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Search for an Optimal Design of a Bioprosthetic Venous Valve: *In silico* and *in vitro* Studies

Henry Y. Chen [a], **Wei-shin Tien** [b], **Sean D. Chambers** [c], **Dana Dabiri** [b], **Ghassan S. Kassab** [a,*]

[a] California Medical Innovations Institute, San Diego, CA, USA
[b] Department of Biomedical Engineering, University of Washington, Seattle, WA, USA
[c] Cook Incorporated, Bloomington, IN, USA

WHAT THIS PAPER ADDS

Valve incompetence is a progressive disease of the venous system that may lead to deep venous thrombosis. There is a need for a venous valve prosthesis to replace incompetent valves. However, computational and experimental studies on venous valve and associated haemodynamics are limited. The current study addresses this gap and creates a scientific platform for potential correlations with clinical pathological development and effective venous prostheses.

Objective/background: Valve incompetence is a progressive disease of the venous system that may eventually lead to venous hypertension, pain, and ulcers. There is a need for a venous valve prosthesis to replace incompetent valves. Computational and experimental investigations on venous valve design and associated haemodynamics will undoubtedly advance prosthesis design and treatments. Here, the objective is to investigate the effect of venous valve on the fluid and solid mechanics. The hypothesis is that there exists a valve geometry that maximises leaflet shear stress (LSS) but minimises leaflet intramural stress (LIS; i.e., minimise stress ratio = LIS/LSS).

Methods: To address the hypothesis, fully dynamic fluid–structure interaction (FSI) models were developed. The entire cycle of valve opening and closure was simulated. The flow validation experiments were conducted using a stented venous valve prosthesis and a pulse duplicator flow loop.

Results: Agreement between the output of FSI simulations and output of pulse duplicator was confirmed. The maximum flow rates were within 6% difference, and the total flow during the cycle was within 10% difference. The simulated high stress ratio region at the leaflet base (five times the leaflet average) predicted the disease location of the vast majority of explanted venous valves reported in clinical literature. The study found that the reduced valve height and leaflet dome shape resulted in optimal performance to provide the lowest stress ratio.

Conclusion: This study proposes an effective design of venous prostheses and elaborates on the correlations of venous valve with clinical observations.

Keywords: Fluid–structure interaction (FSI), Leaflet intramural stress (LIS), Leaflet shear stress (LSS), Valve thrombosis, Venous valve biomechanics
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INTRODUCTION

Chronic venous disease (CVD) of the lower extremities is an important medical problem, constituting approximately 2% of total Western societies' healthcare budget. One of the main causes of CVD is that the venous valves of the patients become incompetent resulting in venous reflux.[1–4] Valve incompetence is a progressive disease of the venous system. Advanced CVD develops as a result of venous hypertension, which may eventually lead to pain, oedema, and gross skin changes such as venous ulcers.[5,6] In the most advanced cases of CVD, the impact of combined reflux and obstruction is significantly higher than reflux alone.[6] Stenting is currently a major treatment to remove obstruction. Although this approach restores venous flow, it does not address persistent reflux, which may be responsible for further deterioration of CVD.[7–9]

Current treatments of patients with deep vein valve incompetence are centred on methods that control the symptoms. Prosthetic valve is one alternative for treating the disease by reducing reflux and venous hypertension.[7,10,11] However, computational and experimental studies on venous valve design and associated

* Corresponding author. California Medical Innovations Institute, 11107 Roselle St., Rm. 211, San Diego, CA 92121, USA.
E-mail address: gkassab@calmi2.org (Ghassan S. Kassab).

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haemodynamics are limited.[4,10,14] Consequently, advances in effective venous valve prosthesis design have been inadequate. Although various bioprosthetic valves have been attempted to treat reflux, clinical success has been limited owing to thrombosis and neointima around the leaflets, which are related to the haemodynamics and design of the valve prosthesis. After relatively positive results of venous valve prostheses in animal studies, various investigators reported on percutaneous venous valves in clinical trials.[7,12,13] Unfortunately, clinical trial results showed 80–87% failure rates. According to these clinical studies, thrombosis tends to be an acute problem occurring within two weeks. Intimal hyperplasia (IH) leading to leaflet thickening and stiffening is the other major mode of valve failure.[7]

Low leaflet shear stress (LSS) can promote thrombosis, which is a major reason for prosthetic venous valve failures.[10] Furthermore, LSS and leaflet intramural stress (LIS) levels can influence the phenotype of the neointima formed on the valve leaflets.[1,10] Low shear stress is related to higher residence time, which enhances low density lipoprotein invasion and platelet deposition, which are important contributors to thrombus initiation and progression of vessel disease. To mitigate thrombosis and neointima, it is necessary to improve both LSS and LIS. The main objective of the current study was to investigate the effect of venous valve design on the fluid and solid mechanics surrounding the valve leaflets. The central hypothesis is that there exists an optimal design for which the stress ratio (SR = LIS/LSS) is minimised. This approach is more time and cost efficient than empirical trial and error attempts to achieve valve optimisation. Virtual experiments using validated predictive computational models may produce an optimal design, which can then be subjected to experimental validation. The goal is to determine the design of a venous valve that provides optimal haemodynamic and stress distributions for long-term patency.

METHODS

Computational model

The fluid was modelled as incompressible with pulsatile flow of 20 beats per minute to mimic the respiration rate.[10,14] The vessel lumen and valve were 10 mm in diameter, representative of a typical femoral vein and valve (Fig. 1A). The fluid density and viscosity were 1050 kg/m^3 and 0.004 kg/m/second, respectively. For the wall interface, no slip was assumed between fluid and the wall, and no permeability of the vessel wall.

Fluid–structure interfaces (FSIs) were defined at the surfaces of the leaflets and boundaries of the fluid. A computational method was used that allows the fluid mesh to deform around the moving leaflets.[10,15] The fully coupled two way FSI (i.e., blood flow and leaflet interaction) model was solved. The detailed methods and mathematical formulations have been published previously.[10,14,15,17]

For the valve optimisation, stress ratio (SR) was defined as SR = LIS/LSS. For coronary arteries, a SR was previously shown to be positively correlated with IH, i.e., smaller SR had less IH.[17] Hence, the objective was to minimise the SR, i.e., lower intramural stresses and higher shear stress.

Experimental validation

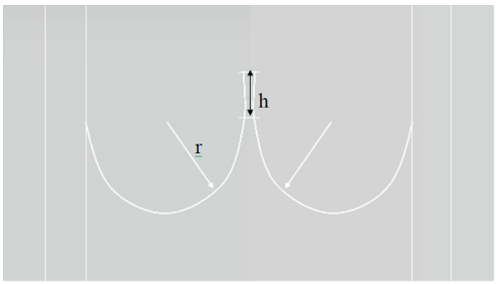
Prosthetic venous valve flow experiments were conducted using a pulse duplicator (PD) flow loop fabricated for venous valve testing (BDC, Denver, CO, USA). The testing fluid used was a glycerol solution, which was 36% glycerol by volume to simulate blood viscosity. The fluid density and viscosity were 1050 kg/m^3 and 0.004 kg/m/second, respectively. The flow was driven by a PD pump. The bioprosthetic valve used for the present study was provided by Cook Biotech (West Lafayette, IN, USA). The valve was a third generation bioprosthetic venous valve (BVV3) frame. Fixed tissue leaflets were sutured onto nitinol frame as described in Pavcnik et al.[7] The stented venous valves were installed in a test section connected to the flow loop (Fig. 1B). An ultrasound flow probe (ME13PXN; Transonic System, Ithaca, NY, USA) was mounted upstream to provide flow rate measurement of the system. Flow straighteners were installed before the flow probe to ensure accurate measurements. The flow system provided flow directional control and mean pressure control (Fig. 1B). The flow rates were measured by the flow probe and associated flow meter (Transonic Systems).

RESULTS

The comparison of flow waveforms from the PD measurements and FSI simulation is shown in Fig. 1C. The agreement between the FSI predictions and the PD measurements of valve flow were very good. The maximum flow rates were within 6% difference, and the total flow during the cycle was within 10% difference. The transient dynamics of the waveforms were similar. The flow reversals were also predicted by the FSI simulation (Fig. 1C). The FSI prediction of the transition point from maximum flow to the valve closing phase had a 7% lag vs. flow PD measurements. The pressure difference across the valve increased during opening, decreased during closing, and became negative after closure (Fig. 2). The pressure difference at leaflet base or hinge was largest during opening.

The flow fields during opening, closing, and closed stages are shown in Fig. 3. Flow accelerates during valve opening when a jet forms at the centre of the flow. Behind the leaflet, a vortex forms, which promotes shear stress on the leaflet surfaces (Fig. 3A). Flow decelerates during valve closure. A well defined vortex is also observed during this stage. This suggests that the leaflet dome is inducive to vortex formation (Fig. 3B). Flow ceases when the valve is fully closed. Only a minimal amount of flow is observed upstream (Fig. 3C). The residence time in the pocket region is shown in Fig. 3D. The cases without dome and 3/4R radius had much longer residence times.

The intramural stress concentrations on the leaflets are shown in Fig. 4A, B. The stresses concentrate at the base region (hinge) during various stages of leaflet motion. The



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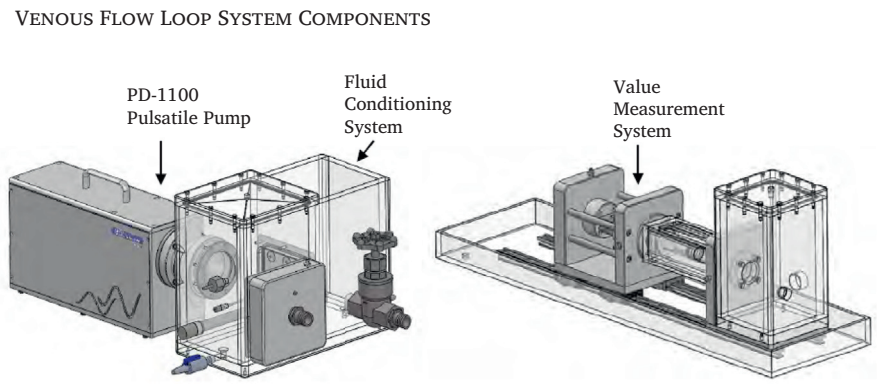

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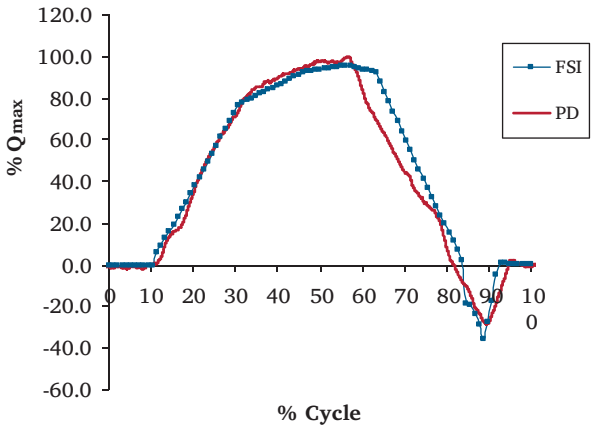

C

Figure 1. (A) Schematic for the leaflets showing the radius, r, and height, h (labelled by arrows). (B) Pulse Duplicator apparatus and system: the pulsatile pump, the flow conditioning system, and the valve measurement system. (C) Comparison of flow waveforms from pulse duplicator (PD) and fluid–structure interaction (FSI) simulation. The transient dynamics of the output waveforms were similar. The reversed flow during final stage of closure was predicted by the dynamic fluid-structure interaction simulation.

base region also experienced the least amount of flow and hence LSS. Thus, this region has the compounded effect of high intramural stress and low endothelial shear (Fig. 4C and D). Consequently, the SR was particularly high at the base. The SR at leaflet base was about five times higher than the leaflet average, as shown in Figs. 4E, 5 shows the dynamics of solid stress and fluid shear stress during the entire cycle. The intramural stress increased until maximum valve opening (Fig. 5A). As the valve was closing, the stresses reduced. When the leaflets returned to their original configuration, the stress was minimised. As the valve closed further, the stress increased. For the fluid LSS, a similar pattern was observed (Fig. 5B). The LSS increased during valve opening due to increased flow. During closing, the LSS reduced as the flow decelerated. After valve closure, the LSS became minimal.

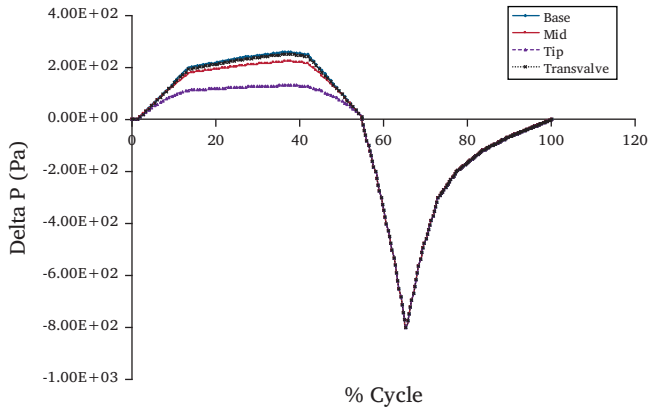

Figure 2. The pressure differential across the valve increased during opening, decreased during closing, and became negative after closure. The delta P at leaflet base (hinge) was largest while it is the least at the tip during opening and closing. After closure, the delta P became about the same at the base, middle and tip. The delta P trans-valve (pre- and post-valve) was similar to delta P at leaflet base. Delta P = change in pressure.

The comparison of mechanical SR of the various dome designs, as well as without dome, is shown in Fig. 6A. The minimum SR was observed at radius = ½ vessel radius. This trend was consistent for using maximum or average values, or during opening stages of the valve. The SR associated with various valve heights with the same dome are shown in Fig. 6B. The SR of ¼ height was much reduced vs. half and full height. Further reduction of height did not result in significant reduction in SR. Therefore, the reduced valve height (1/4 of the original) and leaflet dome shape (1/2 vein radius) resulted in optimal ratio of solid to fluid stresses.

DISCUSSION

The complete cycle of valve opening, closing, and full closure were simulated based on fully dynamic mathematical models. Agreement between the output of model simulations and output of PD was observed. Additionally, the simulated high leaflet SR region at the leaflet base generally agrees with the disease location of the majority of explanted venous valves.[1,7] It was found that an increase of pressure differential across the valve causes the valve to open, whereas a decrease of pressure differential causes the valve to close. Finally, the simulation study suggests a valve design with a specific radius to height ratio for which the mechanical SR was lowest (ratio of solid intramural stress and fluid shear stress).

Simulation validations and valve dynamics

van Bemmelen et al. studied the venous dynamics based on *in vivo* measurements.[18] The valve dynamics were evaluated and it was concluded that the valve motion is flow driven. Lurie et al. found that negative flow velocities are not necessary for the closure of valves.[3] Herein, it was found that the pressure difference on the proximal vs. distal sides of the valve resulted in the driving force on the valve leaflets. The above findings are consistent with the studies

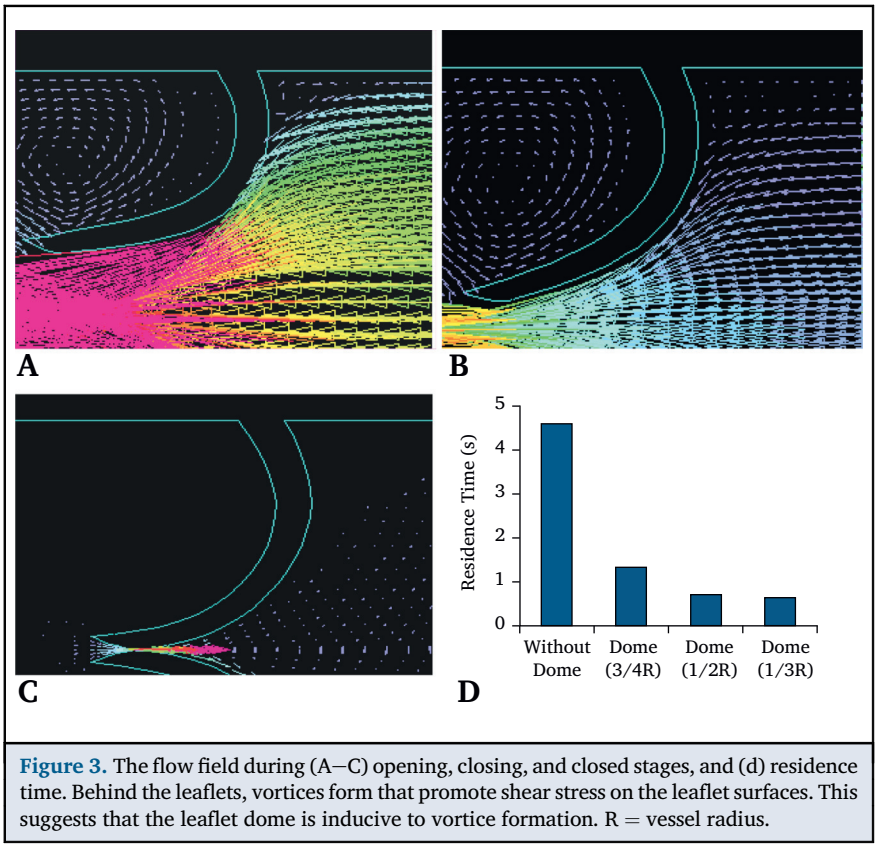

Figure 3. The flow field during (A–C) opening, closing, and closed stages, and (d) residence time. Behind the leaflets, vortices form that promote shear stress on the leaflet surfaces. This suggests that the leaflet dome is inducive to vortice formation. R = vessel radius.

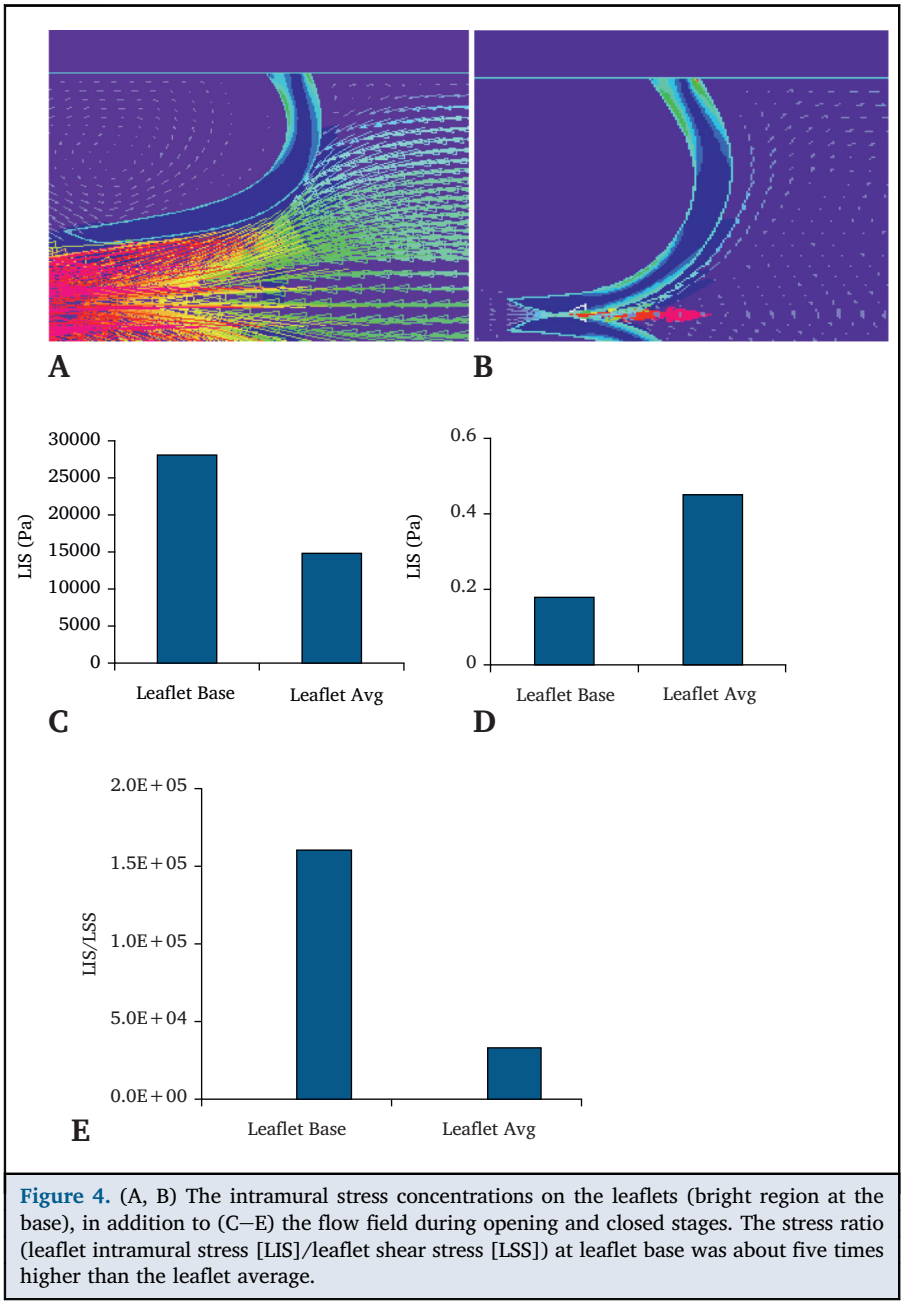

Figure 4. (A, B) The intramural stress concentrations on the leaflets (bright region at the base), in addition to (C–E) the flow field during opening and closed stages. The stress ratio (leaflet intramural stress [LIS]/leaflet shear stress [LSS]) at leaflet base was about five times higher than the leaflet average.

by Lurie et al.,[3] suggesting that the valve is driven by pressure difference across the valve. Muscle pumps help generate the pressure gradient and CVD is often accompanied by failure of the calf and foot muscle pump.[16]

Effects of fluid and solid mechanics on valve pathology

Low shear stress behind the leaflets provides flow stagnation and increased residence time for thrombotic and inflammatory cells.[19,20] Thus, low wall shear stress enhances the deposition of these cells onto the vessel wall. A microarray comparison by Simmons et al. profiled the transcriptional expression of valvular endothelium from both sides of swine aortic valve leaflets.[20] These transcriptional profiles identified distinct endothelial phenotypes on the two sides of the valve. Low shear stress further increases the permeability of vessel wall, which increases platelet deposition, which is important for thrombus initiation and progression.[1,17] Although the prosthesis leaflets are glutaraldehyde fixed (not living tissue) to avoid immune response, LSS affects the residence time of inflammatory and thrombotic cells around the valve and in the vessel wall, which affects valve pathologies such as valve thrombosis and adhesion. Furthermore, the neointima that will form on the surface of the leaflets is affected by the pattern of shear stress. Additionally, although the leaflets are glutaraldehyde fixed, the native vein wall is alive and its permeability also has biological effects. The validated computational models are valuable for identifying stagnant zones and regions susceptible to thrombus formation.

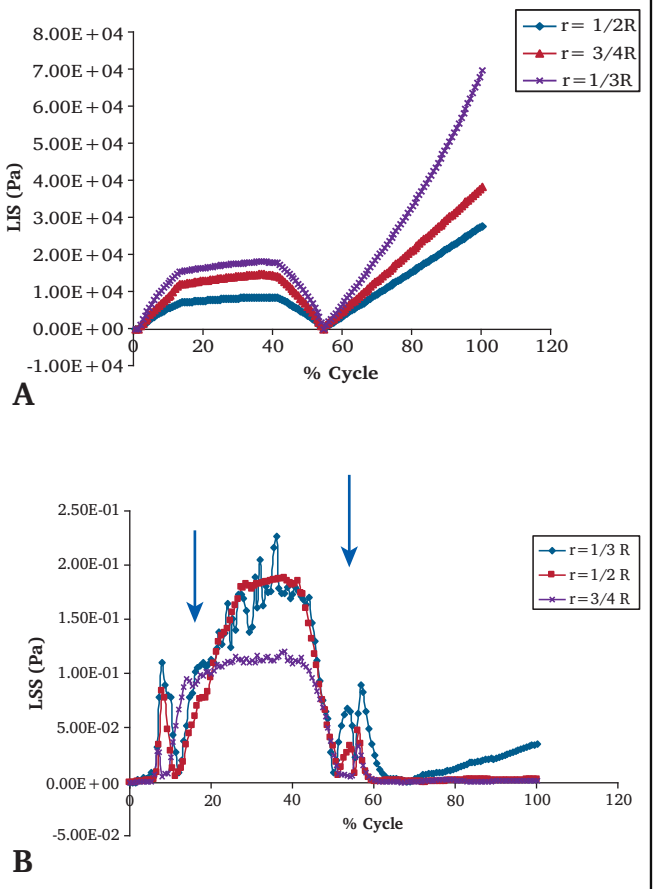

Figure 5. (A) The dynamics of solid stress (leaflet intramural stress [LIS]) and (B) fluid shear (leaflet shear stress [LSS]) at base of leaflets during the whole cycle. The arrows indicate start of opening (left arrow) and closing (right arrow). R = vessel radius.

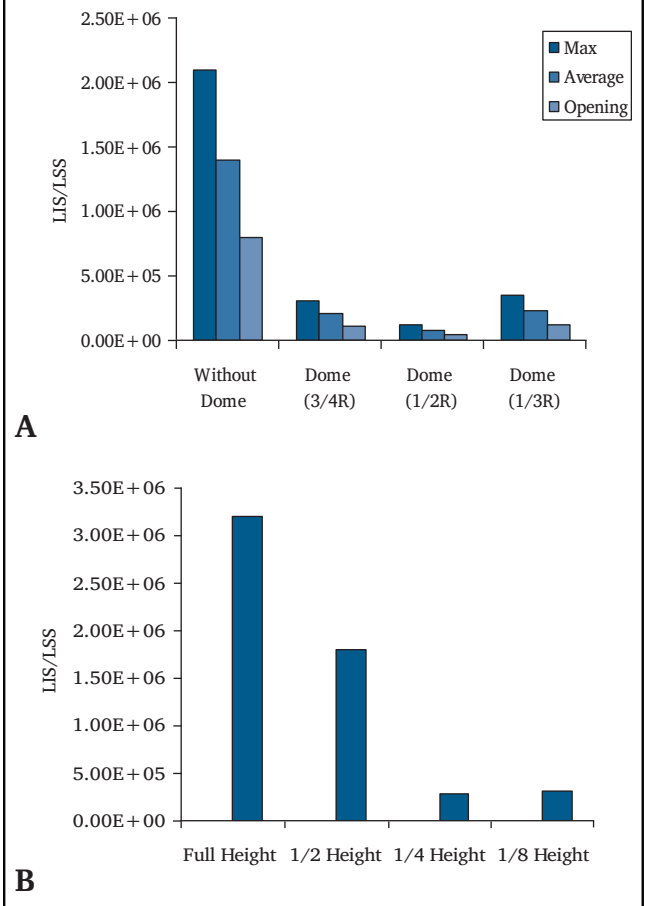

Figure 6. (A) The comparisons of stress ratio (leaflet intramural stress [LIS]/leaflet shear stress [LSS]) of the various dome designs, as well as without dome. The minimum stress ratio was observed at radius = ½ vessel radius. This trend was consistent for using max., average values, or during opening stage. (B) The stress ratio associated with various valve heights. The stress ratio of ¼ height was much reduced compared with half and full height. R = vessel radius.

Reversed flow is known to reduce nitric oxide in arteries which may lead to endothelial dysfunction and platelet adhesion.[21,22] Although the effect of reflux on venous endothelium is not well established, it is also likely to have similar adverse effects as the venous endothelium does not normally experience significant reflux.

Fluid shear stress analysis alone cannot fully explain the leaflet remodelling and thrombus formation patterns. It is highly likely that solid stresses act in synergy with the fluid shear stresses.[14,23–25] The mechanical stretching in response to higher intramural stress can also alter gene expression for endothelin and regulators of fibrinogen. Smooth muscle cells respond to cyclic stretching by increasing synthesis of type I and III collagen, resulting in tissue overgrowth.

The role of solid stresses on mechanobiology

A connection between solid intramural stress and neointimal hyperplasia has previously been established, i.e., the higher the circumferential wall stress of artery, the more extensive the neointima. A close correlation was also found between the solid/fluid SR and hyperplasia ($p < .01$) in studies of the coronary arteries of swine.[17] In chronic preclinical venous valve implants, it was found that the leaflet was thickened with neointima, especially at the leaflet base.[7,9] The focal thickening and intima at the base is highly consistent with the elevated SR found in the current study, i.e., up to five times higher SR at leaflet base vs. the leaflet average. The leaflet thickening can reduce leaflet mobility and affect valve opening and closing, resulting in valve stenosis or reflux.

On the cellular level, the leaflet base presents significant inflammatory response.[2] Solid stress concentrations are known to cause inflammations due to abnormal stress and strains in tissue.[23,24] Additionally, a fully differentiated smooth muscle cell phenotype was found via smooth muscle cell α-actin staining within explanted venous valve leaflets.[7,9] This is a major mechanism for hyperplasia due to elevated solid intramural stress.

Both low fluid shear and high solid stresses are inducive to inflammation. Low fluid shear makes it easier for

inflammatory cells such as leukocytes to initiate the inflammatory process.[26,27] High intramural stresses and strain stretch the cell gap junctions, enhancing inflammatory cells' infiltration into the vessel wall.[17,24,25] A previous simulation study on patient selection found that the prosthetic valve is especially beneficial for CVD CEAP clinical class 4—6 with significant reflux that enhances valve motion.[10]

The validated simulations were used to predict the SR for the various valve designs to assess the potential benefit of a valve implant where a lower SR was haemodynamically and biologically more favourable.

Analysis of clinical trials of previous venous valve prosthesis

After relatively positive results in animal studies of venous valve prostheses, clinical studies were conducted. Serino and Gale et al. reported on percutaneous venous valves in phase I clinical trials.[12,13] Valves were deployed via nitinol self expanding stents into five patients, four of which thrombosed. Another clinical study of 15 patients found that four valves occluded and the rest of the valves had leaflet thickening and rigidity, resulting in reflux and incompetence.[7,9] The leaflets were thickened and covered by neointima, which consisted of fibroblasts and collagen deposits, especially at the leaflet base. Improved haemodynamics on shear stress and residence time reduce propensity for thrombosis. Reducing intramural stress within the leaflet tissue can reduce inflammatory responses associated with leaflet thickening.

In addition to the biomechanical considerations, neo-endothelial cells covering the leaflets may reduce leaflet thickening. Studies found that endothelial cells covered leaflets prevented IH and improved valve function.[28] The improvements in valve design and biomechanics, appropriate patient selection and potential neo-endothelium offer hope for improved clinical outcome.

Limitations

First, the SR did not consider the effects of high shear stress on blood. As the flow velocities in the venous systems are an order of magnitude lower than aortic flow, turbulence or high shear induced platelet activation as in the case of aortic flow is not an issue in the venous system. The WSS in the current study was well below 10 dyn/cm^2 and far from the threshold of platelet activation. Second, although glycerol does not fully replicate blood, it was used for the flow loop only for simulation validation purposes. Third, the vein wall remodelling related to stent apposition was not considered in the current study. In depth studies have previously been performed of the effects of arterial stent sizing on IH.[17] A venous stent sizing study was previously performed using a venous flow loop.[29] It was found that appropriate stent sizing prevented adverse effects on valve haemodynamics. Additionally, the stent implantation *in situ* couples with the venous wall and probably reduces vein wall deformations during filling. As the valve stent frame was made of super elastic nitinol, this deformation limiting effect is probably not as pronounced as stainless steel stent frames. Finally, the currently modelled vein geometry is idealised as tubular, and valves were modelled without sinus. A study has been published on the effects of the sinus on valve haemodynamics.[30] It was found that the sinus pocket alters the flow around the valve and functions as a flow regulator to smooth the flow pattern around the valve. Although the simulated geometry did not use the exact anatomical representation, the findings from the study are aligned with previous clinical work, which suggests that the present assumptions are reasonable. Additionally, the sinus feature of venous valves is not as prominent as in the case of aortic valves.

CONCLUSIONS

In conclusion, a strong agreement between the output of model simulations and output of PD was observed. The simulation results show that the reduced valve height and leaflet dome shape result in optimal haemodynamics and hence mechanics of the venous valve. The simulated high SR region at the leaflet base predicted the disease location of venous valves.[7,9] This study provides the scientific platform that enables the design of prosthetic venous valves based on both fluid dynamics and solid mechanics. The study will enable further prosthesis design optimisation for percutaneous delivery of prosthetic valves and can extend the simulations to virtual implantations of valves in disease conditions. An optimally designed prosthetic venous valve may minimise reflux and improve SR for long-term patency.

CONFLICT OF INTEREST

Dr. Sean Chambers is employed by Cook Medical.

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