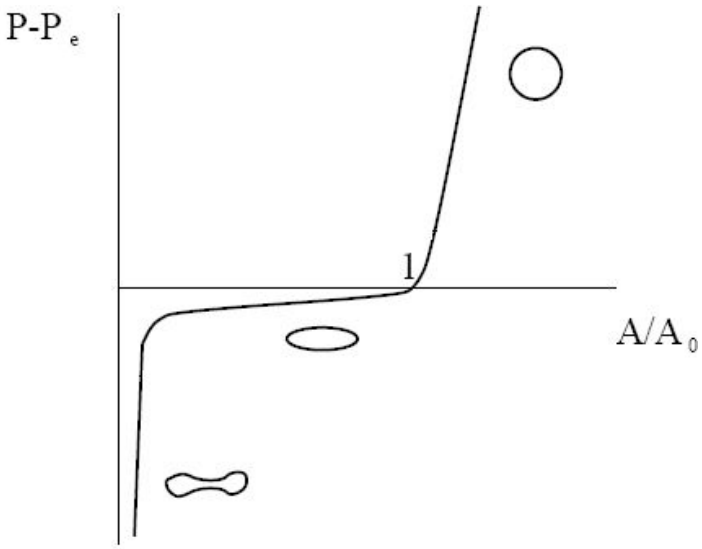

Figure 2. Graphical representation of mathematical law describing transmural pressure (P-Pe) and cross sectional area ratio.

plied. The distal end flow is chosen in such a way to account for the high resistance of the small vessels (capillaries/arterioles) feeding the vein.

This paper focuses on the transient pressure distributions and cross-sectional area changes in a vein segment, with and without a valve, under a near-instantaneous application of gravity. For simplicity, the effects of the muscle pump and other external load factors are neglected. A body force, opposing flow, is applied, to represent the action of gravity under a change of posture from horizontal to vertical. The clinical significance of the results are discussed in the context of avalvulia.

Results

The first analysis simulated a vein segment with no valve using the following physiological parameters:

- vein diameter 1.19 cm [12]
- vein thickness-to-diameter ratio 0.2 [13]
- vein length 1 m
- wall stiffness 1MPa [14]
- blood viscosity 0.004 Pa.s
- blood density 1000 kg/m3
- distal (inlet) flow 15.1 ml/s [12]
- proximal (outlet) pressure 0 mmHg
- nearly instantaneous body-force application

Figure 3 presents the computed pressure against time at the distal end of the vein segment. The real system will have damping due to the effects of the vessel wall, the surrounding tissues and blood viscosity. The only damping considered in our model is that due to blood viscosity, thus, in contrast with the *in vivo* system, higher amplitude oscillations dominate the numerical solution. Nevertheless, the model provides valuable information for qualitative comparison of the valve and valveless systems. After a period of time, the pressure at the distal end reaches the steady state value of 74.5 mmHg. This value is consistent with the hydrostatic pressure due to the fluid within the vessel plus the pressure drop associated with the superimposed steady flow. Examination of the detail of the first pressure peak indicates a transient maximum pressure in the vessel of 136.5 mmHg, which is 1.83 times higher than the steady state hydrostatic pressure.

Figure 4 presents the instant cross sectional area ratio (instant over initial cross sectional area), against time at the distal end of the valveless vessel. The cross sectional area ratio exhibits similar characteristics to the pressure with oscillations about the steady state. After the oscillations die down, the cross sectional area ratio at the distal end of the vessel in the steady state reaches a value of 1.08, indicating an 8% increase in the cross sectional area of the vessel from the starting value. The transient maximum cross sectional area ratio at the distal end of the vessel is 15% greater than the starting value. Although not shown in figures 3 and 4, we observed that the maximum pressure and cross-sectional changes take place at the distal end of the vessel, in line with expectations [11]. This is an indication that the numerical model behaves in an appropriate way.

The second analysis involved the inclusion of a valve at the midpoint of the vessel. This was accomplished by using a mathematical operation which allowed a small amount of reverse flow to pass

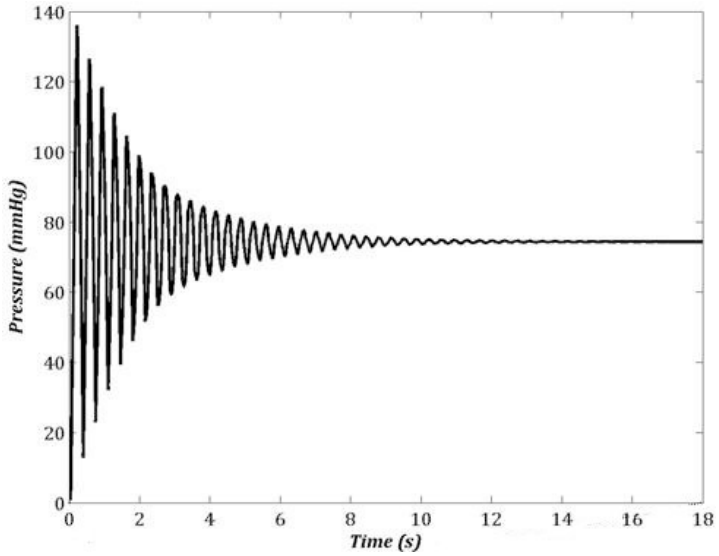

Figure 3. Pressure against time at the distal end of the vessel.

through the valve. As explained previously, this is associated with the swept volume of the valve leaflets during the closing phase. Once this is reached, the flow through the valve is changed to zero simulating valve closure. Zero flow is then enforced until the pressure at the valve inflow is greater than the pressure at the valve outflow, which initiates valve opening.

Using the same parameters as in the first analysis, a simulation was performed to illustrate the effect of a valve on the pressures and cross-sectional area ratios in the system. Figure 5 presents the computed pressure against time at the distal end of this vessel. The change in the characteristics of the dynamic system response, the decrease in the transient maximum pressures and the system oscillations are evident from this plot. Furthermore, steady state is reached more rapidly when compared with the valveless vessel.

Due to the oscillatory nature of the system, the valve opens and closes several times before settling in the open state in the hydrostatic condition. In practice, the first part of the phase is characterized by the flapping of the valve leaflets. This is in agreement with clinical observations reported by Lurie et al. [15]. For this reason, attention is focused on the early phase when the first valve closure and re-opening occurs. Figure 6a illustrates the pressure at the distal end of the vessel during the first half-second after the application of gravity for simulations both with and without a valve.

As already stated, the valve significantly changes the dynamic response of the system. In the first analysis with no valve, high-amplitude oscillations about the hydrostatic pressure value are seen. These oscillations dampen towards the hydrostatic steady state value as time progresses (see Figure 3). When a valve is present, an asymptotic approach towards the steady state, superimposed with small amplitude oscillations, is seen (Figure 6a). The pressure for the valve system remains below 93.0 mmHg indicating that the presence of the valve has reduced the maximum pressure in the vessel by about 30%. Finally, after a period of time, the pressure at the distal end reaches the steady value of 74.5 mmHg, which is identical to the value obtained for the valveless vessel.

Figure 6b, presents the computed cross- sectional area ratio against time at the distal end of the valve vessel for the same timeframe as that shown in Figure 6a. Superimposed are the results obtained for the valveless vessel. The cross-sectional area ratios exhibit similar behaviour to the pressure results shown in Figure 6a. Focusing on the maximum cross sectional area ratio for the valve vessel, a value of 1.1 is obtained. This indicates an increment in the cross sectional area of 10% when compared to the starting condition. This is 5% less than the valveless case and just 2% more than the unavoidable cross-sectional area due to the hydrostatic steady condition. Note, that pressure and area are related to each other through the mathematical law described in the methods section and seen in Figure 2.

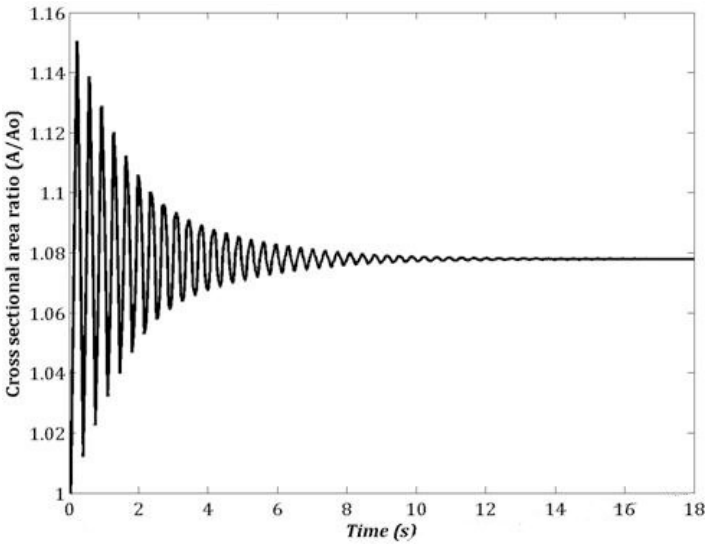

Figure 4. Cross sectional area ratio against time at the distal end of the vessel.

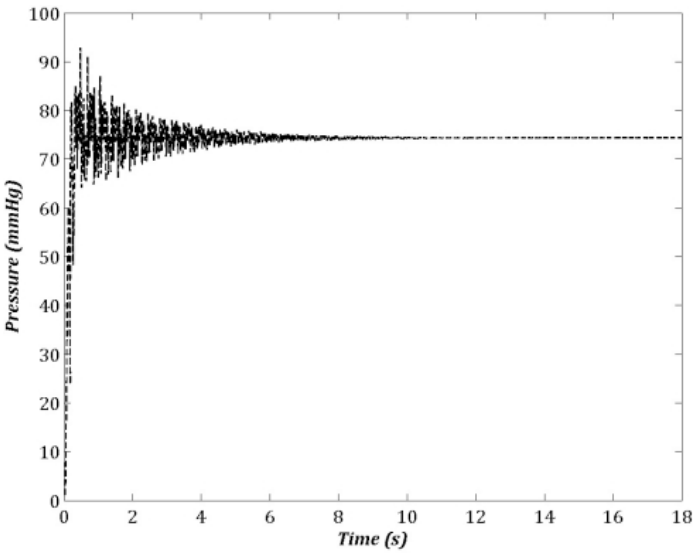

Figure 5. Pressure against time at the distal end of the valve vessel.

Discussion

Having developed a suitable, accurate numerical scheme to solve the equations governing one-dimensional unsteady flow through a collapsible tube [11], the current paper examines the effect of venous avalvulia on a representation of a human vein.

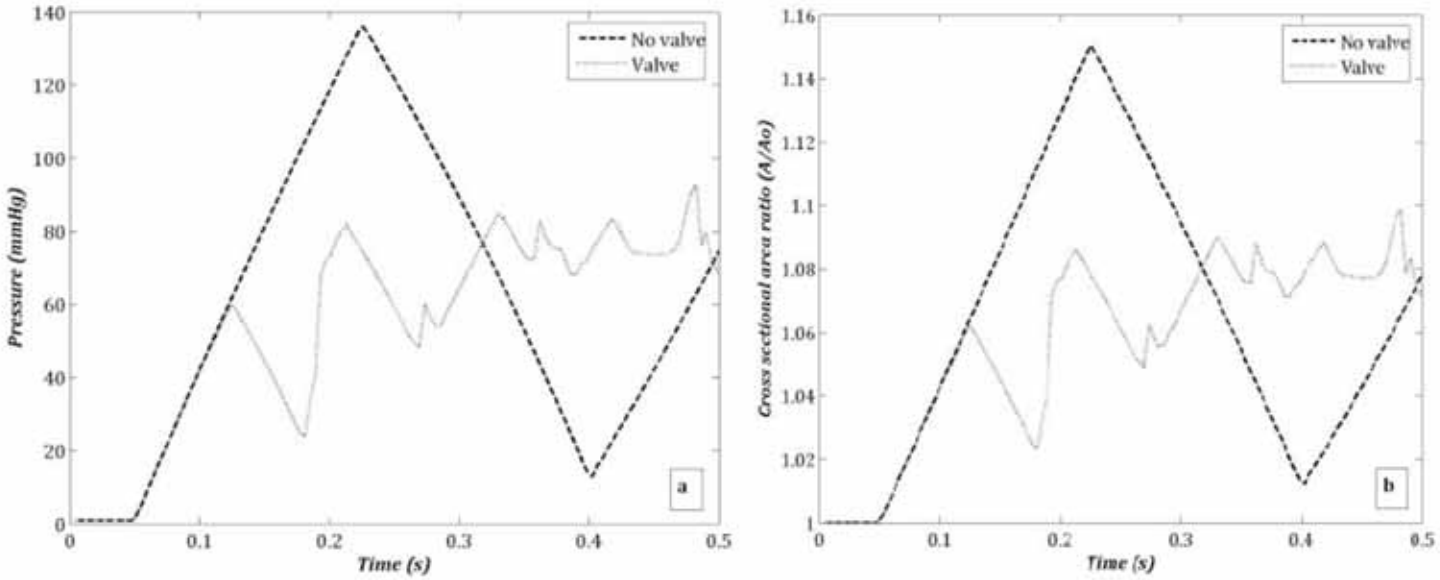

Figure 6. (a) Pressure against time at the distal end of the vessel with and without valve as indicated by the vein section diagrams. (b): Cross-sectional area ratio against time at the distal end of the vessel with and without a valve.

The results obtained in the absence of a valve were very oscillatory and the overshoot associated with the dynamic system, was approximately twice the hydrostatic steady value. Furthermore, the cross-sectional area of the vessel associated with the dynamic system was approximately 15% higher than at the starting condition.

A valve was subsequently introduced at the midpoint of the vein. Because the system was oscillatory, the focus was on the early phase of the simulation. The results obtained from this simulation showed that a single valve in the middle of the vein can have a significant effect on the resultant pressures and cross-sectional area, causing an absolute pressure reduction of over 40 mmHg (Figure 6a). Furthermore, a reduction in vein cross-sectional area of 5% was observed when compared with the results obtained for a vein with no valve. These results also validate the hypothesis that "*venous valves protect the wall of the vein below each valve from the pressure in the vein above it when gravity is applied*" [16].

The above findings shed light on clinical observations in patients with venous avalvulia and the associated development of varicose veins. In the absence of a valve, the vessel is subjected to higher transmural pressures which cause the vessel to expand.

Conclusions

Analyses of a vessel both with and without a valve have provided qualitative and quantitative information on the system behaviour under the instantaneous application of gravity. Furthermore, this allows direct comparison of the two cases and conclusions regarding the effects of avalvulia to be made.

In summary, this paper presents what is believed to be the first attempt at quantitative analysis and critical examination of the effects of venous avalvulia under gravitational loads associated with change of posture.

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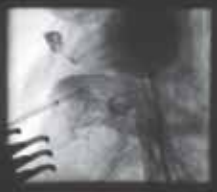

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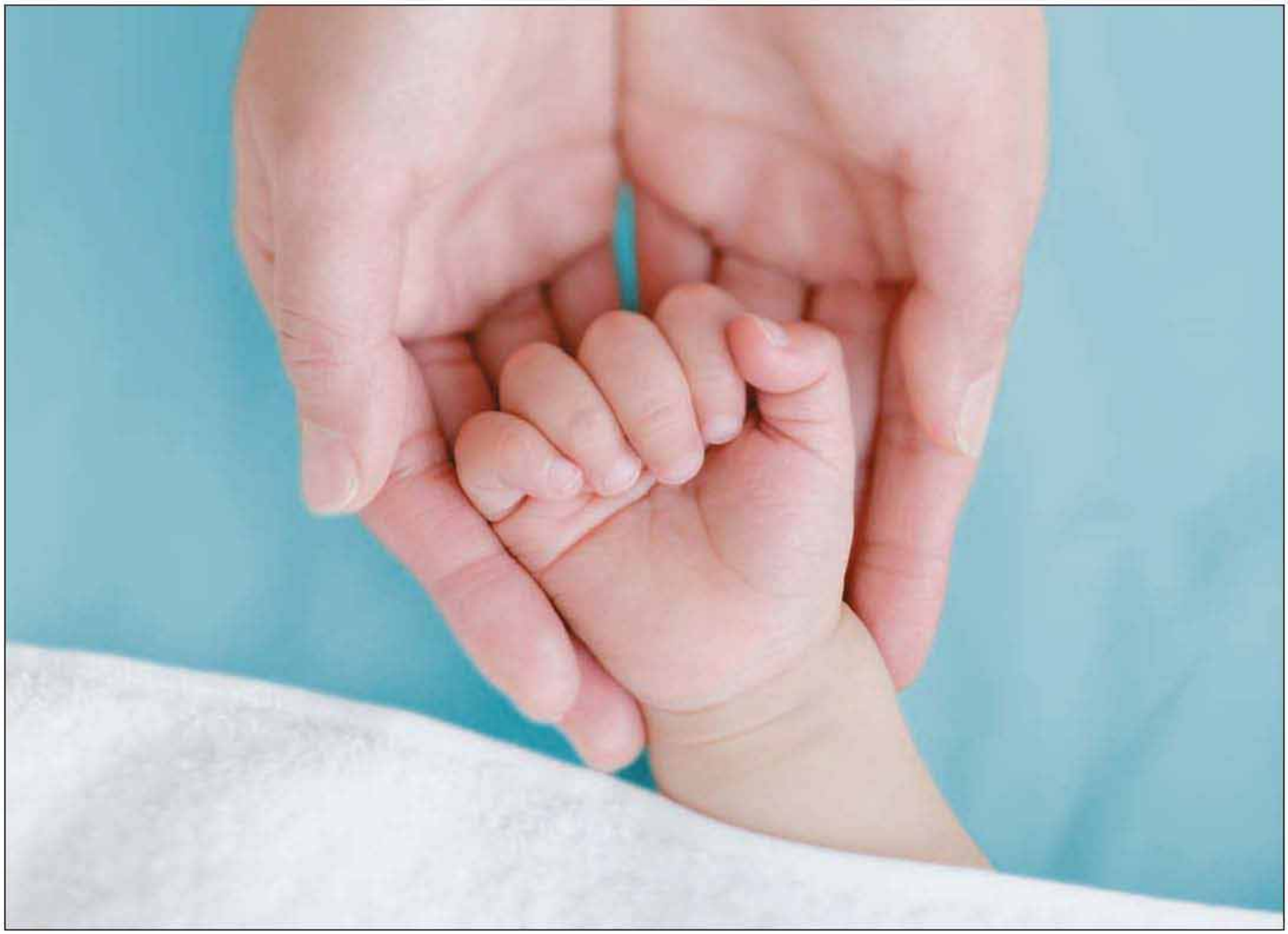

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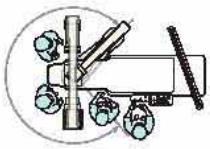

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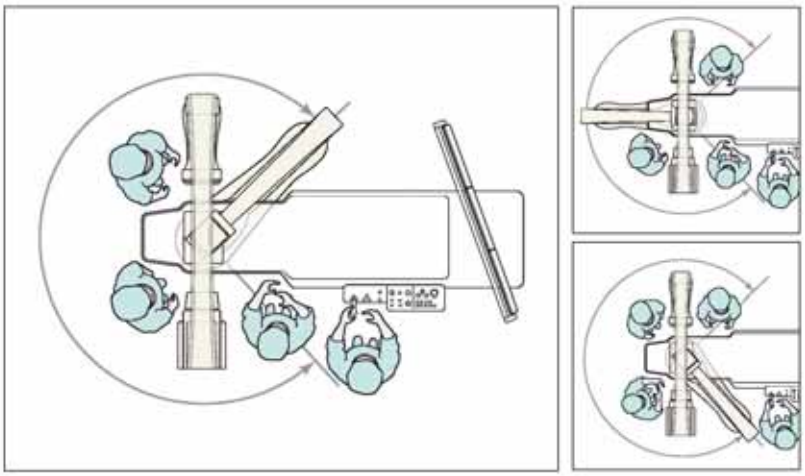

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